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EHA2021 Virtual Congress

26th Congress of the European Hematology Association

ABSTRACT BOOK

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EHA is a non-governmental and not-for-profit membership organization that is guided by its mission to promote excellence in patient care, research, and education in hematology.
In pursuing this mission, EHA acts exclusively in the interest of hematology as well as its practitioners, and is bound by core values of independence, integrity, and transparency.

EHA is an open networking organization - we celebrate collaboration and the sharing of knowledge and experience, assisting hematologists to achieve excellence not only in Europe, but also around the world.



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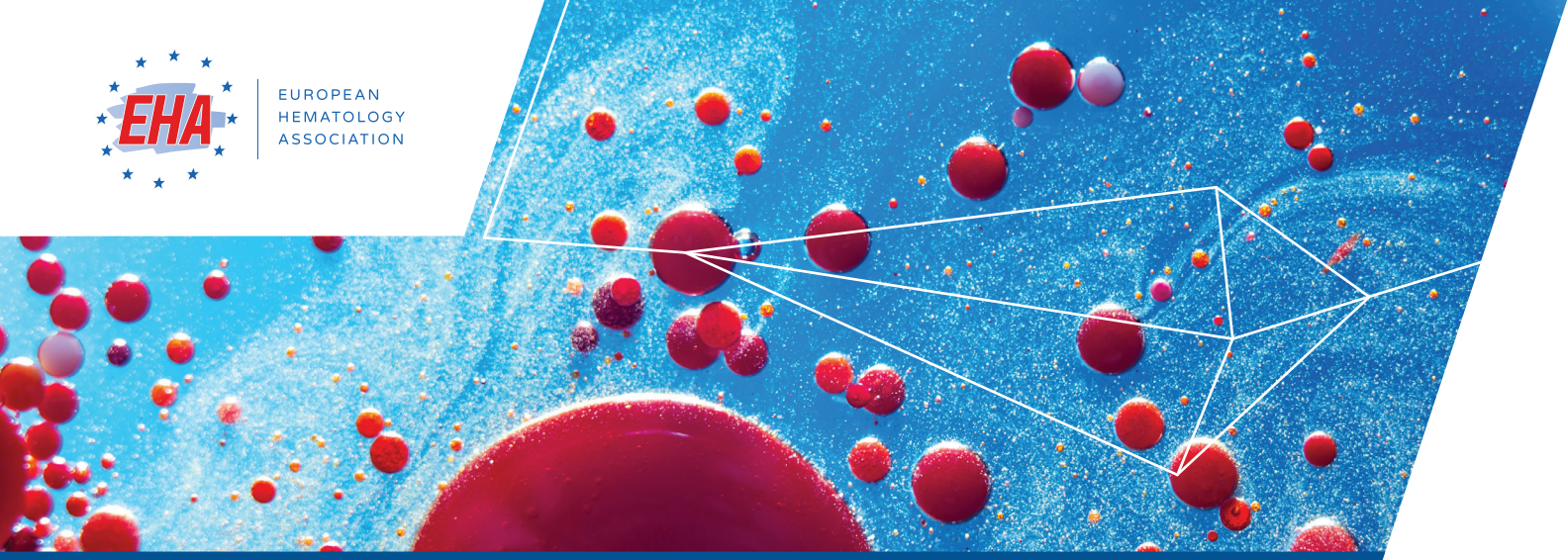
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Word of welcome

On behalf of the EHA Board and the Scientific Program Committee, we are pleased to present to you this year's Abstract Program.

The Scientific Program Committee has compiled an exciting program of oral and e-poster presentations out of more than 1800 abstracts that were submitted. While the number of abstracts is lower compared to other years, the quality is as high as ever and represents all fields of Hematology. The abstracts with the highest scores will be presented during the Presidential Symposium on Friday, June 11 (16:00 – 17:30 CEST), which will be one of the highlights of the Virtual Congress.

The oral presentations and e-posters will be released on the platform as of Friday, June 11 at 9:00 CEST. They will be available for all attendees to be viewed on-demand and to get updated on a broad range of topics and research areas. Although we will not physically meet this year, we aim to give maximum exposure to scientific work and allow for direct interaction between the authors and Congress delegates. Therefore, do not miss the unique opportunity to discuss and ask questions during the Live Q&A Sessions on the Thematic Days from June 13-17.

Supporting the next generation is an important task of EHA and this year we are awarding close to 100 participation grants to junior members who are presenting an abstract. During the Presidential Symposium, we are also awarding the YoungEHA Best Abstract Awards to trainees in with diverse backgrounds and at different stages in their career. Their names and the names of the participation grant winners can be found on the next pages.

The Late-Breaking Abstract Program is designed to provide an opportunity for investigators to submit abstracts with novel data that were not available at the time of the regular abstract submission deadline. Only a small selection of abstracts with the most ground-breaking results have been selected for presentation during the Late-Breaking Oral Session on Saturday, June 12 from 16:00 – 17:30 CEST.

All abstracts are available on the EHA Library and the Virtual Congress platform.

On behalf of the EHA Board, the committees, and all of the people involved in this year's Abstract Program, we trust you will enjoy reading this book and the research presented.



Prof Ruud Delwel

Chair, Scientific Program Committee of the EHA2021 Virtual Congress

Participation grant winners

For this Congress, **92** participation grants have been awarded to junior members of EHA, based on the mean score of their abstracts. EHA congratulates the following participation grant awardees:

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YoungEHA Best Abstract Awards

One of the primary missions of the European Hematology Association is to support young hematology clinicians and researchers. For the fifth year after launching in 2017, we are proud to announce the YoungEHA Best Abstract Awards for 2021. These are awarded to the highest-ranking abstracts in the following four categories: Clinicians or medical students training for a PhD degree, PhD research students, postdoctoral fellows, and clinical hematology trainees. We are honored that these outstanding YoungEHA trainees will be presenting during the EHA Congress - they are the future of hematology!

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The HME Forum is a resource for clinicians with experience in treating patients with a range of hematologic malignancies.

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Chairman: Emanuele Angelucci

Opening remarks
Emanuele Angelucci (Genova, Italy)

Clinical characteristics and diagnosis of BPDCN
Eric Deconinck (Besancon, France)

Contemporary treatments of adults with BPDCN
Naveen Pemmaraju (Houston, USA)

Case-based presentations and discussion
Moderator: Emanuele Angelucci (Genova, Italy)

Case A: Priyanka Mehta (Bristol, UK)
Case B: Marco Herling (Leipzig, Germany)

Closing remarks and adjourn
Emanuele Angelucci (Genova, Italy)

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Table of Contents

Presidential Session

Presidential Symposium	S100 – S104	p. 1

Oral Sessions

ALL - Signaling and beyond	S105 – S109	p. 4
ALL - Novel subgroups and agents	S110 – S114	p. 6
ALL - CAR-T: Alternative targets and age groups	S115 – S119	p. 9
AML epigenetic and transcriptional control	S120 – S124	p. 12
AML mechanisms of resistance	S125 – S129	p. 14
AML classification	S130 – S134	p. 17
Developments in AML therapy	S135 – S139	p. 20
New biological and translational insights in CLL	S140 – S144	p. 23
Clinical trials with targeted therapies in CLL	S145 – S149	p. 26
Response, resistance and treatment-free remission in CML	S150 – S154	p. 29
Population based studies in myeloid disorders	S155 – S159	p. 32
Correlating mutations with phenotype in MDS	S160 – S164	p. 35
Novel targets in MDS	S165 – S169	p. 38
New directions in aplastic anemia and PNH	S170 – S174	p. 40
Basic and translational myeloma research	S175 – S179	p. 43
New treatment strategies for newly diagnosed multiple myeloma	S180 – S184	p. 45
New diagnostic and therapeutic approaches in multiple myeloma and AL amyloidosis	S185 – S189	p. 48
T cell re-directing therapies in relapsed/refractory multiple myeloma	S190 – S194	p. 51
New pathways and molecular mechanisms in MPN	S195 – S199	p. 54
Novel therapies and targets in MPN	S200 – S204	p. 56
Hodgkin lymphoma - Clinical	S205 – S209	p. 59
Indolent & mantle cell lymphoma - Clinical	S210 – S214	p. 62
Aggressive lymphoma - CAR-T & transplant	S215 – S219	p. 64
Aggressive lymphoma - Combination therapies	S220 – S224	p. 67
Lymphoma - Translational research	S225 – S229	p. 70
Stem cell transplantation - Preclinical/experimental	S230 – S234	p. 73
Stem cell transplantation - GvHD	S235 – S239	p. 75
Stem cell transplantation - Clinical	S240 – S244	p. 78
Stem cell biology and microenvironment	S245 – S249	p. 81
Cellular immunotherapy and gene therapy - Experimental	S250 – S254	p. 83
Cellular immunotherapy and gene therapy - Clinical	S255 – S259	p. 85
Changing the scene on sickle cell disease	S260 – S264	p. 88
Changing the scene on thalassemias	S265 – S269	p. 90
Changing the scene on congenital anemias	S270 – S274	p. 93
Focus on iron metabolism	S275 – S279	p. 95
Fungal, bacterial and viral infections in hematology	S280 – S284	p. 98
COVID-19 impact on hematology: How it started - How it's going	S285 – S289	p. 101
Transfusion medicine	S290 – S294	p. 104
ITP: from bench to bedside	S295 – S299	p. 106
Dilemmas in coagulation and thrombosis	S300 – S304	p. 109
Malignancies and thrombosis	S305 – S309	p. 111
Patient's voice and health outcomes in hematology	S310 – S314	p. 114

e-Posters

Acute lymphoblastic leukemia - Biology & Translational Research	EP316 – EP340	p. 117
Acute lymphoblastic leukemia - Clinical	EP341 – EP371	p. 129
Acute myeloid leukemia - Biology & Translational Research	EP372 – EP426	p. 145
Acute myeloid leukemia - Clinical	EP427 – EP494	p. 171
Aggressive Non-Hodgkin lymphoma - Clinical	EP495 – EP565	p. 209

Bleeding disorders (congenital and acquired)	EP566 – EP579	p. 248
Bone marrow failure syndromes incl. PNH - Biology & Translational Research	EP580 – EP584	p. 255
Bone marrow failure syndromes incl. PNH - Clinical	EP585 – EP598	p. 257
Chronic lymphocytic leukemia and related disorders - Biology & Translational Research	EP599 – EP630	p. 265
Chronic lymphocytic leukemia and related disorders - Clinical	EP631 – EP654	p. 281
Chronic myeloid leukemia - Biology & Translational Research	EP655 – EP665	p. 296
Chronic myeloid leukemia - Clinical	EP666 – EP684	p. 301
Enzymopathies, membranopathies and other anemias	EP685 – EP715	p. 312
Gene therapy, cellular immunotherapy and vaccination - Biology & Translational Research	EP716 – EP728	p. 328
Gene therapy, cellular immunotherapy and vaccination - Clinical	EP729 – EP749	p. 333
Hematopoiesis, stem cells and microenvironment	EP750 – EP763	p. 343
Hodgkin lymphoma - Clinical	EP764 – EP781	p. 348
Indolent and mantle-cell non-Hodgkin lymphoma - Clinical	EP782 – EP808	p. 357
Infections in hematology (incl. supportive care/therapy)	EP809 – EP838	p. 373
Iron metabolism, deficiency and overload	EP839 – EP850	p. 388
Lymphoma Biology & Translational Research	EP851 – EP887	p. 393
Myelodysplastic syndromes - Biology & Translational Research	EP888 – EP908	p. 411
Myelodysplastic syndromes - Clinical	EP909 – EP935	p. 422
Myeloma and other monoclonal gammopathies - Biology & Translational Research	EP936 – EP961	p. 437
Myeloma and other monoclonal gammopathies - Clinical	EP962 – EP1056	p. 450
Myeloproliferative neoplasms - Biology & Translational Research	EP1057 – EP1073	p. 503
Myeloproliferative neoplasms - Clinical	EP1074 – EP1123	p. 511
Platelets disorders	EP1124 – EP1161	p. 538
Quality of life, palliative care, ethics and health economics	EP1162 – EP1196	p. 558
Sickle cell disease	EP1197 – EP1222	p. 576
Stem cell transplantation - Clinical	EP1223 – EP1294	p. 589
Stem cell transplantation - Experimental	EP1295 – EP1300	p. 625
Thalassemias	EP1301 – EP1318	p. 628
Thrombosis and vascular biology - Biology & Translational Research	EP1319 – EP1335	p. 638
Transfusion medicine	EP1337 – EP1349	p. 645

Publication Only

Acute lymphoblastic leukemia - Biology & Translational Research	PB1350 – PB1358	p. 652
Acute lymphoblastic leukemia - Clinical	PB1360 – PB1379	p. 656
Acute myeloid leukemia - Biology & Translational Research	PB1380 – PB1389	p. 664
Acute myeloid leukemia - Clinical	PB1390 – PB1427	p. 667
Aggressive Non-Hodgkin lymphoma - Clinical	PB1428 – PB1461	p. 683
Bleeding disorders (congenital and acquired)	PB1462 – PB1466	p. 698
Bone marrow failure syndromes incl. PNH - Biology & Translational Research	PB1467 – PB1468	p. 700
Bone marrow failure syndromes incl. PNH - Clinical	PB1469 – PB1489	p. 701
Chronic lymphocytic leukemia and related disorders - Biology & Translational Research	PB1490 – PB1491	p. 711
Chronic lymphocytic leukemia and related disorders - Clinical	PB1492 – PB1508	p. 712
Chronic myeloid leukemia - Biology & Translational Research	PB1509 – PB1512	p. 719
Chronic myeloid leukemia – Clinical	PB1513 – PB1535	p. 721
Enzymopathies, membranopathies and other anemias	PB1536 – PB1541	p. 729
Gene therapy, cellular immunotherapy and vaccination - Biology & Translational Research	PB1542 – PB1545	p. 732
Gene therapy, cellular immunotherapy and vaccination – Clinical	PB1546 – PB1546	p. 733
Hematopoiesis, stem cells and microenvironment	PB1547 – PB1549	p. 734
Hodgkin lymphoma - Clinical	PB1550 – PB1564	p. 735
Indolent and mantle-cell non-Hodgkin lymphoma - Clinical	PB1565 – PB1580	p. 741
Infections in hematology (incl. supportive care/therapy)	PB1581 – PB1600	p. 750
Iron metabolism, deficiency and overload	PB1601 – PB1608	p. 759
Lymphoma Biology & Translational Research	PB1609 – PB1611	p. 763
Myelodysplastic syndromes - Biology & Translational Research	PB1612 – PB1618	p. 764
Myelodysplastic syndromes - Clinical	PB1619 – PB1629	p. 767
Myeloma and other monoclonal gammopathies - Biology & Translational Research	PB1630 – PB1640	p. 771
Myeloma and other monoclonal gammopathies - Clinical	PB1641 – PB1699	p. 775
Myeloproliferative neoplasms - Clinical	PB1700 – PB1728	p. 804
Platelets disorders	PB1729 – PB1734	p. 817
Quality of life, palliative care, ethics and health economics	PB1735 – PB1759	p. 820
Sickle cell disease	PB1760 – PB1773	p. 829
Stem cell transplantation - Clinical	PB1774 – PB1799	p. 836
Stem cell transplantation - Experimental	PB1800 – PB1803	p. 846
Thalassemias	PB1804 – PB1821	p. 848
Thrombosis and vascular biology - Biology & Translational Research	PB1822 – PB1833	p. 856
Transfusion medicine	PB1834 – PB1836	p. 860

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Presidential Symposium

S100 PIGA GERMLINE MUTATIONS CAUSE DECREASED HEPCIDIN EXPRESSION AND A NOVEL SUBTYPE OF HEREDITARY HEMOCHROMATOSIS

O. Marques [1,*], L. Muckenthaler [1], S. Colucci [1], J. Kunz [1], T. Bast [2], P. Fabrowski [3], S. Altamura [1], B. Höchsmann [4], M. Langlotz [5], N. Hofmeister-Mielke [6], A. Kulozik [1], M. Muckenthaler [1]

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Background: Hereditary Hemochromatosis (HH) is a common genetic disease of systemic iron overload caused by decreased activity of the hepcidin/ferroportin regulatory axis. The most common form of HH is caused by homozygosity for the HFE p.C282Y mutation, while rarer, juvenile subtypes can be caused by mutations in transferrin receptor 2, hemojuvelin, hepcidin or the hepcidin receptor ferroportin. Some patients with inherited hemochromatosis-like phenotypes do not carry mutations in these genes known to be involved in iron homeostasis.
We have recently diagnosed iron overload in 3 patients with epileptic encephalopathy. The clinical picture included normal red blood cell parameters, increased serum transferrin saturation, elevated liver iron and decreased serum hepcidin levels. Exome sequencing excluded mutations in known HH-associated genes and identified novel germline mutations in the phosphatidylinositol glycan class A (*PIGA*) gene. Somatic and germline pathogenic *PIGA* mutations are observed in patients with Paroxysmal nocturnal haemoglobinuria (PNH) and PIGA deficiency, respectively. PIGA is a protein involved in the first step of GPI anchor biosynthesis, which is important for the dynamics and cell membrane attachment of proteins.
Aims: GPI-anchored proteins involved in iron metabolism include HJV and ceruloplasmin. We therefore hypothesized that the iron overload observed in our patients was caused by failure in GPI-anchorage of these proteins. Impaired HJV surface expression would impair iron sensing and result in low hepcidin expression and increased iron uptake while altered ceruloplasmin levels may contribute to enhanced cellular iron retention.
Methods: We performed CRISPR/Cas12a-mediated knockout of *PIGA* in the hepatocytic cell line Hep3B. The expression of key players in iron homeostasis was analysed in WT and *PIGA* KO clones by gene and protein expression analysis. Rescue experiments were performed in *PIGA* KO clones by simultaneously overexpressing HJV and PIGA from constructs that either coded for PIGA WT protein or carried the mutations identified in our patients.
Results: PIGA mRNA transcript and protein were inactivated in the *PIGA* KO clones in comparison with clones that underwent the same CRISPR/Cas12a-mediated procedure but in which *PIGA* was not ablated (*PIGA* WT). Protein analysis detected decreased/absent levels of GPI-anchored proteins, such as CD59, Ceruloplasmin and HJV. We show that WT cells respond with increased hepcidin mRNA expression when HJV is overexpressed, while *PIGA* KO cells fail to do so. Simultaneous overexpression of HJV and a PIGA WT construct rescued hepcidin expression in *PIGA* KO cells to similar levels like WT but hepcidin remained significantly lower when the PIGA mutants L344P, R77Q, L110del and R412* were overexpressed.
Summary/Conclusion: We have discovered that GPI-anchoring of HJV is crucial for its function in regulating hepcidin. The results demonstrate that PIGA mutations are responsible for a novel form of juvenile hemochromatosis.

S101 THE BEYOND STUDY: RESULTS OF A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED MULTICENTER STUDY OF LUSPATERCEPT IN ADULT PATIENTS WITH NON-TRANSFUSION DEPENDENT BETA-THALASSEMIA

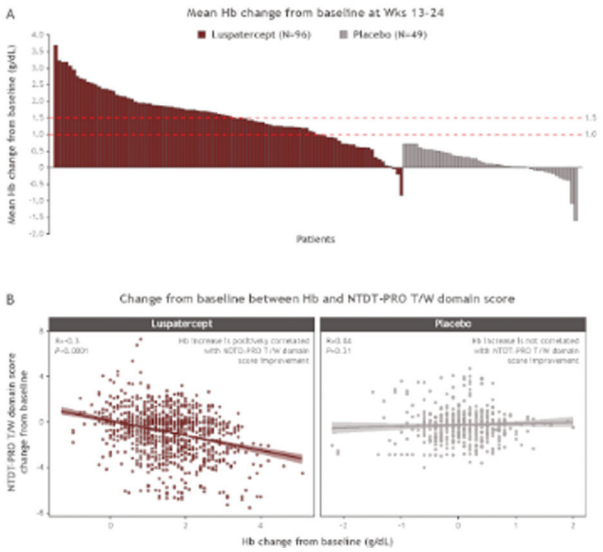
A. T. Taher [1,*], M. D. Cappellini [2], A. Kattamis [3], E. Voskaridou [4], S. Perrotta [5], A. Piga [6], A. Filosa [7], J. B. Porter [8], T. D. Coates [9,10], G. L. Forni [11], A. Thompson [12], J. T. Backstrom [13], O. Esposito [14], W.-L. Kuo [15], D. Miteva [14], T. Zinger [14], J. K. Shetty [14], V. Viprakasit [16]

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Background: β-thalassemia is an inherited hemoglobinopathy characterized by ineffective erythropoiesis and impaired red blood cell (RBC) maturation. Patients (pts) with non-transfusion dependent (NTD) β-thalassemia develop chronic anemia and other serious complications affecting survival and quality of life (QoL). Luspatercept, a first-in-class erythroid maturation agent approved by the EMA for treatment of anemia in adults with transfusion-dependent β-thalassemia, may have potential clinical benefit for NTD pts.
Aims: We report results of BEYOND, a phase 2, double-blind, randomized, multicenter study to determine the efficacy and safety of luspatercept vs placebo (PBO) in adults with NTD β-thalassemia (NCT03342404).
Methods: Eligible pts provided informed consent, were ≥18 years with β-thalassemia or hemoglobin (Hb) E/β-thalassemia and received ≤5 RBC units in the 24 weeks (wks) prior to randomization, with mean baseline Hb ≤10.0 g/dL. Pts were randomized 2:1 to receive luspatercept 1 mg/kg (titration up to 1.25 mg/kg) or PBO subcutaneously every 3 wks for ≥48 wks. Pts in both arms continued to receive best supportive care, including sporadic RBC transfusions and iron chelation therapy.
The primary endpoint was achievement of ≥1.0 g/dL mean Hb increase from baseline over a continuous 12-wk interval from Wks 13–24 in the absence of RBC transfusions. Secondary endpoints included proportion of pts who remained transfusion free over Wks 1–24, who achieved mean Hb increase of ≥1.5 g/dL from baseline to Wks 13–24, and mean change in NTD β-thalassemia pt-reported outcome tiredness and weakness (NTDT-PRO T/W) domain scores (higher scores reflect worse QoL).
Results: 145 pts were randomized: 96 received luspatercept and 49 received PBO. Median age was 40.0 years (range 18.0–71.0); 41.7% were male. Baseline median Hb was 8.2 g/dL (range 5.3–10.1); median NTDT-PRO T/W score was 4.3 (range 0–9.5). 20 (13.8%) pts received RBC transfusions (max 5 units) in the 24 wks prior to treatment.
74 of 96 (77.1%) pts in the luspatercept arm achieved the primary endpoint vs 0 of 49 PBO pts (P<0.0001; Fig. A). The primary endpoint was achieved by 40 of 55 (72.7%) luspatercept pts with mean baseline Hb

<8.5 g/dL (vs 0 PBO; *P*<0.0001), and 34 of 41 (82.9%) with mean baseline Hb ≥8.5 g/dL (vs 0 PBO; *P*<0.0001).
At Wks 13–24, 50 of 96 (52.1%) pts in the luspatercept arm achieved mean Hb increase of ≥1.5 g/dL compared to baseline vs 0 PBO (*P*<0.0001; Fig. A). 89.6% of pts in the luspatercept arm remained transfusion free at Wks 1–24 vs 67.3% PBO pts (*P*=0.0013). Change from baseline in NTDT-PRO T/W scores in luspatercept vs PBO arms were –0.92 vs –0.47 (least squares mean difference [LSMD] –0.48, *P*=0.0924) at Wks 13–24 and –1.00 vs –0.16 (LSMD –0.79, *P*=0.051) at Wks 37–48, respectively. Similar changes were also observed in the subset of luspatercept pts with mean baseline Hb <8.5 g/dL (LSMD at Wks 13–24 luspatercept vs PBO –0.73, *P*=0.0433). Improvement in NTDT-PRO T/W scores correlated with Hb increase (Fig. B).
Treatment-emergent adverse events (≥1, grade ≥3) were reported in 27 (28.1%) and 12 (24.5%) pts in luspatercept and PBO arms. Malignant events were only reported in the PBO arm, affecting 2 (4.1%) pts (diffuse large B-cell lymphoma, hepatocellular carcinoma). No thromboembolic or thrombophlebitis events were reported in either .arm.

Figure. (A) Change in mean Hb and (B) change in NTDT-PRO T/W scores vs change in Hb in pts treated with luspatercept and placebo.



Summary/Conclusion: Treatment with luspatercept resulted in significant improvements of anemia, as measured by Hb levels, vs PBO in adults with NTD β-thalassemia. Changes in NTDT-PRO T/W correlated with increases in Hb. Luspatercept was well tolerated in this pt population.

S102 HEMATOPOIETIC STEM CELL-GENE THERAPY FOR MUCOPOLYSACCHARIDOSIS TYPE I, HURLER: EVIDENCE OF EXTENSIVE METABOLIC CORRECTION AND EARLY CLINICAL RESPONSE

M. E. Bernardo [1,2,*], B. Gentner [3], F. Tucci 1, F. Fumagalli [1], F. Ciotti [1], M. Sarzana [1], G. Consiglieri [1], C. Filisetti [1], S. Pontesilli [3], C. Baldoli [3], S. Darin [1], S. Miglietta [3], E. Zonari [3], R. Parini [1], G. La Marca [4], F. Ciceri [3], L. Naldini [3], A. Aiuti [1]

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the standard of care for mucopolysaccharidosis type I Hurler (MPS-IH) patients showing high overall survival rates and high rate of full donor chimerism when patients are treated at young age and cord blood (CB) hematopoietic stem cells (HSC) are employed. In allo-HSCT, engrafted donor-derived cells constitute a stable endogenous source of the enzyme that can be distributed systemically. However, skeletal abnormalities persist and progress over time severely affecting patient's quality of life together with progressive neurocognitive deterioration.
Aims: Here we report the results of a first-in-human phase I/II clinical trial (NCT03488394) of 8 MPSIH patients treated with autologous HSC genetically modified to overexpress human IDUA and followed-up for a maximum of 2 years (median 12 months).
Methods: Patients (6 M, 2 F; median age at treatment 24 months) lacked a non-heterozygous-HLA-matched CB donor and displayed an IQ/DQ>70. Seven out of 8 patients received enzyme replacement therapy before gene therapy (GT) and 5 of them had a positive anti-IDUA IgG titer at baseline. A high number of autologous HSCs was collected by leukapheresis following mobilization and were transduced with a clinical-grade lentiviral vector encoding human *IDUA* cDNA. Primary endpoint of efficacy was IDUA activity in dried blood spot up to supraphysiologic levels at 1y post-GT. Treatment impact on nervous system and bone was assessed by biochemical, clinical and radiologic parameters.
Results: Median cell dose was 20.7 CD34+/Kg with a median transduction efficiency above 80% and a median vector copy number (VCN) per cell of 2.2 in the drug products. All patients had rapid hematologic recovery, with median neutrophil engraftment on day +20.5 and short thrombocytopenia limited to grade 3 in most patients. The 5 patients that tested positive for IDUA antibodies before GT cleared them within 3 months after GT. Adverse events were generally mild and comparable to those seen with autologous-HSCT, with the exception of one patient who experienced an acute allergic reaction on day+12 which promptly resolved. Gene-marked cells appeared in the bone marrow and peripheral blood in all patients as early as day+30 after GT and were accompanied by achievement of blood IDUA activity to supraphysiological levels in all patients, maintained at 12 months follow-up. All patients had a steep decline in urinary heparan sulfate (HS) and dermatan sulfate (DS) reaching normal or near-normal values by 1 year after treatment. Importantly, undetectable cerebrospinal fluid (CSF) IDUA activity at baseline became detectable by month 3 in all subjects and further increased by month 6 suggesting central enzyme expression, likely provided by local engraftment of microglia-like cells derived from transduced HSC. HS and DS levels in the CSF decreased post-GT suggesting central metabolic correction. With a median follow-up of 12 months, patients show stable cognitive and language performances, stable motor skills corresponding to continued motor development, improved joint stiffness and growth according to expected height percentiles of normal subjects. Brain and spine MRI showed improvements in some of the typical disease features at 1-year follow-up.
Summary/Conclusion: These results suggest that GT accomplishes extensive metabolic correction of peripheral and central compartments and promising preliminary clinical outcomes together with a favorable safety profile, highlighting the therapeutic potential of HSC-GT for the treatment of MPSIH.

S103 PAZOPANIB FOR SEVERE BLEEDING AND TRANSFUSION-DEPENDENT ANEMIA IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare angiogenic and bleeding disorder causing chronic gastrointestinal bleeding, epistaxis, and severe anemia. Pazopanib is an oral multi-kinase angiogenesis inhibitor with promise to treat bleeding in HHT. There are currently no FDA-approved agents to treat bleeding in HHT.
Aims: To evaluate the safety and effectiveness of low-dose oral pazopanib for severe HHT-associated bleeding.
Methods: We analyzed outcomes of HHT patients with severe bleeding and RBC transfusion dependence (per Gale criteria, ≥2 units pRBCs/month for ≥3 months) treated on a predefined institutional pazopanib treatment pathway for ≥12 months. This predefined institutional pathway outlined the eligibility, dosing, visit schedule, laboratory and adverse event monitoring, and endpoints of treatment and their assessment prior to initiation of pazopanib treatment. The primary endpoint was achievement of transfusion independence per Gale criteria (≥3 months RBC transfusion-free). Secondary endpoints included hemoglobin, epistaxis severity score, RBC transfusion and iron infusion requirements, number

of local hemostatic procedures, ferritin and transferrin saturation, compared using paired and repeated measures means tests.
Results: *Patients and Treatment*. 13 transfusion-dependent HHT patients with severe epistaxis and/or gastrointestinal bleeding received pazopanib [median (range) dose 100 (25-300) mg daily)] for a median of 22 months. Patient median (range) age was 66 (53-78) years and 6 (46%) were female. 12 patients (92%) were on medical disability due to severe chronic bleeding and anemia and 5 (38%) had been recommended to pursue palliative care as all available therapeutic options had been exhausted. 8 patients (62%) had previously failed systemic bevacizumab (either primary non-response or secondary loss of response). No patient had a complicating additional etiology of anemia or had received hormonal, antifibrinolytic, or erythropoiesis-stimulating agents in the 6 months prior to or at any point during pazopanib treatment.
Effectiveness. All patients achieved RBC transfusion independence. Compared with pretreatment, pazopanib increased mean hemoglobin by 4.8 (95% CI, 3.6-5.9) g/dL (7.8 vs. 12.7 g/dL, $P<0.0001$) and decreased mean epistaxis severity score by 4.77 (3.11-6.44) points (7.20 vs. 2.43 points, $P<0.0001$) after 12 months of treatment. Freedom from anemia (Hgb>11) was observed in 92% of patients at 12 months. Compared with 3 months pretreatment, RBC transfusions decreased by 93% (median of 16.0 vs. 0.0 units, $P<0.0001$) and elemental iron infused decreased by 92% (median of 4500 vs. 0 milligrams, $P=0.005$) during the first 3 months of treatment; improvements were maintained over time (**FIGURE**). Median ferritin increased 91 ng/mL (31 vs. 122 ng/mL, $P=0.0007$) and median transferrin saturation increased 14% (9% vs. 23%, $P=0.0002$). The number of required hemostatic procedures decreased 90% (median of 4 vs. 0, $P=0.0002$).
Safety. Pazopanib was well-tolerated: hypertension (31%), lymphocytopenia (23%), and fatigue (23%) were the most common adverse events (none were serious). No patient developed LFT abnormalities, venous or arterial thromboembolism, proteinuria or QTc prolongation during treatment. There were no fatal adverse events.

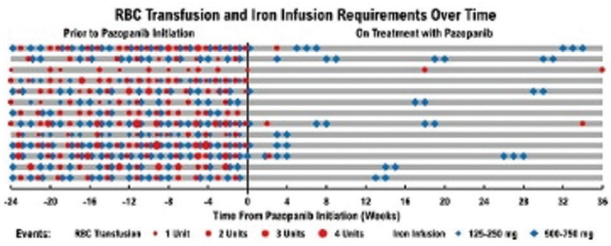


Figure. Swimmer plot detailing timeline of red cell transfusion and iron infusion events for each patient during the 24 months prior to pazopanib initiation and 36 weeks following its initiation. Each "lane" on the plot is representative of a patient over time. Each red circle is a red cell transfusion event and each blue diamond is an iron infusion event (the larger the circle or diamond, the more units of red cells or milligrams of elemental iron infused during that event). Red cell transfusion and iron infusion requirements decreased dramatically after starting pazopanib in all patients.

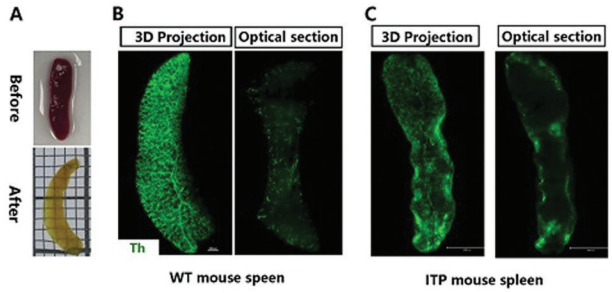
Summary/Conclusion: Pazopanib was safe and effective to manage severe bleeding in HHT, durably liberating all patients from transfusion dependence and normalizing hematologic parameters at doses much lower (median 100 mg daily) than the dose used to treat malignancies (800 mg daily).

S104 A B2 ADRENERGIC RECEPTOR AGONIST CORRECTS DYSREGULATED POLARIZATION OF T HELPER CELLS IN PRIMARY IMMUNE THROMBOCYTOPENIA

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Background: Accumulating evidence has begun to reveal that the nervous system can directly modulate the polarization of Th cells. Indeed, the β2-adrenergic receptor (β2-AR) has been described as the primary adrenergic receptor expressed in immune cells. Emerging studies have reinforced the therapeutic effects of β2-AR agonists in autoimmune diseases by modulating Th cell polarization and enhancing Treg cell function. Immune thrombocytopenia (ITP) is an acquired thrombocytopenia and involves complicated upstream immune dysregulation in which T-cell subsets are supposed to take centre stage. Th cells skewed towards Th1 and Th17 subsets are associated with antiplatelet autoantibody production. Conventional ITP therapies, such as high-dose dexamethasone, RTX and eltrombopag, restore the immune imbalance of Th cells to control levels, resulting in clinical improvement. Therefore, we focused on the role of β2-AR signalling in immune cell development and pathways during ITP.
Aims: To explore the regulation of the sympathetic nervous system on T cell polarization of immune thrombocytopenia (ITP) and describe the 3D distribution of sympathetic nerves in the spleen of active ITP model. Furthermore, to explore the treatment mechanisms of beta2-adrenergic receptor (β2-AR) agonists on ITP models, and provide potential new treatment methods for ITP.
Methods: The active ITP mouse model was established as previously reported (Blood 2010; Blood 2015). We determined the 3D distribution of neural innervations in the ITP mouse spleen by iDisco. For the depletion of sympathetic nerves, the mice were intraperitoneally injected with 150 mg/kg of 6-OHDA (Sigma) dissolved in 0.01% ascorbic acid/saline. Peripheral blood mononuclear cells were isolated from ITP patients and healthy control subjects. The expression of β2-AR and Th cell subsets was assessed by flow cytometry.
Results: Sympathectomized ITP (Syx-ITP) mice experienced a significantly longer platelet recovery time and lower overall survival than nonsympathectomized ITP (non Syx-ITP) mice. mRNA-seq results revealed that syx-ITP mouse CD4+ T cells expressed more Th1-related genes, while non-syx-ITP mice expressed more Th2- and Treg-associated genes. As mentioned above, the beta2-adrenergic receptor (β2-AR) has been described as the primary adrenergic receptor expressed in immune cells. Nonsyx and syx ITP mice both received i.p. injections of terbutaline. Both of these groups exhibited improved platelet counts, and the immune imbalance of Th cells in the spleen returned to control levels. The 3D procedure showed panicle-shaped sympathetic architecture in the ITP mouse spleen parenchyma (Figure 1). Next, we analysed the expression of β2-AR by flow cytometry. The density of β2-AR on CD4 T cells was significantly reduced in patients with ITP. To evaluate whether a β2-AR agonist affects CD4 T-cell polarization, we detected the proportions of T-cell subsets by flow cytometry in ITP patients and healthy controls with or without terbutaline treatment. Terbutaline inhibited the differentiation of Th1 cells but induced the differentiation of Th2 and T regulatory (Treg) cells in ITP patients. However, the percentage of Th17 cells was not affected by terbutaline treatment.



Summary/Conclusion: Impaired sympathetic innervation of the spleen and bone marrow plays a role in the pathogenesis of ITP. Terbutaline treatment corrects the dysregulated polarization of T helper cells during T-cell differentiation, suggesting a potential novel therapeutic approach for patients with ITP.

ALL - Signaling and beyond

S105 DYSREGULATION OF CHROMATIN MODIFIERS DRIVES LINEAGE SWITCH IN MLL-R ACUTE LEUKEMIA

R. Tirtakusuma [1,2], K. Szoltysek [1,3,*], P. Milne [1], V. V. Grinev [4], H. Blair [1], S. Nakjang [1], A. Ptasinska [5], S. Assi [5], C. Meyer [6], R. Marschalek [6], J. Allan [1], J. Vormoor [3], C. Bonifer [5], S. Bomken [1], O. Heidenreich [1,3]

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Background: Rearrangements of the *MLL* gene (also known as *KMT2A*) occur in both acute lymphoblastic (ALL) and myeloid leukemia (AML), with the lineage choice being dependent on the *MLL* fusion partner. The *MLL/AF4* fusion is associated with pro-B lymphoid phenotype and defines high-risk ALL subtype across all age groups. Interestingly, MLLr leukemias can convert from a lymphoid CD19+ to myeloid CD19-negative phenotype, leading to antigen escape and resistance to epitope-directed therapies such as CAR-T cell or BiTE (*e.g.* blinatumomab) approaches.
Aims: Here we aimed to identify the molecular basis of lineage promiscuity in MLL/AF4 acute leukemia and cellular plasticity during lineage commitment decisions in the cell of origin of relapse.
Methods: We investigated a cohort of two mixed-phenotype (MPALs) and 10 matched diagnosis/relapse samples from lineage switched acute leukemia patients (LSALs). All samples were subjected to next generation sequencing to identify lineage switch-associated changes in (i) mutational profiles, (ii) Ig rearrangements, (iii) transcriptomic pattern and (iv) chromatin accessibility. To identify cellular origins of lineage switch relapse, hematopoietic stem/progenitor cells (HSPCs), precursors and mature cells were examined for the presence of *MLL/AF4* fusion gene and composition of pre-selected mutations. Putative drivers of lineage switch were functionally validated *in vitro*, both with MLL/AF4-positive cell lines, human CD34+ cord blood model (Lin et al., 2016) and MLL/AF4-positive PDX cells.
Results: Sorted MPAL populations and LSAL matched pair samples showed identical fusion breakpoints in each patient proving a common clonal origin of lymphoid presentation and myeloid relapse, and arguing against *de novo* or treatment-related secondary leukemias. We observed BCR rearrangements typical for the pro-B stage in all lymphoid cells. Myeloid cells either shared the same, had different clones or no V(D)J rearrangement at all, proving that lineage switch can emerge from leukemic subpopulations of different maturation stage. Lack of V(D)J rearrangement in the myeloid fraction was associated with presence of the *MLL/AF4* fusion in an HSPCs compartment suggesting a very immature cell of origin in these cases. Comparative transcriptomic analyses between lymphoid and myeloid populations revealed changes in surface marker expression (*e.g.* CD19, CD33) and increased expression of genes controlling myeloid differentiation. DNase-seq results linked observed transcriptional changes to altered genome-wide chromatin accessibility, associated with loss of occupancy of lymphoid TFs binding motifs (*e.g.* EBF1) and gain of motifs bound by myeloid C/EBPs. Furthermore, lineage switch cases concurred with mutation, transcriptional downregulation or missplicing of *CHD4*, gene encoding the central helicase subunit of the NuRD complex. Perturbation of *CHD4* by shRNA lead to the conversion of lymphoid to myeloid programmes in both *MLL/AF*-positive ALL and preleukaemic cell models, as exemplified by loss of CD19 and gain of CD33 surface markers.
Summary/Conclusion: This study shows that lineage switch in MLLr ALL can occur at multiple levels and is associated with transcriptional reprogramming including altered splicing. We propose epigenomic and spliceosome regulators as targets for future investigations and potential therapeutic approaches.

S106 IL7R MUTATIONAL ACTIVATION CAN INITIATE PH-LIKE AND PAX5 P80R PRECURSOR B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

A. Almeida [1], J. L. Neto [1], A. Cachucho [1], M. Euzébio [1], X. Meng [2], R. Kim [3], M. Fernandes [1], B. Raposo [1], M. L. Oliveira [1], D. Ribeiro [1], R. Fragoso [1], P. P. Zenatti [4], J. Ronchi Corrêa [4], M. Duque [1], K. Roberts [5], S. Pyne [6], N. Pyne [6], V. Barreto [7], I. Bernard-Pierrot [2], E. Clappier [3], C. Mullighan [5], A. R. Grosso [7], J. A. Yunes [4], J. T. Barata [8,*]

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Background: Interleukin-7 (IL-7) and IL-7 receptor α (encoded by *IL7R*) are essential for normal lymphoid development. *IL7R* gain-of-function mutations were identified in acute lymphoblastic leukemia (ALL) and *IL7R* is a bona fide lymphoid oncogene.
Aims: To determine whether *IL7R* gain-of-function mutations alone can initiate leukemia.
Methods: We generated conditional *Il7r*^{flCPT} knock-in animals that were characterized for disruption of lymphoid development. We analyzed immunophenotype by FACS, transcriptome by RNAseq, and proteome by LC-MS. Tumor mutational profiling was performed by WES. Further methodologies included Sanger sequencing, qRT-PCR, immunoblotting, immunohistochemistry, drug treatment, self-renewal transplant experiments, viral transduction of BM precursors, and cell sorting.
Results: We show that physiological levels of expression of mutant *IL7R* in lymphoid precursors lead to a pre-leukemia stage in which B-cell precursors display self-renewal ability. This is followed by the development of highly penetrant precursor B-ALL that resembles PAX5 P80R or Ph-like human leukemia. Leukemia establishment associates with transcriptional upregulation of oncogenes such as *Myc* or *Bcl2*, downregulation of tumor suppressors such as *Ikzf1* or *Arid2*, and mutations in *Pax5* (precisely P80R) or in signaling genes, such as *Kras, Flt3l, Limk1 or Cdc42bpb*. Transduction of hematopoietic precursors with a *Kras* mutant and subsequent transplantation to lethally irradiated recipient mice shows that Kras upregulates IL7R expression and cooperates in providing a selective advantage to IL-7R mutant-expressing B-cell precursors. In agreement, leukemia establishment associates with striking IL-7R signaling upregulation. This is reflected in the activation of key downstream targets, such as STAT5, MYC and mTOR. Importantly, leukemia cell viability relies on the maintenance of high IL-7R-mediated signaling, as shown by inhibition of JAK1, STAT5 or PI3K/mTOR signaling. To further demonstrate the importance of high IL-7R signaling levels in promoting leukemogenesis, we generated homozygous *IL7R* mutant animals, which display maximal signaling. We find that they display fully-penetrant early leukemia onset. Interestingly, we identify 2 transcriptional subgroups in mouse Ph-like tumors and provide evidence of their existence in human Ph-like ALL. One of the mouse Ph-like ALL subgroups is transcriptionally-enriched in antifolate resistance and JAK-STAT signaling pathways and presents mutations in regulators of chromatin remodeling and transcription, whereas the other shows enrichment for Wnt and Hippo signaling pathways and displays *Cdkn2a* deletions, *Kras* mutations and *Gins2* gains. Finally, we sought to identify therapeutic vulnerabilities in IL-7R-driven B-ALL. Because *IL7R* mutant leukemias exhibit clear upregulation of mTOR signaling, we administered the clinical-grade dual PI3K and mTOR inhibitor dactolisib and show it has a striking impact on the frequency of leukemia cells in the blood, significantly prolonging mouse survival. To identify novel targeted agents against mutant *IL7R* dependence, we performed a chemical screen on Ba/F3 cells ectopically expressing mutant IL-7Rα. We demonstrate that 2 distinct new generation sphingosine kinase inhibitors are effective against mutant *IL7R* mouse B-ALLs both in vitro and in vivo. Importantly, we validated our findings in *IL7R* mutant primary human B-ALLs.
Summary/Conclusion: Our studies provide a novel, powerful in vivo resource to explore the pathophysiology and therapeutic vulnerabilities of B-ALL, and demonstrate for the first time that *IL7R* can initiate this malignancy.

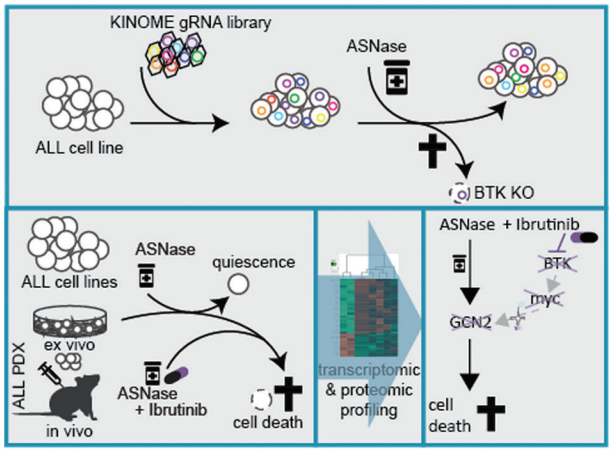
S107 BRUTON'S TYROSINE KINASE INHIBITION SENSITIZES ACUTE LYMPHOBLASTIC LEUKEMIA TO ASPARAGINASE BY INTERFERING WITH THE AMINO ACID RESPONSE - A ROLE FOR C-MYC

M. Butler [1,*], D. van Ingen Schenau [1], J. Yu [1], S. Jenni [2], M. P. Dobay [2], R. Hagelaar [1], B. M. T. Vervoort [1], T. M. Tee [1],

F. W. Hoff [3], J. P. Meijerink [1], S. Kornblau [4], B. Bornhauser [2], J. -P. Bourquin [2], R. P. Kuiper [1], L. T. van der Meer [1], F. N. van Leeuwen [1]

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Background: Amino acid depletion agents, such as Asparaginase (ASNase), are attractive anti-cancer therapies as they do not produce long term toxicities associated with DNA damage. ASNase therapy has been a mainstay of Acute Lymphoblastic Leukemia (ALL) protocols for decades and acts by depleting asparagine from the blood, leading to an intracellular shortage of this amino acid. In contrast to most other cells, lymphocytes and leukemic blasts are dependent on the exogenous supply of asparagine, and as a result, exposure to this drug leads to a cessation of growth and cell death. However, suboptimal depletion of asparagine, as is the case in sanctuary sites such as the bone marrow and the CNS, will allow the leukemic cells to enter a reversible state of cellular quiescence rather than to undergo apoptosis, enhancing the chance of relapse.
Aims: To further optimize ASNase therapies in leukemia, and to broaden its use to other tumor types, a detailed understanding of the cell intrinsic and extrinsic factors that affect the opposing cellular responses to ASNase is needed. We hypothesized that by sensitizing the response to asparaginase, improved survival could be combined with reduced treatment related toxicities.
Methods: We employed a CRISPR/Cas9-based screen to identify actionable signaling intermediates that improve the response to ASNase. The results were validated using targeted knockouts and by using small-molecule inhibitors. We used both ALL cell lines and ALL- patient derived xenografts (ex vivo and in vivo) for these functional validations. Moreover, transcriptomic and proteomics profiling was performed to gain mechanistically insights.
Results: As expected, we identified genes known to be involved in the cellular response to amino acid starvation (GCN2 and TRIB3) to modulate the sensitivity to asparaginase treatment. Since pharmacological targeting of these kinases is expected to lead to treatment related toxicities, we focused on kinases that show a more hematopoietic restricted expression pattern.
Genetic inactivation of Bruton Tyrosine Kinase (BTK) and pharmacological inhibition using different FDA approved BTK inhibitors (Ibrutinib, Evobrutinib, ARQ531) strongly potentiated asparaginase induced apoptosis in a variety of ALL cell lines models. Moreover, we tested the effect of combination treatment in 38 different patient-derived xenografts (PDX) samples, mostly representing high risk leukemia cases and covering a wide variety of ALL subtypes. We observed ex-vivo synergism between ASNase and Ibrutinib in approximately 90% of the PDX models tested. In addition, leukemia formation in mouse PDX models was significantly delayed by the combination treatment.
Using transcriptomic and proteomic profiling, we could demonstrate that BTK inhibition effectively interferes with the ASNase induced amino acid stress response in these cells, a mechanism involving suppression of c-Myc function. As a result of the reduced c-Myc induced proteotoxic stress, GCN2 kinase, a critical regulator of the amino acid response (AAR) pathway, is suppressed. This prevents leukemic cells to adapt to amino acid deprivation, leading to the induction of cell death.



Summary/Conclusion: In conclusion, Ibrutinib or related BTK inhibitors may be used to enhance the clinical efficacy of asparaginase in ALL. Such a combination treatment may not only improve response to therapy but also reduce the need for genotoxic agents associated with long term toxicities.

S108 EHMT2/G9A DRIVES THE EPIGENETIC REGULATION OF GLUCOSE METABOLISM IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

A. Montanaro [1,*], E. Cerretani [1], S. Kitara [2], M. Marchesini [1], C. Rompietti [3], L. Pagliaro [1], A. Gherli [1], B. Lorusso [1], M. L. Minchillo [1], R. La Starza [3], C. Mecucci [3], Y. Xiong [4], J. Jin [4], F. Quaini [1], B. Knoechel [2], P. Sportoletti [3], K. Stegmaier [2], G. Roti [1]

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Background: The identification of genes involved in DNA methylation and post-translational histone modifications in hematologic malignancies offers an opportunity for novel therapeutic intervention, geared towards reversing or modulating epigenetic events underpinning these diseases. In fact, in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) methylation patterns are altered by mutations in *TET2*, *IDH1*, *IDH2*, *DNMT3A*, and *WT1* genes and matched therapies have demonstrated promising clinical activity. In T-cell acute lymphoblastic leukemia (T-ALL) the epigenetic driven approaches are not yet well validated, especially in the relapsed/refractory (R/R) setting.
Aims: In this project, we sought to identify druggable epigenetic dependencies in T-ALL to anticipate potential synergistic interventions in R/R T-ALL.
Methods: We leveraged the results of a chemical and an epigenome-centered shRNA screen to identify chromatin modifier dependencies in T-ALL. We prioritized the conserved protein lysine H3K9me2-1 methyltransferase, G9a/*EHMT2*based on the effect of targeted inhibition on cell viability and the preferential expression in leukemia vs. normal bone marrow. We described the phenotypic consequences of G9a loss due to small molecule inhibition or genetic suppression. The preponderance of results pointed to a role of G9a in the control of effectors of glycogen metabolism. We confirmed this as follows:1) functionally by glycolytic fluxes and mitochondrial dysfunction analysis, 2) transcriptionally by overlapping a geneset in which we suppressed G9a using small molecules or CRISPR/Cas9, with curated transcription factor GEO signatures to identify common denominators of G9a signaling. Finally, we validated our hypothesis in 3D scaffolds and orthotopic xenograft T-ALL models.
Results: We identified *EHMT2* as a transcriptional dependency in T-ALL by the intersection of a shRNA and chemical screens both focused on epigenetic modifiers. Competitive and non-competitive G9a inhibitors, BIX01294, UNC0638 and UNC0642, or genetic G9a suppression decreases T-ALL proliferation drifting the cells into a late apoptotic stage. At the same conditions, the level of H3K9me2 selectively decreases compared to other epigenetic markers, suggesting the on-target effect of the observed phenotype. G9a deprived T-ALL cells present with an increased number of autophagic vacuoles containing glycogen. Interestingly glycogen accumulation is sustained by the inactivation of Glycogen Synthase Kinase 3 (GSK-3) in multiple G9a null T-ALL cell lines. We next asked whether G9a alters glucose metabolism and demonstrated a reduction of oxygen consumption upon G9a inhibitors treatment suggesting that G9a alters the balance between glycolysis and glycogenesis. Consistently the lack of glucose, secondary to 2-deoxy-d-glucose (2-DG) treatment rescues the formation of autophagosomes upon G9a treatment. Transcriptional enrichment analysis of *EHMT2* loss showed that the metabolic sensor *SESN2* is repressed upon G9a modulation, and in turn, loss of *SESN2* recapitulates the effect seen with G9a inhibition. Finally, we demonstrated that UNC0642 impairs leukemia growth both in 3D scaffold T-ALL from clinical samples and in a T-ALL xenograft orthotopic model where the loss of H3K9me2 parallels the antileukemia effect seen with this drug.
Summary/Conclusion: In conclusion, we identified G9a as an epigenetic vulnerability in T-ALL. Corollary to this, we described a role of G9a in

the control of a metabolic circuitry with SESN2 and GSK-3 as downstream effectors of an autophagic cell death.

S109 INDUCIBLE RNA INTERFERENCE IN PATIENTS´ ACUTE LEUKEMIA PDX MODELS IN VIVO TO IDENTIFY AND VALIDATE THERAPEUTIC TARGETS

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Background: Only a small proportion of oncology drugs pass early clinical evaluation and receive approval. To improve prediction, preclinical model systems are required, which faithfully mimic the complex *in vivo* situation of cancer patients, such as patient-derived xenograft (PDX) models. To molecularly mimic anti-leukemia treatment in PDX models, inducible systems are required to evaluate targets independently from confounding biological processes that never occur in patients, such as cell transplantation and homing.
Aims: We aimed at developing inducible RNA interference (RNAi) in PDX models of acute leukemias (AL) *in vivo* to identify and validate vulnerabilities as therapeutic targets.
Methods: We established for the first time a Cre-ER^{T2} based inducible RNAi-mediated gene silencing system in PDX. A total of 7 PDX samples, established from patients with heterogenous AL, were genetically modified to express recombinant Cre-ER^{T2} using lentiviruses. The shRNA cassette was flanked by two different pairs of loxP sites and was expressed in the opposite direction so that shRNA expression was initiated by treatment of mice with Tamoxifen, inducing Cre-mediated inversion and deletion (Stern et al. PNAS 2008). In fluorochrome-guided, competitive *in vivo* trials, with control and gene-of-interest cells in the same animal, the methods was tested for its sensitivity and specificity to validate therapeutic targets.
Results: PDX cells were transplanted and grown in mice until tumors were established and knockdown was induced by feeding mice with Tamoxifen. Using the novel technique, we could prove that the tumor-maintaining potency of the MLL-AF4 fusion protein is restricted to PDX samples carrying the rearrangement, demonstrating specificity of the technique. Induction of knockdown of MCL1 in established PDX tumors induced different intensities of growth disadvantages between individual samples, ranging from weak to strong phenotypes. We demonstrate that MCL1 silencing in acute lymphoblastic (ALL) and myeloid (AML) leukemia PDX models can predict response to pharmacological MCL1 inhibitors *in vivo*, proofing the high sensitivity of the inducible RNAi system. Finally, we demonstrate that inducible knockdown of DUX4 in PDX samples carrying the recently described DUX4-IGH translocation diminishes tumor growth *in vivo*. Transcriptome analysis revealed a reversal of the gene expression signature associated with the DUX4 subtype in PDX models *in vivo* and was used to identify novel therapeutic targets in PDX carrying the DUX4-IGH translocation.
Summary/Conclusion: We developed a highly sensitive and specific inducible knockdown technique in PDX models which enables individualized functional genomics in established tumors *in vivo*. Our molecular approach closely mimics the clinical situation and complements an important step in the evaluation chain of drug development and precision oncology.

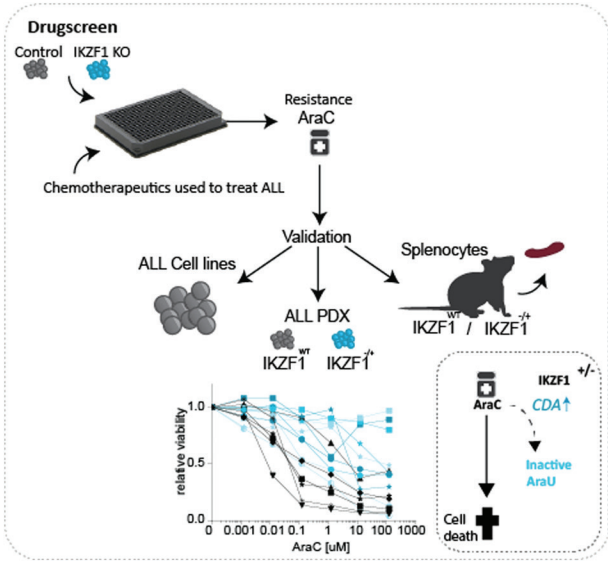
ALL - Novel subgroups and agents

S110 LOSS OF IKZF1 CONTRIBUTES TO CYTARABINE RESISTANCE IN B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

B. Vervoort [1,*], M. Butler [1], D. van Ingen Schenau [1], R. Marke [2], B. Bornhauser [3], J.-P. Bourquin [3], L. van der Meer [1], F. van Leeuwen [1]

[1]Research, Prinses Maxima Centrum, Utrecht, [2]Research, Radboud UMC, Nijmegen, Netherlands, [3]Research, University Children's Hospital Zurich, Zurich, Switzerland

Background: Deletions and mutations affecting lymphoid transcription factor *IKZF1* occur in about 10-15% of patients with B cell precursor acute lymphoblastic leukemia (BCP-ALL) and predict a poor outcome. We have shown previously that loss of IKZF1 function compromises the therapeutic efficacy of glucocorticoids (GCs). Here, we investigated whether loss of IKZF1 function also affects therapy response to other chemotherapeutic agents used in the treatment of ALL.
Aims: To further optimize antimetabolite therapies for IKZF1 deleted leukemia to prevent relapse and therapy resistance.
Methods: We performed a drug screen including all chemotherapeutic agents used in the treatment of ALL. The results were validated using targeted knockouts, shRNA mediated knockdowns as well as a chemical induced breakdown of IKAROS. These assays were performed on ALL cell lines as well as murine splenocytes and ALL- patient derived xenografts.
Results: We observed that CRISPR/CAS9-mediated loss of *IKZF1* in SEM pre-B ALL cells markedly reduced the cellular response to the pyrimidine analogue cytarabine (AraC) relative to *IKZF1* wild type cells. The same drug resistance profile was observed upon shRNA-mediated knockdown of IKZF1 as well as in B-cells isolated from 8 to 14 weeks-old *Ikzf1*$^{+/-}$ mice. We confirmed these findings by *ex vivo* profiling of patient-derived xenografts (PDX), where we observed that *IKZF1*-deleted cases (n=10) were significantly (area under the curve (AUC) 78.690) more resistant to AraC than those wild type for *IKZF1* (n=6) (AUC 26.447). Loss of IKZF1 can also chemically be mimicked by the cereblon-E3 ligase Iberdomide, which specifically targets and breaks down members of the Ikaros protein family. Indeed, we observed that PDX wildtype for IKZF1, developed resistance to AraC in response to this drug. The metabolic enzyme cytidine deaminase (CDA) is an important determinant of AraC therapy response, both in ALL and acute myeloid leukemia (AML). Consistent with these findings, we observed that IKZF1 loss increases the expression of CDA in BCP-ALL cell lines as well as mouse primary B cells and PDX models. In addition, treatment of *IKZF1*$^{+/-}$ cells using pharmacological inhibitors of CDA, restored pyrimidine analogue sensitivity to control levels.



Summary/Conclusion: Together, these results demonstrate that loss of *IKZF1* confers resistance to AraC, both in experimental models and in patient-derived cells. We are currently performing CRISPR/CAS9 based reverse genetics screens to identify genes/pathways that enhance response to AraC or other antimetabolites. We expect that this approach will allow us to identify (hematopoietic cell-specific) pathways that can be targeted to sensitize responses to AraC in *IKZF1* deleted ALL and possibly AML. Preclinical validations of these findings, using representative PDX models, will guide the development of more effective antimetabolite therapies for this high-risk patient group.

S111 REDEFINING LOW RISK HIGH HYPERDIPLOIDY IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

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Background: High hyperdiploidy (HeH) with a modal number of 51 to 67 chromosomes occurs in ~30% of B-cell precursor acute lymphoblastic leukaemia (ALL). Although strongly associated with good outcome, relapses do occur and its prevalence means that HeH accounts for up to 25% of all relapses. No consensus exists regarding risk factors in this subgroup.
Aims: The objective of this study was to comprehensively evaluate all relevant risk factors to define a very low risk subgroup within HeH which could be used prospectively to define patients eligible for treatment de-escalation.
Methods: Analysis was performed using the UKALL97/99 (n=456, discovery) and UKALL2003 (n=725, validation) cohorts with median follow-up times of 10.6 and 9.4 years, respectively. Event-free survival (EFS), relapse rate (RR) and overall survival (OS) rates were calculated at 10 years and compared using univariate and multivariate analyses Cox regression models. To determine the optimal number of chromosomes needed to predict outcome, we used area under ROC curve, general linear model and targeted projection pursuit. We measured C-index, Mallows' Cp for each combination for selecting the fittest model. Multivariate analysis, general linear model, network analysis and coefficient of the risk model determined the optimal combination of chromosomes for predicting outcome and Bayesian information criterion with forward stepwise criteria for model selection.
Results: HeH karyotypes gain between 5 and 19 chromosomes so analysing all possible combinations and permutations of trisomies was impossible. Hence, we calculated the optimum number of chromosomes required to maximise prediction. Using the discovery cohort, we generated all possible combinations of one to six trisomies and found that four chromosomes produced the maximum prediction power. Multivariate Cox modelling defined chromosomes 5, 17, 18 and 20 as the optimal prognostic set. Using these four chromosomes, we developed and validated good risk (GR) and poor risk HeH profiles. The GR profile comprised patients with (a) +17 and +18 together or (b) either +17 or +18 but not +5 or +20. The poor risk (PR) comprised all other HeH cases. The size of the risk groups were similar in the validation and discovery cohorts: GR 80-82%, PR 18-20%. There was no correlation between HeH risk group and age, sex, white cell count or end of induction MRD. Patients with a HeH-PR profile had an increased RR in both cohorts: hazard ratio 2.50 (95% CI 1.51-4.14) & 3.80 (2.14-6.75), both p<0.001; which was independent of MRD. Threshold analysis revealed 0.03% to be the optimal MRD threshold and the RR for HeH-GR cases by MRD</≥0.03% was 4%/8% compared with 11%/27% for HeH-PR cases. The excellent outcome of HeH-GR patients was observed among the patients who received the least intensive therapy. Whereas the outcome of HeH-PR patients akin to that associated with intermediate risk cytogenetics (Table). Although smaller than a standard HeH subgroup, the HeH-GR group had a better outcome. In addition, it outperformed TT in terms of group size and prediction accuracy (Table).

	All HeH cases	HeH-PR	HeH-GR	Triple trisomy (+4,+10,+17)
	n (%)	n (%)	n (%)	n (%)
Number of cases	725	146	579	299
Proportion of HeH cases	100%	20%	80%	41%
NCI risk group				
Standard	550 (76)	107 (73)	443 (77)	229 (77)
High	175 (24)	39 (27)	136 (23)	70 (23)
End of induction MRD				
<0.03%	462 (73)	85 (70)	377 (74)	187 (73)
≥0.03%	170 (27)	37 (30)	133 (26)	68 (27)
Relapse				
No	670 (93)	122 (85)	548 (96)	284 (97)
Yes	47 (7)	22 (15)	25 (4)	10 (3)
Outcome at 10 years (95% CI)				
Relapse risk	7% (5-9)	16% (10-23)	5% (3-7)	4% (2-7)
Event Free survival	90% (87-92)	81% (73-86)	92% (90-94)	92% (88-94)
Overall survival	94% (92-95)	86% (79-91)	96% (94-97)	96% (93-97)
Prediction Accuracy				
C-index	-	0.64		0.60
Area under the curve	-	0.64		0.61

Summary/Conclusion: The UKALL-HeH profile defines two distinct HeH risk groups. Patients with a UKALL-HeH GR profile have an excellent outcome and represent low risk subgroup of HeH which could be considered for treatment de-escalation.

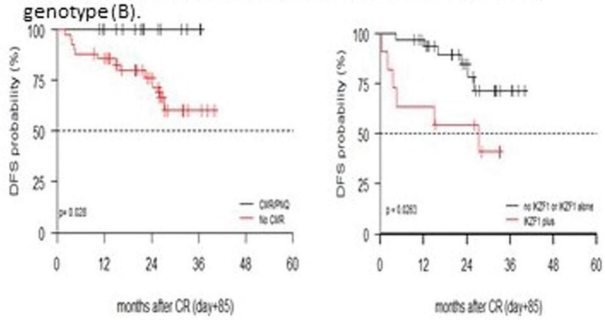
S112 UPDATED RESULTS OF THE GIMEMA LAL2116, D-ALBA TRIAL, FOR NEWLY DIAGNOSED ADULTS WITH PH+ ALL

S. Chiaretti [1,*], R. Bassan [2], A. Vitale [1], L. Elia [1], M. Messina [3], P. Viero [4], M. Annunziata [5], M. Lunghi [6], F. Fabbiano [7], M. Bonifacio [8], N. Fracchiolla [9], P. Di Bartolomeo [10], L. Gorreo Renzulli [3], M. S. De Propris [1], M. Vignetti [3], A. Guarini [11], A. Rambaldi [12], R. Foà [1]

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Background: Outcome of Ph+ ALL has dramatically changed since the advent of tyrosine kinase inhibitors (TKIs). To further improve the outcome of this subset of patients, we designed an induction/consolidationchemo-free trial (GIMEMA LAL2116, D-ALBA) based on the administration of dasatinib plussteroids followed by at least two cycles of blinatumomab (maximum 5) and central nervous system (CNS) prophylaxis. Post-consolidation treatment was left at the investigator's choice. The first results at a median follow-up of 18 months have been recently published (Foà et al, NEJM2020): after the 2nd cycle of blinatumomab, a molecular response was achieved in 60% of the cases, which increased further after additional cycles of blinatumomab, translating into an overall survival (OS) and disease-free survival (DFS) of 95% and 88%, respectively.
Aims: To provide an updated follow-up of the study
Methods: After the primary endpoint, patients were followed for 12 months; data on subsequent treatment and survival are being collected in the ancillary study GIMEMA LAL2217.
Results: As reported, 63 patients were enrolled (median age 54 years, 24-82; no age limit); the median follow-up is 27.2 months (0.9-45.2). In line with previous data, molecular responses were recorded in the majority of patients also at the subsequent follow-ups (range 73%>89%). Overall, 3 additional relapses were observed (total: 9): 4 hematologic, 4 at the CNS and 1 nodal; the median time to relapse was 4.4 months (1.9-25.8). Three additional deaths in complete hematologic remission (CHR) were recorded (total: 6). Of the 58 patients who started blinatumomab, 29 were allografted: 9 from a sibling, 13 from an unrelated donor, 6 from a haploidentical donor and 1 from a cord blood (6 transplants were carried out in 2nd CHR). Before transplant, 8 patients received 2 and 3 cycles of blinatumomab, respectively, 5 4 cycles and 6 5 cycles (2 patient were allografted after the 1 cycle). Five deaths occurred, 2 in patients transplanted in 2nd CHR.
29 continued treatment with a TKI: 21 with dasatinib (85% after receiving all the 5 cycles of blinatumomab), 3 switched to imatinib due to intolerance (all after 5 cycles of blinatumomab) and 5 switched to ponatinib for a molecular increase or medical decision (66% received all 5 cycles of blinatumomab).
In the updated follow-up, 24 months OS is 87.8% and DFS is 79.8%. DFS was better in patients achieving a molecular response upon induction/consolidation than in those who did not (100% vs 75.9%, p=0.028, Fig 1A). Furthermore, we confirmed the inferior DFS for patients carrying an *IKZF1*-plus genotype compared to that of cases with no *IKZF1* deletions or with *IKZF1* deletions alone (84.5% vs 54.5%, p=0.026, Fig 1B).

Fig 1. DFS according to molecular response (A) and *IKZF1* plus genotype (B).



Summary/Conclusion: In the updated analysis of the D-ALBA trial, we confirm the very favorable outcome previously reported, as well as the deleterious prognostic impact of the *IKZF1*-plus genotype and the low transplant-related mortality rate. Among the few relapses, we observed a rather high incidence of CNS involvement. In the upcoming trial for newly diagnosed adult Ph+ ALL, CNS prophylaxis will be increased.

S113 INTERIM RESULTS OF A PHASE II STUDY OF BLINATUMOMAB PLUS PONATINIB FOR PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Ponatinib and blinatumomab both produce high rates of molecular remission in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The combination of these two agents may lead to deep and durable responses, thereby reducing the need for allogeneic hematopoietic stem cell transplant (HSCT).
Aims: We evaluated the efficacy and safety of a chemotherapy-free combination of blinatumomab and ponatinib in patients with newly diagnosed (ND) or relapsed/refractory (R/R) Ph+ ALL. For patients with ND Ph+ ALL, the primary endpoint was the complete molecular response (CMR) rate, defined as absence of a quantifiable PCR transcript for *BCR-ABL1*. For patients with R/R Ph+ ALL, the primary endpoint was the overall response rate (defined as the composite of CR/CRi). Secondary endpoints included safety measures, event-free survival (EFS) and overall survival (OS).
Methods: This is a single-arm phase 2 study in adults with ND or R/R Ph+ ALL. Patients were required to have a performance status of ≤2, total bilirubin ≤2x the upper limit of normal (ULN), and alanine aminotransferase and aspartate aminotransferase ≤3x the ULN. Patients with uncontrolled cardiovascular disease or clinically significant central nervous system comorbidities were excluded. Patients received up to 5 cycles of blinatumomab as a continuous infusion at standard doses. Ponatinib 30mg daily was given during cycle 1. Ponatinib was decreased to 15mg daily once CMR was achieved. After completion of blinatumomab, ponatinib was continued for at least 5 years in responding patients. Twelve doses of prophylactic intrathecal chemotherapy were administered.
Results: Between February 2018 and February 2021, 28 patients were treated (19 ND and 9 R/R). The median age for the entire cohort was 59 years (range, 25-83 years); 62 years (range, 34-83 years) and 36 years (range, 25-61 years) in the ND and R/R cohorts, respectively. *BCR-ABL1* transcripts were p190 in 69% of patients in the ND cohort and 100% in the R/R cohort. 44% of patients in the R/R cohort were in salvage 2 or beyond. Overall, 95% of patients responded; the CR/CRi rate was 100% in the ND cohort and 88% in the R/R cohort. No early death within 4 weeks were observed. 86% of responding patients achieved CMR (87% in the ND cohort and 86% in the R/R cohort). The median time to CMR was 1 month (range, 1-13 months). None of the patients in the ND cohort underwent HSCT; 4 patients (44%) in the R/R cohort underwent subsequent HSCT. With a median follow-up of 14 months, the estimated 1-year OS rate was 94% and the EFS rate was 81% for the entire study cohort. In the ND cohort, no patients have relapsed or died, and the 1-year OS and EFS rates were both 100%. In the R/R cohort, 1-year OS and EFS rates were 88% and 55%, respectively. The treatment was well-tolerated, and most side effects were grade 1-2. No patient has discontinued ponatinib due to toxicity. One patient discontinued blinatumomab due to recurrent grade 2 tremor.
Summary/Conclusion: The chemotherapy-free combination of ponatinib and blinatumomab shows encouraging safety and efficacy in Ph+ ALL, with high rates of CMR and durable remissions, particularly when used in the frontline setting. All ND patients remain in remission without HSCT, suggesting that this regimen may obviate the need for HSCT in this setting.

S114 PRELIMINARY RESULTS OF THE GIMEMA LAL2317 SEQUENTIAL CHEMOTHERAPY-BLINATUMOMAB FRONT-LINE TRIAL FOR NEWLY DIAGNOSED ADULT PH-NEGATIVE B-LINEAGE ALL PATIENTS

R. Bassan [1,*], S. Chiaretti [2], I. Della Starza [2], O. Spinelli [3], A. Santoro [4], L. Elia [2], A. Vitale [2], A. Taherinasab [2], M. Piccini [5], F. Ferrara [6], S. Sica [7], P. Zappasodi [8], E. Borlenghi [9], M. Bocchia [10], C. Califano [11], F. Di Raimondo [12], F. Pane [13], A. Candoni [14], M. Ruggeri [15], E. Audisio [16], M. Lunghi [17], A. M. Mianulli [18], M. Messina [19], M. R. Marino [19], V. Arena [19], A. Rambaldi [3], R. Foà [2]

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Background: The outcome of adult patients with Ph-negative acute lymphoblastic leukemia (ALL) has improved with survival rates nowadays in the range of 50% and greater, particularly for minimal residual disease (MRD) responsive subjects. To optimize the rate of MRD response and improve survival, in the GIMEMA LAL2317 trial two doses of the bispecific monoclonal antibody blinatumomab were added to chemotherapy. The study was designed for adult patients with B-lineage Ph-ALL aged 18-65.
Aims: To evaluate the efficacy of blinatumomab in increasing the early MRD negativity rate. MRD was measured by RQ-PCR with a cut-off for negativity set at <10-4.
Methods: The trial was based on the same chemotherapy backbone of GIMEMA LAL1913 (EHA 2018, #919) with two blinatumomab cycles given sequentially after early consolidation cycle 3 (high-dose methotrexate and Ara-C) and late consolidation cycle 6, respectively. While conversion to MRD negativity following blinatumomab 1 was the primary objective, the drug was intentionally given to all study patients regardless of MRD being assessable or not. Patients were stratified for risk-oriented therapy: very high risk (VHR, for early switch to allo-SCT) with a WBC count >100 x 10^9/l and/or highly adverse cytogenetics/genetics (the Ph-like signature was routinely investigated but did not enter into the risk model); high risk (HR) with >30 x 10^9/l WBC, a pro-B phenotype, or a late complete remission (CR); and standard risk (SR) with no risk factors. HR and SR patients were allocated to allo-SCT only when found to be MRD-85 positive at weeks 10-22. The sample size was calculated at 149 patients, with at least MRD-evaluable patients necessary to collect evidence for an improved blinatumomab-related response.
Results: Patients' recruitment closed in June 2020. 149 patients were enrolled and 146 are evaluable; 78 were male (54%), the median age was 41 years (range 18-65, 18% >55 years). Thirty-nine patients (48%) were VHR/HR, with 8.5% *KMT2A*+ and 28% expressing the Ph-like signature. A hematological CR was achieved in 131 patients (90.4%), 7 were resistant, 7 died early and 1 was not evaluable. Regarding the primary study endpoint, i.e. the MRD clearance after blinatumomab course 1, 85 patients with paired MRD samples were evaluable. After early consolidation, 73% of these patients were MRD-negative (<10^{-4}). This increased to 96% after the first blinatumomab administration (P=0.018), with a conversion rate from MRD positivity to MRD negativity of 87% (20/23 patients). Blinatumomab was also capable of eradicating MRD in Ph-like patients: 10/25 evaluable patients were MRD-positive after early consolidation and all became MRD-negative. With a median follow-up of 10 months (range 0.5-27.4), the 12-month overall and disease-free survival (OS, DFS) rates are 83.8% and 71.6%, respectively. Favorable prognostic factors were age <56 years (OS 65.4% in >55 years, 88% 41-55 years, 91% in 18-40 years, P<0.001 vs age >55) and week 10 MRD negativity (OS 94%, P=0.0073; DFS 88%, P=0.0036). Fifteen relapses occurred, translating into a 12-month relapse incidence of 11%, with no difference in blinatumomab-treated patients, whether MRD-positive, negative or unknown.
Summary/Conclusion: This preliminary analysis highlights the efficacy of blinatumomab added to chemotherapy in increasing MRD negativity (<10-4) in CD19+ B-lineage Ph-ALL, with the primary study endpoint fully achieved. This effect appears to translate into a lower early relapse rate and appears detectable in all risk subsets.

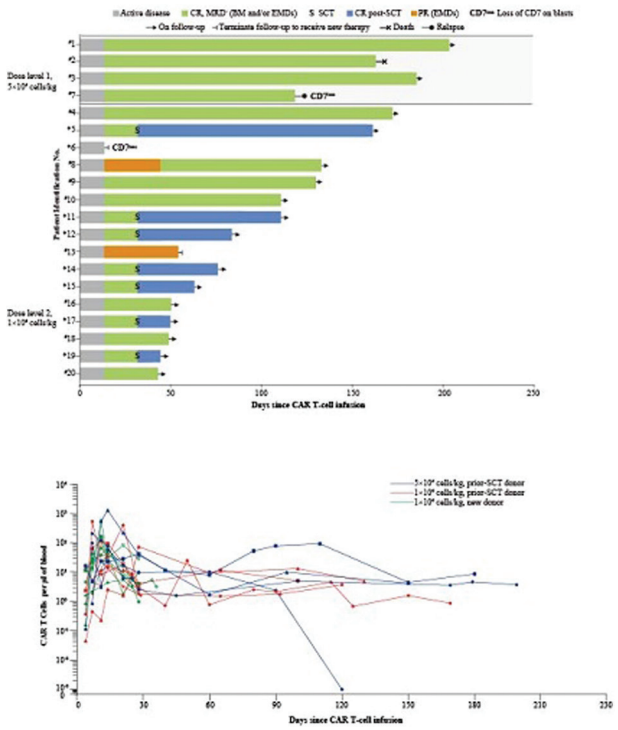
ALL - CAR-T: Alternative targets and age groups

S115 DONOR-DERIVED CD7 CAR T CELLS FOR T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

J. Pan [1,2,*], Y. Tan [3], B. Deng [4], Z. Ling [1], W. Song [1], J. Xu [2], J. Duan [2], Z. Wang [2], A. H. Chang [5], X. Feng [3]

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Background: Despite the success of chimeric antigen receptor T cell therapy in B cell malignances, there is currently no proved CAR T treatment for T cell neoplasms. We provide first evidence support the use of donor derived CAR T cells in T cell leukemia.
Aims: To assess the safety, tolerability, pharmacokinetic profile, and anti-tumor activity of donor-derived CD7 CAR T cells in patients with r/r T-ALL.
Methods: In this phase 1 trial, CD7 CAR T cells were manufactured with T cells from prior SCT prior to a single infusion at doses of 5 × 105 or 1 × 106 (± 30%) cells per kilogram of body weight. donors, or from new donors who were HLA-matched or haploidentical, via leukopheresis and transduced with a lentiviral vector which carries a CD7 CAR construct. The primary endpoint was safety. Short-term efficacy was also assessed.
Results: Results of 20 enrolled patients who received infusion are reported. Of 20 patients, 12 received previous HSCT-donor derived CAR T cells and 8 received fresh haplo-identical donor derived CAR T cells and plan to received transplantation as consolidation after remission.Adverse events included grade 3-4 hematologic toxicity in all (100%), grade 3-4 and grade 1-2 cytokine release syndrome in 2 (10%) and in 18 (90%), grade 1 neurotoxicity in 3 (15%), grade 1-2 graft-versus-host disease in 12 (60%), and grade 1 viral activation in 3 (15%) patients. Nineteen (95%) patients had a response, including 18 (90%) with complete remission and 1 (5%) with partial remission. Of 19 responders, 7 were bridged to SCT and remained minimal residual disease (MRD)-negative until last visit; 12 were followed up at a medium of 4.4 months, among whom 9 remained MRD-negative, 1 had a relapse, 1 discontinued for other treatment, and 1 died of pulmonary fungal infection at 5.5 months. CAR cells mostly persisted beyond 3 months. Patient CD7-positive healthy T cells were depleted, while CD7-negative T cells increased.



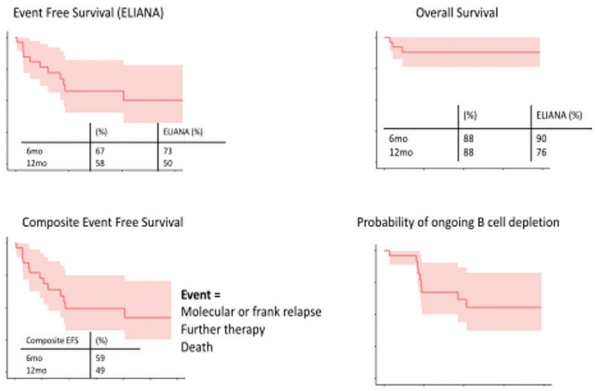
Summary/Conclusion: We report the initial toxicity profile and anti-leukemia activity of a donor-derived CD7-targeted cellular immunotherapy for patients with relapsed or refractory T-ALL. (Funded by the National Key R&D program; ChiCTR.org number, ChiCTR2000034762.)

S116 OUTCOMES OF CHILDREN AGED UNDER 3 YEARS TREATED WITH TISAGENLECLEUCEL FOR B-ALL

S. Ghorashian [1,*], E. Jacoby [2], B. De Moerloose [3], S. Rives [4], D. Bonney [5], G. Shenton [6], N. Bodmer [7], M. Algeri [8], F. Locatelli [9], P. Bader [10], K. Vettenranta [11], B. Herrero Velasco [12], A. Molinos-Quintana [13], B. Gonzalez [14], A. Attarbaschi [15], J. -P. Bourquin [16], A. Baruchel [17]

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Background: The pivotal ELIANA study defined outcomes for tisagenlecleucel in children and young adults with B-ALL aged 3 to 25 years. However, outcomes in children younger than 3 years, including those with infant ALL have not been fully documented.
Aims: To define outcomes of tisagenlecleucel therapy in children less than three years of age for B-ALL
Methods: Retrospective, standardised data collection was undertaken for all patients assessed for tisagenlecleucel for B-ALL aged under 3 years at the point of screening from centres represented in the I-BFM Resistant Disease Committee. Survival outcomes were assessed using Kaplan-Meier estimates. These included overall survival (OS, interval to death from any cause); event- free survival (EFS) as defined in the ELIANA study (interval to death, morphological disease relapse, or treatment failure by day 30, with censoring of patients receiving further therapy) as well as a stricter composite EFS (events included treatment failure, interval to death, molecular or morphological relapse or further therapy). Median follow up was calculated by a reverse Kaplan-Meier method
Results: 30 patients from 15 centres were screened and eligible. 3 patients were not infused due to: manufacturing failure (n=2), disease progression (n=1), giving a 90% feasibility rate. One patient had not reached the 1 month disease assessment, leaving 26 evaluable for disease outcomes and 27 for toxicity. 24 of 30 patients (80%) had MLL rearranged ALL, most had high risk features: 21 (70%) had had a prior stem cell transplant (SCT).
Two patients failed to respond, giving a CR/CRi rate of 24/26 (92%), all were MRD negative. The median follow-up was 15.5 months. EFS and overall survival OS are shown in Figure 1. OS at 6 and 12 months was 88%. EFS as per ELIANA criteria was 67% and 58% at 6 and 12 months respectively. Using the more stringent composite EFS, the 6 and 12 month EFS were 59%, and 49%. Of 27 patients infused, 10 (37%) received further therapy including 3 given maintenance therapy for poor CAR T cell persistence, 2 receiving chemotherapy for relapse and 5 (19%) who received allogeneic SCT: for relapse (n=2), B cell recovery (n=2), or as a planned procedure (n=1). For patients relapsing following CR (n=6/27 (22%) infused) there were 2/6 (33%) CD19- relapses.
Severe (grade ≥3) CRS, neurotoxicity, or cytopenia after day 30 post infusion occurred in 2/22 (10%), 1/22 (5%), and 8/22 (36%) respectively. 17/22 (77)% of the cohort developed hypogammaglobulinaemia. The 6 and 12 month probabilities of ongoing B cell depletion were 82% and 68%.



Summary/Conclusion: This cohort with predominantly MLL-rearranged leukaemia, represents the largest series of children aged under 3 treated with tisagenlecleucel. Median age at infusion was 17 months. It was feasible to leucapheresе and manufacture a product in 90%. The MRD negative CR/CRi response, 6 and 12 month EFS, and OS rates were equivalent to those of patients on the ELIANA study (median age 11 years). The toxicity profile i.e. rates of severe CRS, neurotoxicity and cytopenias were broadly similar, as were rates of hypogammaglobulinemia and infection. The rates of relapse and CD19- relapses were also similar to real-world data from the US, France and UK.
This was a cohort of very high-risk patients with predominantly infant ALL, traditionally a disease entity with very poor outcomes. The remarkably good EFS and OS documented strongly support use of tisagenlecleucel in the youngest children, even in the setting of very high-risk infant ALL.

S117 PHASE 2 RESULTS OF THE ZUMA-3 STUDY EVALUATING KTE-X19, AN ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN ADULT PATIENTS WITH RELAPSED/REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

B. D. Shah [1,*], A. Ghobadi [2], O. O. Oluwole [3], A. C. Logan [4], N. Boissel [5], R. D. Cassaday [6], E. Forcade [7], M. R. Bishop [8], M. S. Topp [9], D. Tzachanis [10], K. M. O'Dwyer [11], M. L. Arellano [12], Y. Lin [13], M. R. Baer [14], G. J. Schiller [15], J. Dong [16], T. Shen [16], F. Milletti [16], B. K. Masouleh [16], R. Houot [17]

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Background: ZUMA-3 is a Phase 1/2 multicenter study evaluating KTE-X19, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL). Phase 1 efficacy results at the recommended Phase 2 dose (1×10^6 CAR T cells/kg) were encouraging (Shah et al. *J Clin Oncol*. 2019;37[suppl, abstr]:7006).
Aims: To present the pivotal Phase 2 results of ZUMA-3.
Methods: Eligible adults had R/R B-ALL, >5% bone marrow blasts by local evaluation, and Eastern Cooperative Oncology Group performance status of 0–1. Patients received a single infusion of KTE-X19 after conditioning chemotherapy. The primary endpoint was the overall complete remission (CR) rate (CR + CR with incomplete hematologic recovery [CRi]) by central review. Key secondary endpoints were duration of remission, relapse-free survival, overall survival, measurable residual disease negativity rate by flow cytometry, and safety. Data are reported in all treated patients.
Results: As of 9/2020, 55 of 71 enrolled patients received KTE-X19, with a median follow-up of 16.4 months (range, 10.3–22.1). Adverse events (n=8) and ineligibility (n=4) were the most common reasons enrolled patients did not receive KTE-X19 infusion. Median age was 40 years (range, 19–84); median bone marrow blasts at screening were 65% (range, 5–100); and 47% of patients had ≥3 prior therapies, with 45%, 22%, and 42% having previously received blinatumomab, inotuzumab ozogamicin, or allogeneic stem cell transplant, respectively.
The CR + CRi rate was 71% (95% CI, 57–82; 56% CR, 15% CRi); 31% of responders had ongoing responses. Medians (95% CI) for duration of remission, relapse-free survival, and overall survival were 12.8 months (8.7–not estimable), 11.6 months (2.7–15.5), and 18.2 months (15.9–not estimable), respectively. In responders, medians (95% CI) for relapse-free survival and overall survival were 14.2 months (11.6–not estimable) and not reached (16.2–not estimable). The measurable residual disease negativity rate was 97% among patients with CR + CRi. Among 25 patients with prior blinatumomab treatment, the CR + CRi rate was 60%. Ten patients (18%) received subsequent allogeneic stem cell transplant at a median of 98 days post–KTE-X19 infusion. Median duration of remission remained unchanged when not censoring for allogeneic stem cell transplant.
Grade ≥3 adverse events occurred in 95% of patients, most commonly anemia (49%) and neutropenia (49% [febrile 13%]). Grade ≥3 cytokine release syndrome (per Lee et al. [*Blood*. 2014;124:188-195]) and neurologic events occurred in 24% and 25% of patients, respectively, and were generally reversible. Two Grade 5 KTE-X19–related events occurred (brain herniation, n=1; septic shock, n=1). Median times to onset of cytokine release syndrome and neurologic events were 5 days and 9 days, with median durations of 7.5 days and 7 days, respectively. Median peak CAR T-cell levels (cells/µL) were 40.5 (range, 1.3–1533.4) in patients with CR and 0 in nonresponders. CAR T cells were undetectable by 9 months in ongoing responders.
Summary/Conclusion: After a median follow-up of 16.4 months, KTE-X19 demonstrated compelling clinical benefit in heavily pretreated adults with R/R B-ALL, with the median overall survival not yet reached for responding patients and a manageable safety profile.

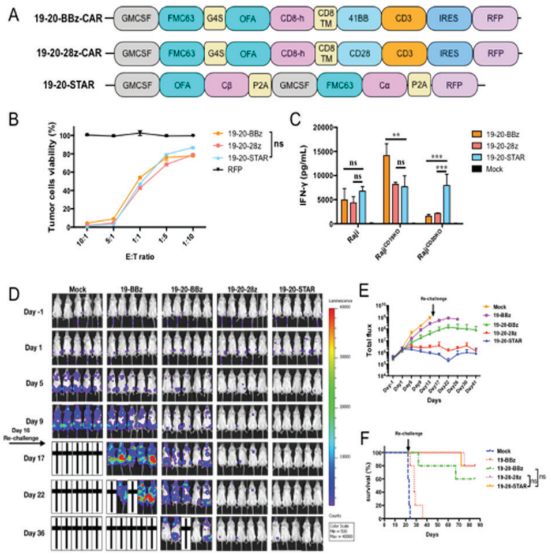
S118 A NOVEL CD19/CD20 DUAL SYNTHETIC T-CELL RECEPTOR AND ANTIGEN RECEPTOR (STAR) T CELL THERAPY FOR REFRACTORY AND RELAPSED (R/R) B CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL)

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Background: While Chimeric Antigen Receptor (CAR)-T cell approach has proved to be effective to treat hematopoietic malignancies, its therapeutic potential, the safety, antigen escape and the duration of remission can be further improved. We developed a TCR complex-based CAR called Synthetic TCR and Antigen Receptor (STAR). STAR consists of two protein modules, each containing an antibody light or heavy chain variable region and the T-Cell Receptor (TCR) a or b chain constant region fused to the OX-40 co-stimulatory domain.
Aims: We report pre-clinical and phase I clinical data on an anti-CD19/CD20 (dual) STAR-T cell therapy (www.clinicaltrials.gov, NCT04260945) in patients with R/R B-ALL.
Methods: We constructed a novel, double-chain chimeric receptor STAR (Fig.1A). Peripheral blood (PB) mononuclear cells were obtained from healthy donors and patients for the pre-clinical and clinical studies, respectively. T-cells were transduced with the dual STAR lentiviral vector and a leukemia xenograft mouse model was used to assess the anti-tumor activity of the dual STAR-T. Ten R/R patients with either CD19+ or CD19/CD20+ B-ALL were enrolled (median age of 23 years [11-55]). Patients received a conditioning regimen of intravenous fludarabine and cyclophosphamide followed by STAR-T infusion. Patients that achieved complete remission (CR) had the option to proceed to allogeneic hematopoietic stem cell transplantation (allo-HSCT) or not.
Results: In preclinical studies, the dual STAR-T had comparable killing ability to both CD19/CD20-BBz (4-1BB) and CD19/CD20-28z (CD28) CAR-T (Fig. 1B) in Raji cell, and comparatively higher IFN-γ production in Raji^{CD20KO} cell(Fig.1C). In a leukemia xenograft mouse model, dual STAR-T resulted in more potent anti-leukemia activity when compared with CD19/CD20 CAR-T in 28z group (Fig.1D and 1E) or to the CD19 CAR-T group (19-BBz Fig. 1F).

The median observation time in the phase I trial was 194 days (14-276). The median pre-treatment bone marrow blast level was 7.0% (0.5%>53%). Except for 1 manufacturing failure, 9/10 patients received a single infusion of dual STAR-T at a median dose of 1×10^6/kg (6 of 1×10^6/kg and 3 of 2×10^6/kg). The median transduction efficacy was 47.7% (32.6%>58.8%). Two weeks post dual STAR-T therapy, 8/9 (88.9%) patients achieved minimal residual disease (MRD)-negative CR. One patient who failed to response had central nervous system leukemia. After CR was achieved, 6/8 patients pursued allo-HSCT. Post allo-HSCT, 1 had MRD-positive relapse at 3 months and 1 died of infection on day 73. The remaining 4 were still in CR after a median observation time of 258 days (179-276) post-transplant. Of the 2 patients who did not undergo allo-HSCT, one patient became MRD-positive on day 30 and another one relapsed 218 days post-STAR-T therapy. Cytokine release syndrome occurred in 7/9 (77.8%) patients, all of which were grade I. Three patients developed neurotoxicity (2 with grade I and 1 with grade III). We saw a high *in vivo* proliferation and persistence regardless of the infused STAR-T dose. The median peak level was reached on day 10 (7-14 days) with 6.35×10^5 copies number/ug PB genomic DNA.



Summary/Conclusion: This study demonstrates the superiority of dual STAR-T in its anti-tumor potency compared to conventional CAR-T in an animal model. The CD19/CD20 STAR-T demonstrated technical feasibility and the ability to achieve a high CR with low toxicity in a phase I study of R/R B-ALL. Longer-term observation of these patients and larger patient studies are warranted. Given that is a TCR complex-based CAR, we see a potential for future development for solid tumor.

S119 LONG-TERM FOLLOW-UP OF SEQUENTIAL CD19-22 CAR T-CELL THERAY IN 20 CHILDREN WITH REFRACTORY OR RELAPSED B-ALL

J. Pan [1], K. Tang [2,*], B. Deng [3], Z. Ling [1], W. Song [1], A. H. Chang [4]

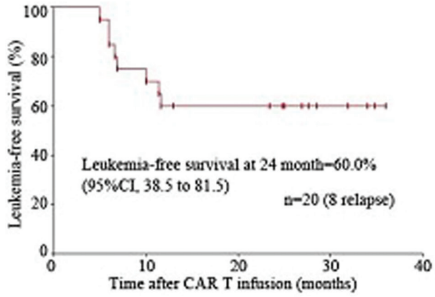
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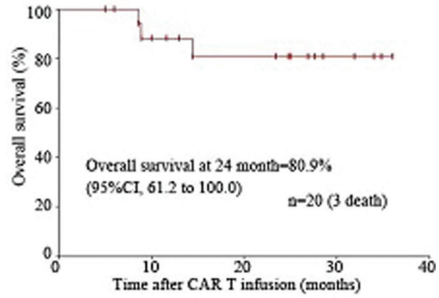
Background: Despite high response rates induced by CD19 chimeric antigen receptor (CAR) T-cell therapy in refractory or relapsed B-cell acute lymphoblastic leukemia (r/r B-ALL), a majority of patients relapsed due to either target antigen loss or insufficient CAR T-cell persistence in long-term follow up. Here, we report updated results from a phase 1 trial, demonstrating long-term outcome of pediatric patients with r/r B-ALL after sequential CD19-22 CAR T-cell therapy.

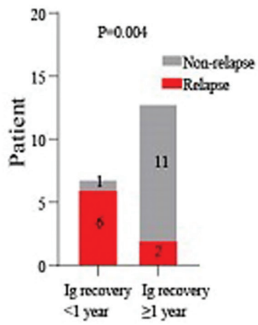
Aims: To evaluate long-term outcome of sequential CD19-22 CAR T-cell therapy in 20 r/r B-ALL children without post-CAR stem cell transplantation.

Methods: Between August, 2017 and February, 2021, consecutive 20 pediatric patients (pts) with r/r B-ALL received sequential CD19-22 CAR T-cell therapy in Beijing Boren Hospital. There were 13 males and 7 females, with a median age of 6 (range, 1 to 15) years. Fourteen pts relapsed and 6 pts had refractory minimal residual disease by flow cytometry (FCM-MRD$^+$) after previous chemotherapies. The previous median treatment time were 19 (range, 3 to 95) months in relapsed pts and 19.5 (range, 4 to 47) in FCM-MRD$^+$ pts. Severn pts had extramedullary diseases (EMDs), including 4 with exclusive EMDs. The median marrow blasts were 19.94% (range, 0.16%>93.18%) by FCM. Chromosome aberration and gene mutations were commonly observed including *TP53* mutation. All pts expressed CD19 and CD22 on blasts. CD19 or CD22 CAR lentiviral vector comprised ScFvs fragments derived from a murine anti-CD19 antibody or a humanized anti-CD22 antibody, and 4-1BB co-stimulatory and CD3z signaling domains. CAR T cells manufacture from PBMCs commenced since leukapheresis and was completed within 7-8 days, and protocols of 19 and 22 CAR T cell manufacturing were the same. CD19 and CD22 CAR T cells were infused with a median interval of 1.7 (range, 1.1 to 5.2) months. The median dose of infused 19 CAR T cells (cycle 1) was 10 (range, 3.3 to 42.8) × 10^5/kg and CD22 CAR T cells (cycle 2) was 10 (range, 0.25 to 47.4) × 10^5/kg (P=0.813). The 19 and 22 CAR T cell expansion and cytokine release syndrome (CRS) were monitored after infusion. The BM status and EMDs firstly evaluated on day 30 after CD19 CAR T cell infusion (cycle 1). Long term follow-up was carried out since infusion of 22-CART cells (cycle 2), at a median follow up time of 27.3 (range, 9.8 to 36) months.

Results: Median peak expansion of CD19 and CD22 CART cells were 9.84% (range, 0.19% to 68.7%) and 23.9% (range, 0.30 to 85.20%) among CD3$^+$ T cells respectively. All 20 pts achieved CR/CRi, FCM-MRD$^-$ and resolution of EMDs after cycle 1. CRS occurred in 18/20 (90.0%) pts in cycle 1 and 16/20 (80.0%) in cycle 2. Grade 1 neurotoxicity occurred in 3/20 (15%) pts in cycle 1 and 3/20 (15%) in cycle 2. Only 1 pt had grade 3 neurotoxicity in cycle 1 but he fully recovered after interventions. At a median follow-up time of 27.3 (range, 9.8 to 36) months, 8 pts relapsed and 3 of them died. Two (25%) of the 8 relapsed pts had CD19 antigen loss. The 8 relapsed patients included 6 out of 7 patients (85.7%) who had early Ig recovery (within 1 year), and 2 out of the 13 (15.3%) pts who had late Ig recovery (beyond 1 year) (P=0.004), suggesting that long-term disease free survival were associated with longer duration of CAR T cell persistence. 2-year LFS and OS was 60% (95%CI, 38.5-81.5%) and 80.9% (95%CI, 61.2-100.0%) respectively.







Summary/Conclusion: Sequential CD19-22 CAR T cell therapy can achieve promising long-term outcome with a 2-year LFS of 60% in pediatric patient with r/r B-ALL without post-CAR transplantation. Early Ig recovery has high risk of relapse.

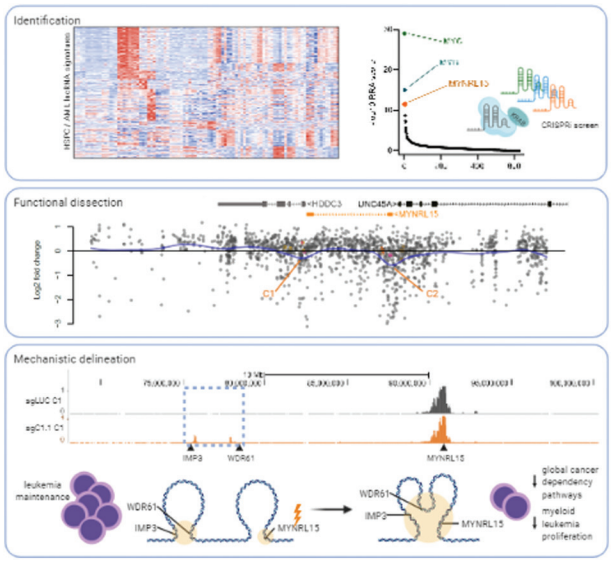
AML epigenetic and transcriptional control

S120 NONCODING REGULATORY LOCUS MYNRL15 MODULATES CHROMATIN ARCHITECTURE AND REPRESENTS A NOVEL MYELOID LEUKEMIA DEPENDENCY

M. Ng [1,*], L. Verboon [1], R. Bhayadia [1], H. Issa [1], L. Gack [1], E. Regenyi [2], A. Kovacsovics [2], V. Amstislavskiy [2], A. Schwarzer [3], M. -L. Yaspo [2], D. Heckl [1], J. -H. Klusmann [1]

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Background: The noncoding genome presents a largely untapped source of new biological insights, including tens of thousands of long noncoding RNA (lncRNA) loci. While emerging evidence implicate lncRNAs as important regulators of normal and malignant hematopoiesis, the vast majority lack functional characterization.
Aims: We aimed to identify and characterize lncRNAs that contribute to acute myeloid leukemia (AML) pathophysiology.
Methods: We screened lncRNA signatures from hematopoietic stem and progenitor cells (HSPC) and pediatric AML patient samples in six myeloid leukemia cell lines using CRISPR interference (CRISPRi). Leveraging low- and high-throughput CRISPR/Cas9-based strategies, we carried out in-depth functional dissection of the top candidate *in vitro* and *in vivo*, and defined its molecular mechanism through transcriptome and chromatin interaction profiling.
Results: To identify novel AML vulnerabilities, we performed a targeted CRISPRi screen of HSPC/AML lncRNAs (619 genes, 2009 sgRNAs) and marked *MYNRL15* – *m*yeloid leukemia *n*oncoding *r*egulatory *l*ocus on chromosome *15* – as a dependency in myeloid leukemia cells of diverse genetic backgrounds. Interestingly, *cis* and *trans* perturbation approaches revealed both the *MYNRL15* transcript and its flanking protein-coding genes to be dispensable. High density CRISPR tiling of a 15kb area surrounding *MYNRL15* (1671 sgRNAs) instead uncovered two candidate *cis*-regulatory DNA elements in the locus, which drive the *MYNRL15* perturbation phenotype. To determine the molecular basis of *MYNRL15* dependence, we performed RNA sequencing, and established *MYNRL15*'s involvement in maintaining key cancer dependency pathways (e.g. cell cycle, ribosome, spliceosome). Further, *MYNRL15* perturbation associated with coordinated dysregulation of several chromosome 15 neighbourhoods, and formation of a long-range chromatin interaction between the locus and the base of a distal loop, as detected via next-generation Capture-C. Integrative analysis of this chromatin conformation and transcriptome data, combined with a small CRISPR/Cas9 knockout screen of genes from the gained interaction region (31 genes, 178 sgRNAs), pinpointed two potent cancer dependency genes that are located in the region and down-regulated following *MYNRL15* perturbation: namely, *WDR61* and *IMP3*. Individual knockout of both genes robustly depleted myeloid leukemia cells, recapitulating the *MYNRL15* perturbation phenotype and positioning *WDR61* and *IMP3* as its regulatory targets. Importantly, in primary cells, *MYNRL15* perturbation eradicated AML blasts while sparing 50-60% of CD34$^+$ HSPCs *in vitro*, and reduced patient-derived AML xenografts up to 10-fold *in vivo*, indicating a potential therapeutic window. Remarkably, an exploration of external AML patient cohorts revealed hundreds of noncoding loci with similar features as *MYNRL15*, nearly half of which associated with cytogenetics and/or survival. Such loci may embody new class of noncoding regulatory regions with profound implications for AML and cancer pathophysiology, as exemplified by *MYNRL15*.



Summary/Conclusion: This work highlights the wealth of biologically and clinically relevant information that can be gained from studying noncoding regions, and the power of CRISPR/Cas9 systems for interrogating complex genomic loci. Leveraging these concepts, we describe the novel noncoding regulatory locus *MYNRL15*, and, through its detailed functional and molecular dissection, provide evidence for pan-myeloid leukemia vulnerabilities found at noncoding loci involved in chromatin architecture.

S121 HUMAN ENDOGENOUS RETROVIRUSES CHARACTERIZE THE DIFFERENT SUBPOPULATIONS OF NORMAL AND LEUKEMIC CELLS AND REPRESENT A SOURCE OF EPITOPES FOR CANCER IMMUNOTHERAPY IN ACUTE MYELOID LEUKEMIA

V. Alcazer [1,2,*], B. Paola [1], L. Tonon [3], E. Michel [4], V. Mutez [4], N. Chuvin [4], Y. Estornes [4], A. Viari [3], K. Metzeler [5,6], W. Hiddemann [6], A. Batcha [7], T. Herold [6], C. Caux [1], S. Depil [1,4,8]

[1]Centre de Recherche en Cancérologie de Lyon, [2]Department of Hematology, Hospices Civils de Lyon, [3]Synergie Lyon Cancer, [4]ErVaccine Technologies, Lyon, France, [5]Dept. of Hematology and Cell Therapy, University of Leipzig, Leipzig, [6]Laboratory for Leukemia Diagnostics, Department of Medicine III, University Hospital, LMU Munich, [7]Institute of Medical Data Processing, Biometrics and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Munich, Germany, [8]Centre Léon Bérard, Lyon, France

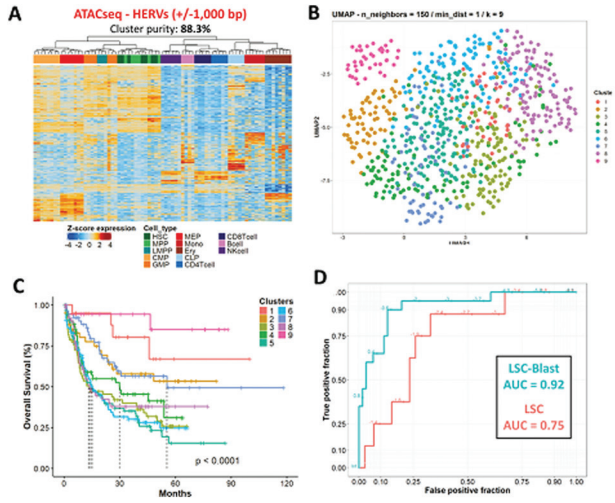
Background: Human endogenous retroviruses (HERVs) represent 8% of the human genome. To date, HERVs expression and their immune impact have never been extensively studied in Acute Myeloid Leukemia (AML).
Aims: The aims of the study were to provide a thorough quantification of HERVs expression in AML, to assess their ability to classify normal and leukemic cells (including leukemia stem cells (LSC)) and to identify relevant CD8$^+$ T cell epitopes among AML-specific HERVs.
Methods: Using a custom pipeline based on Telescope (Bendall et al., 2019), we quantified the expression of 14,968 HERVs loci in several RNA-seq and ATAC-seq datasets from sorted normal and leukemic bone marrow cells (n=81 RNA and n=122 ATAC samples) and bulk bone marrow samples from AML patient at diagnosis (n=788 samples from 4 independent international cohorts). HERVs were also quantified in 42 different normal tissues from the Genotype-Tissue Expression database for AML-specific HERVs definition (>1000 samples). For epitope validation, bone marrow infiltrating lymphocytes (MILs) were cultured during 14 days in RPMI with 8% human serum and high-doses IL2 (6000 UI/mL). Specific CD8$^+$ T cells against the selected peptides were stained using dextramer at day 14.
Results: Unsupervised hierarchical clustering based on the top 20% most variable HERVs showed a robust classification of normal hematopoietic cell types with a cluster purity of 77.6% (versus 65.3% with

a gene-based approach). Clustering of samples based on active HERVs regions (defined by peaks surrounding HERVs regions +/- 1000bp in ATAC-seq data) further improved the clustering, reaching 88.3% cluster purity (Figure 1A). Adding AML samples with the same classification approach showed a clustering of AML cells with their cell-of-origin. Differential peak-count analysis showed a distinct open-chromatin profile at HERVs regions between leukemic cells and normal bone marrow cells.

We then explored HERVs expression in the 4 independent AML RNA-seq datasets. Unsupervised hierarchical clustering based on the most variable HERVs defined 9 clusters (Figure 1B) that presented distinct cancer hallmark profiles (assessed by single sample gene-set variation analysis) and that were associated with significant overall survival differences (Figure 1C), regardless of established prognosis factors such as age, ELN2017 and white blood count in a multivariate Cox model.

To further demonstrate the value of HERVs as pertinent biomarkers, we established a LSC signature based on HERVs correlated with the previously published LSC17 score in the 4 independent bulk datasets. The resulting 47-HERVs LSC signature allowed separation of LSCs versus all the other cell populations in the independent sorted-cells validation set (Figure 1D).

Finally, 262 HLA-A*02 CD8$^+$ T cell epitopes were predicted among AML-specific HERVs identified by differential HERVs expression between AML and normal tissues. Among the top scoring peptide according to their tumor abundance, eight peptides (P1, P2, P4, P6, P15, P16, P18 and P20) were selected for biological validation. MILs from AML patients at diagnosis were then screened for specific CD8$^+$ T cells using dextramer, showing spontaneous responses against P1 in all patients and against P4, P6, P15 or P16 in some patients (n=10 patients).



Summary/Conclusion: HERV retrotranscriptome characterizes normal and leukemic cell subpopulations, including LSCs, and defines new AML subtypes of different prognosis. Moreover, HERVs represent an important reservoir of non-conventional T cell epitopes relevant for cancer immunotherapy.

S122 ISOFORM-SPECIFIC AND SIGNALING-DEPENDENT PROPAGATION OF ACUTE MYELOID LEUKEMIA BY WILMS TUMOR 1

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Background: Acute myeloid leukemia (AML) is caused by recurrent mutations in members of the gene regulatory machinery controlling hematopoietic progenitor cell growth and differentiation. We have demonstrated each AML-subtype displays a specific gene regulatory network (GRN) with transcription factors (TFs) forming differently connected network nodes and regulating sub-type specifically expressed target genes. Our analyses showed that each AML sub-type establishes its own cellular identity distinct from that of normal cells. We showed that some TFs forming prominent network nodes within an AML-subtype specific GRN are required for the maintenance of their own sub-type but not others (Assi et al., 2019, Nature Genetics). Moreover, they are not essential for the growth of normal cells, highlighting an increased dependency of cancer GRNs on specific pathways which could be exploited for therapeutic purposes. Importantly, our analysis found TF families forming network nodes in more than one AML sub-type. One such network node is formed by the Zn^{++}-finger transcription factor and tumour suppressor Wilms Tumor 1 (WT1).

Aims: WT1 is mutated in about 10% and overexpressed in 90% AML patients conferring a poor prognosis. However, little is known about how WT1 drives a more aggressive AML and why it is upregulated. It is unclear how WT1 mutant proteins alter cellular phenotypes, whether WT1 is an essential factor for leukemic maintenance, how it cooperates with other oncogenes and which target genes are bound by it, and whether the binding pattern and the impact on gene expression differs between isoforms. Here we addressed these questions at the global level by studying the role of WT1 in two major AML sub-types, t(8;21) and FLT3-ITD.

Methods: To answer these questions, we used the culture of cell lines and primary cells from patients to perturb the expression of WT1 by knockdown, the activation of the endogenous gene by CRSPR activation and by the expression of different WT1 isoforms, followed by the analysis of leukaemic growth together with genome-wide analyses of gene expression, chromatin accessibility and chromatin immunoprecipitation assays

Results: Our most important results are (i) that WT1 is essential for leukaemogenesis in a xenograft model of AML, (ii) that it is an important component of AML maintenance of multiple subtypes of AML but not in normal cells, (iii) that it acts in an isoform-specific fashion, (iv) that specific mutants and isoforms drive increased growth, iv) that overexpression of the endogenous gene causes aberrant growth thus linking its expression to increased fitness, (vi) that increased expression is linked to oncogenic signaling and, most importantly, (vi) that its binding within chromatin changes the expression of many different genes, but in an AML sub-type-specific fashion. We also show that WT1 regulates differential splicing in an isoform-specific fashion, indicating that this protein regulates AML maintenance at multiple levels.

Summary/Conclusion: Our work shows that the transcription factor WT1 forms a major node in the rewired mutation-specific gene regulatory networks of multiple AML sub-types. For two main AML subtypes we demonstrate that different WT1 isoforms exhibit different gene-specific patterns of binding, and support contrasting biological activities, including enhanced proliferation and directing differential splicing. We also show that *WT1* responds to oncogenic signaling and is part of a sub-type specific signaling-responsive transcription factor hub that controls AML growth. WT1 therefore plays a central and wide-spread role in AML biology.

S123 MYC SUPER-ENHANCER HIJACKING BY EVI1 IN LEUKEMIA IS CTCF DEPENDENT

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Background: Chromosomal rearrangements are a frequent cause of oncogene deregulation in human malignancies. In acute myeloid leukemia (AML) with inv(3)/t(3;3) rearrangements a *GATA2* enhancer at 3q21 is hijacked by *EVI1* at 3q26, causing *EVI1* overexpression and *GATA2* haploinsufficiency (Groschel et al, Cell 2014). Besides inv(3)/t(3;3), many other AML cases with 3q26 rearrangements and *EVI1* overexpression have been reported, including t(2;3), t(3;7), t(3;6) and t(3;8). It has been suggested that *EVI1* overexpression in all 3q26-rearranged AML is induced by the repositioning of an enhancer to the *EVI1* promoter (Ottema et al., Blood 2020), but a common mechanism remains to be elucidated.

Aims: In this study we aimed to investigate how enhancer-promoter interactions drive oncogenic *EVI1* expression in 3q26-rearranged leukemias. AML with t(3;8)(q26;q24), hereafter referred to as t(3;8) AML,

was used as a model of such leukemias. In this AML subgroup, a region containing a *MYC* super-enhancer (*MYC* SE) is translocated to the vicinity of *EVI1*.
Methods: We generated a patient-based t(3;8) AML cell line to study the transcriptional activation of *EVI1* by the *MYC* SE. First, we introduced e*GFP* in frame with a T2A self-cleavage site downstream of *EVI1* in K562 cells. Next, we generated a t(3;8) *in vitro* using CRISPR-Cas9 targeted at breakpoints detected in a t(3;8) AML patient. To investigate which *MYC* SE modules drive oncogenic *EVI1* transcription in t(3;8) AML, we designed sgRNAs to sequentially delete these individual enhancer modules. The effects of these deletions were measured by flow cytometry, followed by 4C-seq and ChIP-seq.
Results: We showed that *MYC* SE is translocated to *EVI1* in t(3;8) AML patients, resulting in promoter activation and *EVI1* overexpression. Further supporting this notion, introduction of t(3;8) in K562 *EVI1-eGFP* also led to *EVI1* overexpression. 4C-seq revealed specific interaction between the *EVI1* promoter and *MYC* SE in t(3;8) cells, which was not found in the parental K562 line. This was accompanied by increased activity of the *EVI1* promoter, as shown by H3K27ac and H3K9ac ChIP-seq.
The *MYC* SE is a cluster of individual enhancer modules that may recruit different sets of transcription factors. Upon sequential deletion of these modules by CRISPR-Cas9, only the deletion of one specific module caused loss of *EVI1* expression and partial loss of enhancer-promoter looping. ChIP-seq revealed binding of early hematopoietic regulators to this module in CD34+ hematopoietic stem and progenitor cells (HSPCs). This module also contained a CTCF binding site in convergent orientation with a CTCF binding site at the *EVI1* promoter. Targeting either of these CTCF binding sites resulted in loss of enhancer-promoter interaction and strong downregulation of *EVI1* expression.
In t(3;8) and other 3q26-rearranged AMLs, the translocations preserved the CTCF binding site upstream of *EVI1* and relocated an enhancer normally active in HSPCs. These commonalities suggest a shared mechanism for *EVI1* activation in all 3q26-rearranged leukemias, whereby an active hematopoietic enhancer is hijacked by a CTCF-mediated loop with the *EVI1* promoter.
Summary/Conclusion: Here we demonstrate that the *MYC* SE hyperactivates *EVI1* expression in t(3;8) AML. One specific *MYC* SE module binding early hematopoietic transcriptional regulators is critical for *EVI1* expression and promoter-enhancer looping. We propose a common mechanism by which *EVI1* uses a CTCF-bound enhancer-docking site to hijack enhancers active in early hematopoiesis.

S124 TET3 PROMOTES GROWTH AND EPIGENETICALLY REGULATES GLUCOSE METABOLISM AND LEUKEMIC STEM CELL ASSOCIATED PATHWAYS IN ACUTE MYELOID LEUKEMIA

A. J. Pulikkottil [1], S. Bamezai [1,*], F. Mohr [1], K. Feder [1], N. Vegi [1], U. Kohlhofer [2], L. Quintanilla-Martinez [2], K. Döhner [3], H. Döhner [3], A. Sinha [4], M. Feuring-Buske [3], C. Buske [1], V. P.S. Rawat [3]

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Background: Metabolic studies in acute myeloid leukemia (AML) demonstrate that altered glucose metabolism signatures and overexpression of several glycolytic enzymes is a hallmark of the disease and critical for its progression. However, the reasons for aberrant expression of glucose metabolic genes is poorly understood. The TET family (TET1-3) of dioxygenase enzymes regulate active gene expression via establishment of 5-hydroxymethylcytosine (5hmC) epigenetic marks and are deeply embedded in the pathobiology of AML. Recent studies demonstrate that *TET3* is required for normal human erythropoiesis. But the functional role of TET3 in human AML remains uninvestigated.
Aims: To investigate the functional role of TET3 in AML biology, its associated 5hmC marks and gene regulation in AML
Methods: Expression in patients and healthy cells were analyzed by qRT-PCR, TET3 expression was depleted by using shRNA or sgRNA, and impact on AML growth was tested by performing in vitro and in vivo assays. Impact on global gene expression and 5hmC marks was analyzed by next generation sequencing.
Results: We report that the epigenetic factor *TET3* is overexpressed in the majority of human AML patients and functionally validated human leukemic stem cells (LSCs) compared to their normal counterparts. In line with its high expression, the TET3 promoter is enriched for euchromatic histone marks such as H3K4me3 and lacks the repressive mark H3K27me3 in AML cell lines and murine MLL-AF9 (MA9) c-kit+ LSCs. TET3 knockdown (KD) or knockout (KO) in AML cell lines and MA9 c-kit+ LSCs suppressed their clonogenic potential *in vitro* and resulted in severely reduced leukemic engraftment in vivo. The overexpression of wild type TET3 or the form lacking DNA binding, TET3$^{\Delta CXXC}$, augmented growth of AML cells and skewed normal myeloid-erythroid differentiation program of healthy human CD34^{+} cord blood derived hematopoietic stem progenitors (HSPCs) in vitro. *TET3* KD in NB-4 cells caused differential regulation of 1,409 genes. GSEA revealed the downregulation of the LSC signature, STAT5 signaling and glucose metabolism pathways. Factors central to glucose metabolism and glucose transport were downregulated, such as enzymes *HK1-2*, *ENO2*, which also positively correlated with *TET3* expression in AML patients. Conversely, overexpression of TET3 in healthy HSPCs upregulated the expression of glycolysis, STAT5A and AML associated genes. CellRadar analysis showed that TET3 maintained the expression of early myeloid progenitor associated gene signature in AML cells and suppressed the expression of mature myeloid lineage associated gene signature in AML and healthy HSPCs. TET3 depletion in NB-4 cells resulted in a global reduction of 5hmC marks in Hydroxymethylated DNA immunoprecipitation-sequencing (hMe-DIP-Seq) analysis. Several critical glucose metabolism genes exhibited loss of 5hmC marks. Our own and published ChIP-seq data sets demonstrated that glucose metabolism genes are enriched for 5hmC marks and TET3 binding sites in AML cells. Finally, TET3 depleted or overexpressing AML cells showed reduced or increased ability to metabolize glucose to glucose-6-phosphate. TET3 depletion rendered AML cells highly sensitive to the glycolysis inhibitor 2-Deoxy-D-glucose (2-DG) or an STAT5 inhibitor (STAT5i). Combination therapy of 2-DG and STAT5i antagonized murine AML MLL-AF9 LSC and human AML cell growth.
Summary/Conclusion: In this study, we uncover the growth-promoting role of TET3 in AML and describe a close link between TET3 induced 5hmC epigenetic marks, glycolysis and the STAT5 pathway.

AML mechanisms of resistance

S125 RELEASE OF INTERFERON-GAMMA BY AML CELLS REMODELS BONE MARROW IMMUNE MICROENVIRONMENT BY INDUCING REGULATORY T CELLS

M. Ciciarello [1,*], G. Corradi [2], B. Bassani [3], G. Simonetti [4], J. Vadakekolathu [5], M. C. Fontana [4], M. Pazzaglia [4], A. Gulino [6], C. Tripodo [6], G. Cristiano [2], L. Bandini [7], E. Ottaviani [7], G. Martinelli [4], M. P. Colombo [3], S. Rutella [5,8], M. Cavo [2,7], A. Curti [7]

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Background: For a long time, acute myeloid leukemia (AML) onset and progression were considered exclusively due to critical mutations in hematopoietic stem cells. Recently, it comes out that additional cellular components of the stroma and immune bone marrow (BM) microenvironment play a supportive role. AML cells can provide their signals able to create their permissive niche through the microenvironment modulation. Among those signals, interferon (IFN)-γ has a prominent role in conferring immuno-suppressive capacity to mesenchymal stromal cells (MSCs), primary elements of the BM niche harnessing the AML immune-tolerant microenvironment. In this AML-protecting scenario, T regulatory cells (Tregs) play a pivotal role. Although it is known that the AML microenvironment favors Treg expansion, the mechanisms underlying their induction in the AML BM microenvironment are poorly elucidated.
Aims: We aimed at investigating the role of AML-produced IFN-γ in initiating microenvironmental modifications in favor of AML expansion.
Methods: We isolated AML cells and generated MSCs from AML patient BM. Gene expression profile (GEP) (AML, N=61; healthy donors, HDs

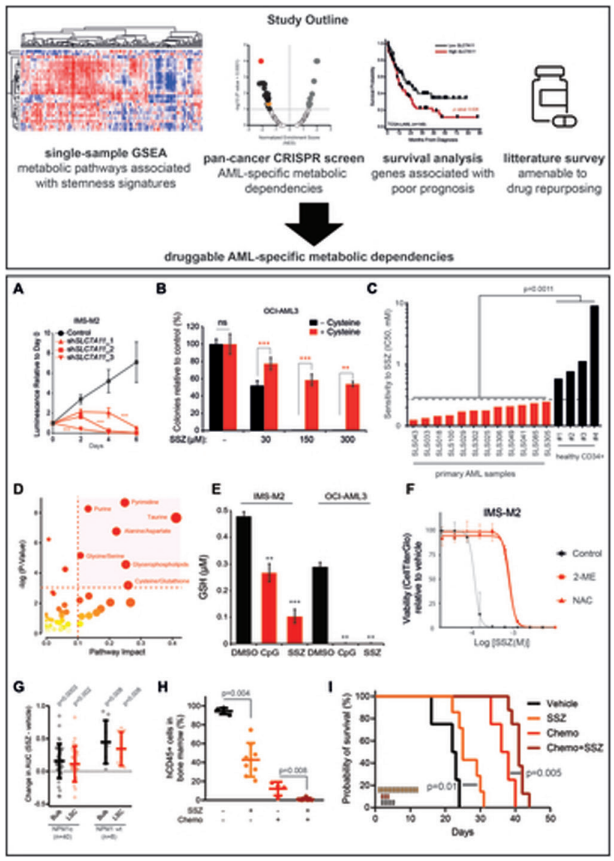
N=7) and NanoString analysis (AML, N=24) on BM-derived cells were also done. Next, we set up MSC/AML cell co-culture experiments and we investigated gene expression in MSCs and AML cells before and after co-cultures. We also set up a murine model in which the IFN-γ-expressing C1498 AML cells were knockdown for the *ifng* gene by RNA interference and inoculated intra-bone in mice. BM infiltrate was analyzed in mice and AML patients.
Results: We found that AML patients variably express and release IFN-γ allowing us to stratify them according to *IFNG* expression and cytokine production. Genome-wide and immune-targeted GEP revealed that AML patients with high *IFNG* level hold an inflammatory/immune-modulating gene signature distinct from AML patients with lower *IFNG* level, including the up-regulation of IFN-γ-stimulated genes (e.g. indoleamine 2,3-dioxygenase (IDO)1 and Nitric Oxide synthase (NOS)-2), which are known to regulate immune-tolerance. *In vitro*, AML cells with higher IFN-γ cytokine production subverted the transcriptome of MSCs by inducing IFN-γ-dependent genes related to Treg recruitment and differentiation, including IDO-1. Functionally, IFN-γ release by AML cells drove MSCs to induce Tregs in an IDO1-dependent manner. *In vivo*, mice injected with IFN-γ expressing cells showed a higher percentage of engraftment associated with an increased frequency of BM Tregs. Conversely, mice injected with IFN-γ not expressing cells presented a reduced Treg infiltration with the concomitant decrease of IDO1 expression in MSCs and ultimately with an inhibited leukemia engraftment. In patients, high *IFNG* expression correlated with an increased frequency of suppressive Tregs in the BM and predicted poor overall survival.
Summary/Conclusion: In summary, this study shows that IFN-γ release by AML cells remodels BM transcriptome and immune landscape toward Treg induction contributing to create an immune-tolerant microenvironment. In such process, tolerogenic MSCs behave as professional Treg-inducers. In perspective, our data may help in selecting patients who may benefit from an immunotherapy approach and in designing novel strategies where the activation of effector cells is combined with Treg inhibition.

S126 INHIBITION OF CYSTINE IMPORT BY REPURPOSING OF SULFASALAZINE TO TREAT ACUTE MYELOID LEUKEMIA

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Background: Expression of leukemic stemness programs is associated with resistance to anthracycline-cytarabine chemotherapy in Acute Myeloid Leukemias (AML). The metabolic rewiring of leukemic cells may generate targetable vulnerabilities.
Aims: We aimed to identify metabolic pathways associated with leukemic stemness programs targetable by drug repurposing.
Methods: We queried 2 AML patients datasets (TCGA LAML n=179, GSE14468 n=526) by single-sample GSEA and cross-compared hits with a pan-cancer CRISPR screen (AVANA n=517 cell lines) to identify metabolic pathways associated with stemness signatures representing AML-specific vulnerabilities. We next nominated within these pathways druggable genes with poor prognostic value (**Figure top cartoon**). We then validated these candidate therapeutic targets by genetic (shRNA) and chemical inhibition in AML cell lines, primary AML samples and PDX models and sought synergistic combinations with standard-of-care AML therapies.
Results: Analysis of public trancriptomic and CRISPR screen datasets identified the cysteine/methionine pathway as an AML-specific dependency associated with expression of stemness signatures. Among genes with poor prognostic value in patients datasets, SLC7A11, encoding the cystine importer xCT, was the only one validated as an AML dependency by shRNA-mediated inhibition (**Figure A**) and 3 different chemical inhibitors, including the broadly available medicine sulfasalazine (SSZ) in multiple AML cell lines. SSZ inhibited colony formation of AML cell lines in a cysteine-dependent manner (**Figure B**).
In vitro, SSZ impaired the viability of primary AML cells with a >10-fold increased sensitivity compared to healthy CD34+ cells (**Figure C**), and reduced the long-term culture initiating potential of primary AML samples (n=6, p=0.03).
xCT inhibition by SSZ or the chemically unrelated inhibitor CpG resulted in broad metabolic rewiring (**Figure D**) including depletion of intracellular gutathione pools (**Figure E**), leading to a ROS-dependent cell death (**Figure F**, NAC N-Acetyl Cysteine, 2-ME 2-mercaptoethanol) that was only partly reverted by the ferroptosis inhibitor ferrostatin-1.
Anthracyclines were identified among a panel of 8 AML drug classes as the one with top synergism with SSZ in AML cell lines. In a cohort of 48 primary AML samples, addition of low doses SSZ mimicking trough plasma concentrations in humans (4 µM) significantly increased the anti-leukemic activity of a combination of the anthracycline daunorubicin (DNR) with araC in a niche-like ex vivo drug screening assay, regardless of NPM1 status (**Figure G**).
In a PDX model harboring multiple AML mutations (NPM1, DNMT3A, FLT3-ITD and IDH1), SSZ decreased the leukemic burden and significantly prolonged survival as a single-agent, but also improved the anti-leukemic activity of a doxorubicin-cytarabine regimen at maximally tolerated concentrations (**Figure H-I**).
Finally, compassionate treatment with SSZ in a refractory AML patient with high white blood cell counts resulted in transient peripheral blood blast clearance.



Summary/Conclusion: Our results nominate the cystine importer xCT as a therapeutic target in AML and warrant clinical evaluation of SSZ in combination with 7+3 in AML.

S127 FUNCTIONAL IN VIVO CHARACTERISTICS OF PDX AML SINGLE CELL CLONES PREDICT OUTCOME IN LARGE AML PATIENT COHORTS

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Background: Acute myeloid leukemia (AML) is characterized by major clonal diversity and the most adverse clone determines patient´s outcome. Single cell sequencing describes inter- and intra-patient diversity and discriminates aggressive subpopulations, while functional insights lag behind.
Aims: We aimed at functionally characterizing AML subclones *in vivo*, in order to identify the most adverse subclone and correlate its features to clinical patient data.
Methods: Primary tumor cells from an AML patient's first and second relapse were transplanted into NSG mice to generate patient derived xenograft (PDX) models. In an innovative approach, limiting dilution transplantation was combined with genetic barcoding to generate PDX single stem cell clones. Clones were subjected to functional assays, using molecular marking and competitive *in vivo* trials. Clones were molecularly characterized on the level of exome, transcriptome and proteome.
Results: Twelve PDX single stem cell clones were generated, eight from relapse one and four from relapse two. Each clone was derived from a single AML stem cell, as proven by presence of a single barcode. AML related mutations and data from exome sequencing revealed a clear evolutionary tree, consisting of four different clusters, two from each relapse. Two clusters showed increased capacity to generate single stem cell clones, indicating increased stemness potential. A different third cluster showed major signs of *in vivo* aggressiveness, with increased growth rates combined with increased *in vivo* resistance towards Cytarabine treatment. These data suggest that stemness and treatment response developed independently from each other in distinct clones in this sample. The resistant cluster revealed yet undescribed characteristics in gene expression and proteomic profile. This gene expression data was compared to genes significantly associated with treatment resistance in three independent cohorts of AML patients to construct a prediction model for Cytarabine resistance using penalized logistic regression. Of clinical relevance, the score obtained from PDX *in vivo* functional data predicted clinical outcome in an additional independent cohort of 281 AML patients.
Summary/Conclusion: We provide proof of concept that clonal variances within a single AML sample mimics the complex heterogeneity between different AML samples. Complementing omics data with *in vivo* functional data allows identifying novel characteristics of general relevance in AML.

S128 STANDARDIZING NGS-MRD IN AML: AN INTERNATIONAL STUDY BY THE ELN-MRD WORKING PARTY

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Background: Measurable residual disease (MRD) assessment in acute myeloid leukemia (AML) patients is recommended to refine response assessment in patients being treated with intensive chemotherapy. However, the analysis of MRD results may vary by method and laboratory, and comparability of MRD results across different laboratories is limited. Next-generation sequencing (NGS) has been shown to be a sensitive and prognostic methodology for MRD detection. The reproducibility and repeatability of NGS-MRD across different laboratories has not been systematically studied.
Aims: To evaluate the reproducibility of NGS-MRD analysis among 12 laboratories using a) the established local NGS approach of the participating laboratory or b) a standardized central protocol.
Methods: Two sets of twenty DNA samples with defined mutation frequencies were centrally prepared and shipped to the participating centers. Tru-Q7 DNA was used to assess mutated *IDH1*, *IDH2* and *KIT*, and a patient sample or OCI-AML3 cells were used to assess mutated *TP53* and mutated *NPM1*, respectively (in total 24 variants in 18 MRD positive samples and 2 MRD negative samples). Each mutation was evaluated at 3 different variant frequencies, ranging from 0.039 to 1.55%. Each laboratory quantified MRD with their local NGS-MRD approach, if available, which included error-corrected targeted amplicon sequencing and myeloid panel sequencing using Illumina or Ion Torrent sequencers. The second DNA set was evaluated with a standardized protocol published previously (Thol et al. Blood 2018). Briefly, amplicon libraries were generated by a two-step PCR. After sequencing on an Illumina sequencer error correction was applied following an established analysis pipeline. Local protocols were analyzed with local bioinformatics algorithms. Data generated with the central protocol were analyzed centrally. Descriptive statistics were used to summarize and compare the results.
Results: Twelve laboratories from seven countries contributed MRD data using the central protocol and also, in ten cases, their local protocol. The median number of aligned reads was 21,233 reads (range 59 reads to 1.37 million reads) by local and 124,911 reads (range 11,944 reads to 998,396 reads) by central protocols. The median limit of detection (LOD) was 0.0752% variant alleles (range 0.0031% – 2.0%) by local and 0.0053% variant alleles (range 0.0006% – 0.0507%) by central protocols. The median variant allele frequency (VAF) of the target mutations was 0.169% (range 0.0% – 2.93%) by local and 0.155% (range 0.007% - 1.59%) by central protocols. The median coefficient of variation of the target VAFs was 57.3% (range 11.6% – 213.8%) by local and 12.0% (range 4.0% – 102.4%) by central protocols. The sensitivity for MRD detection was 100% in 6 laboratories and 38-96% in the other four laboratories using the local protocol, while it was 100% in all 12 laboratories when the central protocol was used. The specificity for MRD detection was 100% in 7 and 0-50% in the other laboratories using the local protocol, while it was 100% in all 12 laboratories with the central protocol.
Summary/Conclusion: This is the first international interlaboratory test for NGS-MRD in AML patients. It shows a high sensitivity and specificity for the various local protocols for the majority of participating laboratories. The central analysis shows that a standardized protocol can be quickly and successfully incorporated in the local laboratories, and that NGS-MRD is highly reproducible in a multicenter setting especially when using standardized methods.

S129 ACUTE RESISTANCE TO BET INHIBITORS REMODELS COMPENSATORY TRANSCRIPTIONAL PROGRAMMES VIA P300 CO-ACTIVATION

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Background: Targeting the epigenetic reader BRD4 with bromodomain and extraterminal protein inhibitors (BETi) serves as a paradigm for novel transcriptional/epigenetic therapies in Acute Myeloid Leukemia (AML). However, clinical trials with single BETis indicate non-genetic resistance, a situation that appears recapitulated with other epigenetic inhibitors. Novel treatment combinations are therefore essential for the rational utilization of BETi in AML.
Aims: To comprehensively explore early routes of epigenetic adaptation to BETi and prevent pending BETi resistance.
Methods: We studied the initial transcriptional and epigenetic response to BET inhibition. Comparing DMSO and BETi-treated KASUMI-1 cells after 24 hours of treatment, we assessed the dynamics of nuclear RNA-Seq, ATAC-Seq and binding (via ChIP-Seq) of *RUNX1-RUNX1T1*-associated transcription factors and chromatin regulators. We then comprehensively explored the functional relevance of the inferred results in a broader range of AML models. Finally, we tested our proposed adaptive resistance mechanism in a novel resistance model to BETi using RNA-Seq and proliferation assays along the longitudinal stages of resistance development.
Results: Dissecting early transcriptional and epigenetic events following BETi, we observed an "acute" compensatory feedback loop that attenuated the consequences of BRD4 release from chromatin. This adaptation loop preserved transcription and led to an aberrant increase of chromatin accessibility at and around promoters and (super)-enhancers of key AML maintenance genes such as *RUNX1, MYC, KIT* and others. Critically, this adaptation was mediated by increased binding of the global transcriptional co-activator protein p300 that normally recruits BRD4. Moreover, as demonstrated by treatment combination assays across a number of AML cell lines of varying genotypes, patient samples and primary murine AML cells, this increased p300-dependency also provided a rational therapeutic opportunity. The sequential treatment with BETi followed by inhibition of p300 HAT activity synergistically suppressed AML proliferation in almost all tested models. This suppression was generally less synergistic using BETi and p300 inhibition concomitantly, while only one cell line demonstrated synergism when p300i was applied ahead of BETi, results in accord with our hypothesis of acute p300-dependence following BETi.
To determine if this acute resistance state persisted, allowing a therapeutic opportunity at relapse, we generated a model of the evolution of acquisition of resistance to BETi in AML using OCI-AML3 cells. Remarkably, p300 addiction was highest only during the earlier stages of adaptation, but declined with full-blown resistance to BETi. Moreover, although p300 inhibition significantly suppressed the AML-maintenance MYC transcriptional programme throughout resistance evolution, this did not correlate with the anti-proliferative response to p300i which attenuated with time. However, we could determine transient transcriptional evolution of a programme of genes, including S100A8/9 and MCM genes, that were only suppressed by p300 inhibition during the earlier stages of resistance and that we speculate are involved with "emergency" AML-maintenance, a hypothesis we are currently testing.
Summary/Conclusion: Taken together, our data identify a novel "acute" resistance state to an epigenetic therapeutic, define a window of therapeutic opportunity before this resistant state becomes fixed and identify a rational up-front sequence combination, BETi followed by p300i, to potentially overcome this in AML patients.

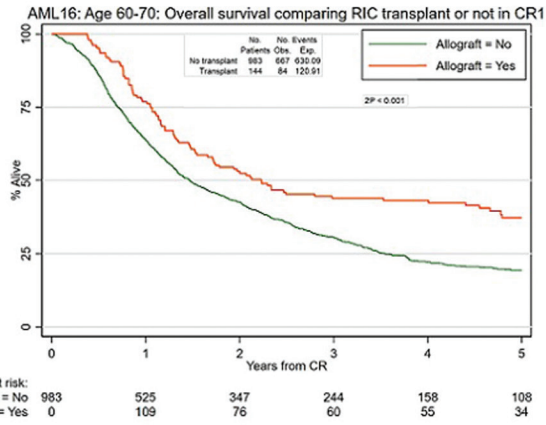
AML classification

S130 SEQUENTIAL NCRI AML TRIALS SHOW CONSISTENT BENEFIT FOR RIC TRANSPLANT IN CR1 FOR OLDER PATIENTS >60YEARS THAT IS INDEPENDENT OF MRD STATUS AFTER FIRST INDUCTION

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Background: Reduced Intensity Conditioning (RIC) transplantation is one option for post remission therapy in older patients with acute myeloblastic leukemia (AML).
Aims: Here we report on two consecutive front line NCRI trials for patients >60 years, the AML16 trial (2006-2012) and AML18 (2015-) performed with the aim of identifying which patients benefit from RIC transplantation in CR1.
Methods: Both trials employed a double induction with daunorubicin and clofarabine or AraC +/- Gemtuzumab in AML16 and daunorubicin and AraC (DA) + Gemtuzumab in AML18 which also employed a post course-1 intensification randomization to either FLAG-Ida or DA+Cladribine or DA alone for those patients not in MRD–ve remission after course 1. In AML16, 983 patients in CR1 were studied, with RIC transplant given to 144 (15%) with median follow-up for survival from CR of 60 months. In AML18, 648 out of 847 patients achieved CR of whom 201 (31%) were transplanted with a median follow up of survival from CR of 45 months. Comparisons of RIC transplant in 1st remission versus not were carried out using Mantel-Byar analysis.
Results: In AML16 when comparing allograft versus chemotherapy alone, survival at 5 years for patients 60-70 years was significantly improved (37% vs 19%, HR 0.65 (0.52-0.82) p<0.001) (Figure 1). While the survival for sibling allografts (44%) was better than that for MUDs (34%) this did not reach statistical significance (p=0.19). To avoid selection bias for transplant, analyses when stratified by Wheatley risk group (a prospectively validated risk score for older patients based on age, cytogenetics, WCC, PS and secondary or de novo AML) into good, standard and poor risk showed consistent benefit for RIC across all groups (HR 0.66 (0.53-0.83), p<0.001) with no evidence of interaction (p value for trend =0.75) When stratified by post course-1 flow MRD status (MRD-ve, MRD unknown, MRD+ve, and no CR/CRi post course 1 respectively) there was again consistent benefit for allograft. (HR 0.68 (0.54-0.85) p<0.001) with no heterogeneity (p= 0.20). The benefit for RIC was seen in patients with a *FLT3* ITD or *NPM1* mutation with no evidence of a differential effect by genotype (p-value for heterogeneity by subgroups 0.61). As AML16 had found no group that did not benefit, decision for transplant in the ensuing AML18 trial was based on health status and donor availability. In AML18 interim analysis confirmed the overall benefit of transplant with 3 year survival from remission of 48% versus 37.4% (p 0.027) with chemotherapy; observed benefit was independent of post course 1 MRD status consistent with the AML16 result (HR 0.71 CI. 0.54-0.95, p 0.02). As the transplant rate in AML18 was higher in MRD+ve patients (36% vs 24.8% in MRD-ve) and the survival of post course 1 MRD+ve and MRD-ve patients was not different (51.1% vs 46.6% at 3 years, p0.84) we examined the impact of a second induction course on transplant outcome in those not initially achieving a MRD-ve CR. Although the benefit for transplant appeared greater in patients who converted to an MRD-ve remission post course 2 (HR 0.32 CI 0.11-0.92) lack of heterogeneity (p=0.22) means that benefit for those remaining MRD+ve post course 2 cannot be excluded.



Summary/Conclusion: Two consecutive trials demonstrate benefit for RIC transplant in first remission for older adults that is independent of post course 1 response and MRD status. The overall improvement in outcome for post course1 MRD+ve patients in AML18 compared to AML16 may reflect treatment intensification post course 1 and the impact of the increased uptake of RIC transplant

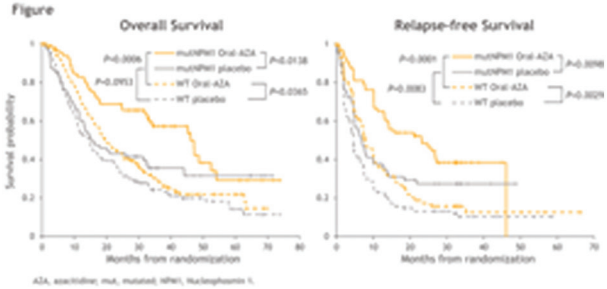
S131 SURVIVAL OUTCOMES FROM THE QUAZAR AML-001 TRIAL WITH ORAL AZACITIDINE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN REMISSION BY DISEASE SUBTYPE, CYTOGENETIC RISK, AND NPM1 MUTATION STATUS AT DIAGNOSIS

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Background: Oral azacitidine (Oral-AZA; CC-486) is approved in the US for adult patients (pts) with acute myeloid leukemia (AML) who have achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive chemotherapy and are ineligible for intensive curative therapy. In the phase 3 QUAZAR trial, Oral-AZA significantly improved overall survival (OS) vs placebo (PBO) (median [med] 24.7 vs 14.8 months [mo], respectively; *P*<0.001). It has not been elucidated which subgroups of pts may derive greater benefit from Oral-AZA maintenance treatment (Tx) based on prognostic features or mutational profile.
Aims: Investigate the relationship between Oral-AZA and survival in *post hoc* analyses based on cytogenetic risk classification, AML subtype (*de novo* or secondary), and *NPM1*/*FLT3* status at diagnosis (Dx).
Methods: Cytogenetic risk classification of intermediate- (int) and poor-risk pts was based on the 2012 NCCN Guidelines; pts with favorable risk were excluded. Pts were randomized 1:1 to Oral-AZA 300 mg or PBO within 4 mo of achieving first CR/CRi. Mutant (mut) or wild-type (WT) *NPM1*/*FLT3*-ITD status was determined at Dx. OS and relapse-free survival (RFS) were estimated using Kaplan-Meier methods. Cox Proportional Hazard Regression was used to obtain hazard ratios (HR; *P* values, Log-rank test). Measurable residual disease (MRD) analysis used a cutoff of ≥0.1% (*P* values, Fisher's exact test).
Results: Of 472 randomized pts, 90.9% had d*e novo* AML, and Oral-AZA provided a significant increase in med OS vs PBO (23.2 vs 14.6 mo; HR 0.73; *P*=0.0068) and RFS (10.2 vs 4.9 mo; HR 0.66; *P*=0.0002). For the underpowered pt group with secondary AML (n=43), there was a trend for increased OS with Oral-AZA vs PBO (28.2 vs 15.7 mo; HR 0.58; *P*=0.11) and significantly increased RFS (4.7 vs 2.4 mo; HR 0.47; *P*=0.0118). 86% of pts had int-risk cytogenetics, and within this population, OS was significantly increased with Oral-AZA vs PBO (25.4 vs 15.9 mo; HR 0.73; *P*=0.0093), as was RFS (11.0 vs 5.8 mo; HR 0.66; *P*=0.0004). The poor-risk cohort (14%; n=66), though underpowered, showed a trend for increased OS with Oral-AZA vs PBO (13.9 vs. 7.4 mo; HR 0.61; *P*=0.06), and RFS was similar (Oral-AZA 4.6 mo, PBO 3.7 mo; HR 0.63; *P*=0.08). Overall, 29.2% of pts had mut*NPM1* at Dx (137/469), 9.8% (n=48) were *FLT3*-ITD positive, and 6% (n=30) had co-mutated *NPM1*/*FLT3*-ITD. In the PBO arm, mut*NPM1* status vs WT was prognostically favorable for RFS (6.9 vs 4.6 mo; HR 0.64; *P*=0.0083) with a trend in increased OS (15.9 vs 14.6 mo; HR 0.75; *P*=0.10). Comparing treatment arms, the med OS for pts with mut*NPM1* was considerably longer in the Oral-AZA arm vs PBO (46.1 vs 15.9 mo; HR 0.57; *P*=0.0138), and med RFS was significantly prolonged (23.2 vs 6.9 mo; HR 0.55; *P*=0.0098) (**Figure**). A larger fraction of pts with mut*NPM1* were MRD– (61.7%) than were MRD+ (38.4%) at screening (*P*=0.0178). For pts with WT *NPM1* (Oral-AZA n=170; PBO n=162), Tx with Oral-AZA significantly increased OS (19.6 vs 14.6 mo; HR 0.77; *P*=0.0365) and RFS (7.7 vs 4.6 mo; HR 0.69; *P*=0.0029). Pts with WT *NPM1* were evenly distributed between MRD– (49.2%) and MRD+ (50.8%) status at screening.

Figure



Summary/Conclusion: Oral-AZA considerably improved survival for pts with *de novo* AML and int-risk cytogenetics. Additionally, pts with mut*NPM1* in the Oral-AZA arm derived an extended OS benefit of more than 2.5 years vs PBO, whereas OS for all pts in QUAZAR AML-001 was lengthened by 9.9 months with Oral-AZA vs PBO. This suggests that mut*NPM1* status is both prognostically favorable in general and independently predictive of increased OS with Oral-AZA.

S132 RUNX1 MUTATIONS IN NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA DO NOT ADVERSELY IMPACT CLINICAL OUTCOMES IN THE MODERN ERA

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Background: European LeukemiaNet 2017 risk stratification classifies mutated *RUNX1* (m*RUNX1*) as an adverse risk factor in newly diagnosed (ND) acute myeloid leukemia (AML). However, outcomes of m*RUNX1* in ND AML in the current era, including with venetoclax (Ven)-based therapies, are not well defined.
Aims: We characterize the impact of *RUNX1* mutations and variant allelic frequency (VAF) on outcomes of patients with ND AML across contemporary treatment regimens.
Methods: We conducted a retrospective analysis of patients (pts) with ND AML treated at our institution from 11/2009 to 7/2020. Pt were divided into AML with m*RUNX1* and wild type *RUNX1* (wt*RUNX1*); only those with presumed somatic variants based on previous annotation in literature and publicly available databases were included in the m*RUNX1* group. Treatment was classified as intensive chemotherapy (IC) or low intensity chemotherapy including hypomethylating agents (LIC) with and without Ven. Response was defined as achievement of CR or CRi.
Results: Among 907 pts with ND AML, 137 (15%) had AML with m*RUNX1*. The median *RUNX1* VAF was 33% (range, 1-96%); 29 pts (21%) had ≥2 *RUNX1* mutations. Pts with m*RUNX1* AML were older (median age: 71 vs. 66 years; P<0.001), more likely to have secondary AML (20% vs.13%; P=0.03), and less likely to have adverse-risk cytogenetics (20% vs. 34%; P=0.001) compared to pts with wt*RUNX1*. AML with m*RUNX1* was more likely to have a co-mutation of *SRSF2* (40% vs. 12%; P<0.001), *ASXL1* (24% vs. 9%; P<0.0001), and *IDH1/2* (38% vs. 25%; P=0.002), and less likely to have co-mutated *TP53* (5% vs. 25%; P<0.0001).
Frontline therapies received were IC in 35 pts (26%), LIC without Ven in 66 pts (48%) and LIC with Ven in 36 pts (26%). Response rates were similar between pts with m*RUNX1* and wt*RUNX1* AML across therapies (IC, 77% vs. 80%; LIC without Ven, 44% vs. 52%; LIC with Ven, 72% vs. 73%). Among pts with m*RUNX1* AML treated with LIC, response rates were significantly higher in those who received Ven (72% vs. 44%, P=0.007). The benefit of adding Ven to LIC was similar among pts with *RUNX1* VAF <30% (response rate: 82% with Ven vs. 46% without Ven; P<0.05) and VAF ≥30% (68% vs. 43%, respectively; P<0.05). Among pts who received IC, response rates were higher in AML with m*RUNX1* VAF <30% than ≥30% (100% vs. 69%; P=0.06).
Overall survival (OS) was similar in m*RUNX1* and wt*RUNX1* AML in both pts <60 years (P=0.8) and ≥60 years (P=0.8). *RUNX1* mutation status also did not impact OS in those treated with IC (P=0.7) or LIC without Ven (P=0.8); however, among pts who received LIC with Ven, there was a strong trend towards superior OS for pts with m*RUNX1* AML compared to wt*RUNX1* AML (median 25.1 months [m] vs. 11.3 m; P=0.12). Pts with m*RUNX1* AML who received LIC with Ven had superior OS compared to those who received LIC without Ven (median OS 25.1 m vs. 14.9 m; P=0.02).
Among those with m*RUNX1* AML who received IC, OS was higher for those with VAF <30% vs. ≥30% (median OS not reached vs. 18.3 m; P=0.10). Among those with m*RUNX1* VAF <30%, the addition of Ven to LIC significantly improved OS compared to LIC without Ven (median OS 25.4 m vs. 14.9 m; 2-year OS 81% vs. 12%; P=0.02); in contrast, the benefit of adding Ven to LIC in pts with m*RUNX1* VAF ≥30% was less pronounced (median OS 16.4 m vs. 15.3 m; 2-year OS 43% vs. 26%; P=0.2).

Summary/Conclusion: The comparable outcomes between pts with m*RUNX1* and wt*RUNX1* AML question the inclusion of *RUNX1* mutations as an adverse risk group. With Ven-based regimens, a median OS >2 years was observed in pts with m*RUNX1* AML.

S133 A UNIFIED CLASSIFICATION AND RISK STRATIFICATION ALGORITHM TO SUPPORT CLINICAL DECISIONS IN ACUTE MYELOID LEUKEMIA

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Background: Despite a detailed understanding of the genomics underlying AML pathogenesis, clinical recommendations for AML classification and risk stratification remain heavily reliant on cytogenetic findings and only consider a few well-characterized gene mutations. In the absence of informative markers, a significant proportion of AML patients are categorized as intermediate risk and display significant heterogeneity in clinical presentation and outcomes.
Aims: To examine the role of acquired gene mutations in clinical decision support algorithms for disease classification, risk stratification and treatment decisions in AML.
Methods: We mapped recurrent gene mutations across 128 genes implicated in myeloid pathogenesis across 2,113 patients. Gene mutations were integrated with cytogenetic findings (fusion genes and chromosomal aneuploidies). Unsupervised clustering using Bayesian Dirichlet Processes was implemented to characterize novel molecular subgroups or biological and clinical relevance. Associations with clinical presentation and outcomes as measured by measurable residual disease (MRD), overall survival, relapse risk and hematopoietic stem cell transplantation (HSCT) response were assessed. Multi-state Hiden Markov Models were implemented to assess class specific risk associations across clinical transitions (complete remission, relapse, death). Findings were validated in 1,540 patients from the AMLSG trials.
Results: 92% of patients were assigned into one of 14 molecular classes. These classes define clinical and prognostic AML subgroups; each associated with a distinct likelihood of response to induction chemotherapy, risk of relapse and death over time. We characterize molecular subgroups that retain independent prognostic relevance irrespective of MRD status post course 1, and define molecular subgroups that derive benefit from HSCT at first remission. Secondary AML-2, a class enriched in secondary like mutations represents the second largest group (24% of patients) in AML. sAML-2 associates with high-risk disease, retains poor prognosis irrespective of flow MRD negativity after course 1, and derives significant benefit from HSCT. Guided by class membership we derive a 3-tier risk stratification score, that re-stratifies 26% of patients with significant improvement in c-index and variance explained. We characterize 32 genes that, with cytogenetics, result in complete patient classification and risk stratification and develop an open-access web calculator that considers molecular, clinical and demographic parameters to deliver individual patient tailored management.
Summary/Conclusion: Using data from 3,653 patients, we identify 14 novel molecular subgroups, and characterize associations with clinical presentation, MRD and treatment response (Induction chemotherapy and transplant). We develop and validate a unified framework for disease classification and risk stratification in AML based on cytogenetics and information from 32 genes that would enable practical adoption in clinical practice.

S134 A NATIONAL DANISH PROOF OF CONCEPT ON FEASIBILITY AND SAFETY OF HOME -BASED INTENSIVE CHEMOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

K. Nørskov [1,*], K. Fridthjof [2], P. Kampmann [1], A. Dünweber [1], T. Renaberg [1], C. Schöllkopf [1], S. Azar Ahmad [1], K. Schou [3], C. F. Jensen [3], P. Mølller [3], B. Wolf Lundholm [4], C. Marcher [4], A. K. Ørntoft [5], H. Beier Ommen [5], L. Andersen [6], C. F. Hasselgren [6], M. Severinsen [6], M. Klinten Grand [7], M. Jarden [1], T. Møller [8], L. Kjeldsen [9]

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Background: Advances in treatment modalities have made it possible to offer chemotherapy to patients at home without health care professionals being present. Home-based chemotherapy treatment has shown to provide several benefits in patients with cancer however existing evidence does not include patients with hematologic malignancies. In addition, there is no best practice models which can guide coordination and standardization of home-based chemotherapy treatment. Thus, it is relevant to investigate the feasiblity and safety of home-based treatment in this population.
Aims: To investigate the feasiblity and safety of home-based intensive chemotherapy in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome, and to examine quality of life and psychological wellbeing.
Methods: A national multicenter single-arm feasibility study that included patients from six sites in Denmark with newly diagnosed with acute leukemia or high-risk myelodysplastic syndrome receiving intensive induction and consolidation like chemotherapy (n=104). Participants received intensive chemotherapy on programmed CADD Solis infusion pumps through a central venous catheter. Supportive care was offered in the outpatient unit every second or third day for transfusion or surveillance of infection. Outcome measures included feasibility (primary outcome), safety, anxiety and depression measured by the Hospital Anxiety and Depression Scale, and quality of life by the Functional Assessment of Cancer Therapy – Leukemia and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.
Results: In total, 104 patients were included, receiving 264 treatments during the intervention. Total number of days slepping at home during treatment was 1.096 (mean 4.57, SD 3.0) out of 1.644 treatment days (66 %). Patients with no admissions during treatment were in cycle one (n=2), cycle two (n=29), cycle three (n=22), and cycle four (n=11). An overall trend showed a decrease in participants not discharged during treatment and hospital admission days with the greatest decline from treatment cycle one to cycle two. Patients reported high satisfaction with home-based treatment which had positive influence on their ability to be involved in their own treatment as well as socially and physically active. Most participants felt safe while receiving treatment in their home. Reasons for contacting the hospital were either due to fever, nausea or bleeding (n=60), or pump alarm (n=65) which in the majority of cases could be solved by phone (72%). No unexpected adverse events occurred during the intervention. Overall, patients improved in all quality of life
Summary/Conclusion: Providing home-based intensive chemotherapy treatment was feasible and safe in this population and provided a valuable alternative to receiving treatment in an inpatient setting. This may

strengthen the existing supportive care services in Denmark for this population, and the findings are potentially transferable and valuable to a broader context of patients with cancer or other life-threatening diseases. With home-based treatment of acute leukemias, a considerable number of hospital beds can be freed up for other patients in need of in-hospital treatment.

Developments in AML therapy

S135 EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY FLT3-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

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Background: The FMS-like tyrosine kinase 3 (*FLT3*) inhibitor gilteritinib (Gilt) improves survival compared with standard salvage chemotherapy in patients (pts) with *FLT3*-mutated (*FLT3*$^{mut+}$) acute myeloid leukemia (AML) who are relapsed/refractory (R/R) to standard chemotherapy. Interim analysis of an ongoing, multicenter, open-label, Phase 1b trial (NCT03625505) of Gilt + the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax (Ven) in pts with R/R *FLT3*$^{mut+}$ AML reported high rates of marrow blast elimination and a modified composite complete remission (mCRc) rate of 84% (Daver et al. ASH 2020; Abstract 333).
Aims: To provide updated results from a Phase 1b trial of Ven + Gilt in R/R *FLT3*$^{mut+}$ AML.
Methods: The study design has been described previously (Daver et al. ASH 2020; Abstract 333). In brief, pts with R/R AML *FLT3*$^{mut+}$ received dosages up to Ven 400 mg daily with Gilt (80 mg or 120 mg) daily in 28-day cycles, following Ven ramp-up. The primary endpoint was mCRc (complete response [CR] + CR with incomplete platelet recovery + CR with incomplete blood count recovery [CRi] + morphologic leukemia-free state) to align with the Phase 3 ADMIRAL trial CRc responses. Duration of response (DOR) of mCRc was a secondary endpoint; overall survival (OS) and changes in FLT3 allelic burden were exploratory. Safety evaluation included adverse event (AE) monitoring.
Results: At the data cutoff of November 30, 2020, 43 pts with *FLT3*$^{mut+}$ had been enrolled. Median age (range) was 63 years (23–85). *FLT3* internal tandem duplications (ITD) were identified in 37 pts (86%) and 6 pts (14%) had only tyrosine kinase domain (TKD) mutations. Baseline cytogenetic risk was favorable in 2 pts (5%), intermediate in 23 pts (55%), poor in 13 pts (31%), and 5 pts (12%) had no mitoses/missing data. The median (range) prior lines of therapy was 2 (1–5), and 33 pts (77%) had 2 or more prior lines of therapy; 28 pts (65%) had received at least one prior *FLT3* inhibitor and 3 pts (7%) received prior Ven. Fourteen pts (33%) had prior transplant.
Grade 3/4 AEs were reported in 42 pts (98%). Grade ≥3 cytopenias occurred in 34 pts (79%) and were predominantly managed by Ven and/or Gilt dose interruptions and shorter Ven duration on subsequent cycles. The only grade 3/4 nonhematologic AE reported in >20% of pts was pneumonia (n=9; 21%). There was 1 instance of clinical tumor lysis syndrome. Serious AEs were reported in 32 pts (74%). Overall, 30- and 60-day mortality rates were 0% and 12%, respectively. AEs led to either Ven or Gilt interruptions in 24 pts (56%), reductions in 3 pts (7%), and discontinuations in 6 pts (14%).
mCRc was achieved by 86% of the *FLT3*$^{mut+}$ efficacy population (36/42) with a median time to first response of 1.0 month (range: 0.7–4.6), and by 86% of pts with prior *FLT3* tyrosine kinase inhibitor (TKI) exposure (24/28). *FLT3* molecular clearance (<10^{-2}) was observed in 69% of pts with mCRc who had PCR analyzed at baseline and at least one follow-up timepoint (18/26). DoR and OS are summarized in the **Table**.

Table: Summary of median DoR and OS in patients with *FLT3* mutations

	All *FLT3*$^{mut+}$ pts N=42	All ITD pts N=37	Prior TKI use	
			Yes	No
Median OS, months (95% CI)	N=42 10.5 (9.6–NE)	N=36 10.5 (8.0–NE)	N=28 10.5 (7.4–NE)	N=14 10.6 (6.6–NE)
Median DoR, months (95% CI)	N=36 5.6 (4.0–6.6)	N=32 5.6 (3.4–8.3)		

CI, confidence interval; DoR, duration of response; *FLT3*, FMS-like tyrosine kinase 3; *FLT3*$^{mut+}$, *FLT3*-mutated; ITD, internal tandem duplications; N, number of patients with data available for analysis; NE, not estimable; OS, overall survival; TKI, tyrosine kinase inhibitor.

Summary/Conclusion: These updated analyses show that Ven + Gilt achieved high rates of mCRc in pts with heavily pretreated and prior TKI-exposed R/R *FLT3*$^{mut+}$ AML with encouraging molecular clearance rates. Using similar response criteria to previously studied *FLT3*$^{mut+}$ populations, the high mCRc rate with Ven + Gilt reported here suggests strong antileukemic activity. Cytopenias were prominent but manageable. Updated follow-up and molecular data will be presented at the meeting.

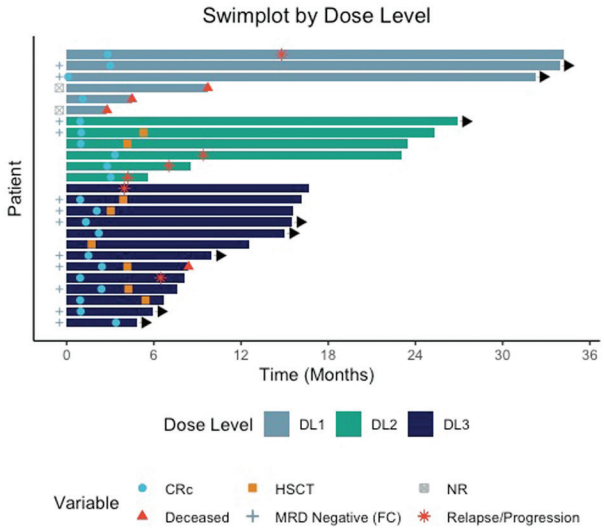
S136 A PHASE IB/II STUDY OF IVOSIDENIB WITH VENETOCLAX +/- AZACITIDINE IN IDH1-MUTATED MYELOID MALIGNANCIES

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Background: Isocitrate dehydrogenase-1 (*IDH1*$^{+}$) mutations are present in 5-15% of myeloid malignancies, promoting leukemogenesis through production of the oncometabolite 2-hydroxyglutarate resulting in arrested myeloid differentiation. *IDH1*$^{+}$ malignancies demonstrate increased reliance on the anti-apoptotic protein BCL-2, enhancing susceptibility to the BCL-2 inhibitor venetoclax (VEN).
Aims: We report an interim safety and efficacy analysis of the IDH1 inhibitor ivosidenib (IVO; 500 mg PO daily D15-continuous) combined with VEN (D1-14) +/- azacitidine (AZA; 75mg/m^2 D1-7 every 28 days).
Methods: Eligible patients age ≥18 with *IDH1*$^{+}$ MDS, newly diagnosed (ND: treatment naïve [TN], secondary/treated secondary AML [sAML]), or relapsed/refractory (R/R) AML were enrolled into three dose levels (DL): DL1 (IVO+VEN 400 mg), DL2 (IVO+VEN 800 mg), DL3 (IVO+VEN 400 mg+AZA). Primary objectives included safety and tolerability, and IWG defined overall response (ORR: CR+CRi+CRh+PR+MLFS). Prior receipt of IVO or VEN was exclusionary.
Results: 25 evaluable patients (DL1: 6, DL2: 6, DL3: 13) enrolled with a median follow-up of 16.1 months (DL1: 34 months, DL2: 24 months, DL3: 13 months). Median age was 67 (range: 44-84). 84% (N=21) of patients had AML (ND: N=13 [TN: 8, sAML: 5], R/R: N=8), while 16% (N=4) had MDS. ELN risk was intermediate and adverse in 16% (n=4) and 56% (N=14). Median *IDH1* VAF at enrollment was 22.7% (range: 5.1%>47.8%). Two patients had received a prior IDH1 inhibitor. The ORR was 92% (DL1: 67%, DL2:100%, DL3: 100%), with both non-responding patients (N=2) treated within the DL1 cohort. Composite CR (CRc:CR+CRi+CRh) was 84% (DL1: 67%, DL2: 100%, DL3: 85%) including 92% (TN: 100%, sAML: 80%), 63%, and 100% of patients with ND-AML, R/R-AML, or MDS. Median time on study was 5 months (DL1: 9 months DL2: 6 months DL3: 5 months), and the median number of cycles received was 4 (DL1: 8.5, DL2: 6, DL3: 4) with ongoing responses in 62% (DL1: 33%, DL2: 50%, DL3: 82%) at 1-year. 8 patients transitioned to SCT (DL1: 0, DL2: 2, DL3: 6), and 8 patients remain on study (DL1: 2, DL2: 1, DL3: 5). 1-year OS was 68% for the entire study population (DL1: 50%, DL2: 67%, DL3: 78%), 75% in ND-AML (TN: 86%, sAML: 60%), 50% in R/R-AML, and 100% in MDS. Measurable residual disease negative CRc by multiparameter flow cytometry was attained in 60% (ND-AML: 75%, R/R-AML: 60%, MDS: 33%) correlating with improved OS (median OS: NR vs. 8.5 months, p-value: 0.038).

Signaling mutations at treatment initiation were enriched in non-responding or relapsing patients with AML (83% vs.27%, p-value: 0.046), and trended with inferior OS (median OS NR vs. 9.7 months, p-value: 0.063). Common grade 3/4 adverse events included febrile neutropenia (28%) and pneumonia (24%). Tumor lysis and differentiation syndrome occurred in two and four patients; all cases resolved with medical management.



Summary/Conclusion: IVO+VEN +/- AZA is an effective treatment regimen in patients with *IDH1*+ myeloid malignancies. The combination therapy is associated with an acceptable and expected toxicity profile with notable efficacy and high rates of MRD-negative CRc in AML. Enrollment into the study continues.

S137 MEASURABLE RESIDUAL DISEASE RESPONSE IN ACUTE MYELOID LEUKEMIA TREATED WITH VENETOCLAX AND AZACITIDINE

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Background: In the phase 3 VIALE-A trial, rates of composite complete remission (CRc; complete remission [CR] + CR with incomplete hematologic recovery [CRi]) and measurable residual disease response (MRD<10^{-3}) were higher in patients (pts) treated with venetoclax (Ven) + azacitidine (Aza) compared to Aza alone (23.4%/7.6%, p<0.001). There is limited evidence of the clinical significance of MRD monitoring in pts receiving low-intensity chemotherapy.

Aims: We explored the outcomes of pts treated with Ven+Aza who achieved both CRc and MRD<10^{-3} in the VIALE-A trial (NCT02993523).

Methods: Enrolled pts were ≥18 years and unfit for intensive chemotherapy. Pts received Ven 400 mg orally; days 1–28 and Aza 75 mg/m^2; days 1-7/28-day cycle. Bone marrow aspirate samples for multiparametric flow cytometry assessments by integrated leukemia-associated immunophenotypes and different than normal procedures were collected for central analysis (Covance Central Laboratory Services) at baseline, end of cycle 1, and every 3 cycles thereafter. Assessments were performed independent of disease responses. MRD response was defined as <1 residual blast /1000 leukocytes (<10^{-3}). CRc, DoR, OS, and EFS were assessed. Disease assessments were per modified International Working Group response criteria for AML.

Results: 211/286 (74%) pts treated with Ven+Aza with at least one valid post-baseline MRD assessment were considered MRD evaluable; 78/211 (37%) achieved MRD<10^{-3} and 133/211 (63%) had MRD≥10^{-3}. Median age (MRD<10^{-3}/ MRD≥10^{-3}) was 76 (range: 49-89)/77 (58-91) years.

Pts (MRD<10^{-3}/ MRD≥10^{-3}) received median of 14.5 (range: 1-28) /7.0 (1-30) cycles of Ven+Aza. At a median follow-up of 22.0 (range: 20.1-23.0)/20.8 (19.8-22.3) months (mos), CRc + MRD<10^{-3}/ MRD≥10^{-3} was achieved by 67 (86%)/ 97 (73%); 20/67 (30%) achieved CRc + MRD<10^{-3} by end of cycle 1.

Median DoR, OS, and EFS were not reached in pts with CRc + MRD<10^{-3} response (Table). The 12-mo estimates for DoR, OS, and EFS for pts with CRc + MRD<10^{-3}response were 81.2%, 94.0%, and 83.2%, respectively. Adverse events ≥grade 3 (MRD<10^{-3}/ MRD≥10^{-3}) were febrile neutropenia (50%/43%), neutropenia (50%/35%), and thrombocytopenia (44%/44%), similar to the overall population.

Table: DoR, OS, and EFS in patients with composite complete response treated with venetoclax and azacitidine

	12-mos estimate % (95% CI)		Median months (95% CI)	
	MRD<10^{-3} n=67	MRD≥10^{-3} n=97	MRD<10^{-3} n=67	MRD≥10^{-3} n=97
Duration of response	81.2(69.3, 88.9)	46.6(35.6, 56.8)	NR(19.3, NR)	9.7(8.0. 15.8)
Overall survival	94.0(84.7, 97.7)	67.9(57.6, 76.2)	NR(24.4, NR)	18.7(12.9, NR)
Event-free survival	83.2(71.6, 90.3)	45.4(35.2, 55.0)	NR(19.7, NR)	10.6(9.0, 13.9)

CI: Confidence interval; MRD: measurable residual disease; NR: not reached

Summary/Conclusion: Pts with best response of CRc who achieved MRD<10^{-3}response with Ven+Aza treatment had longer DoR, OS, and EFS than pts who were CRc and MRD positive.

S138 EFFECT OF OLUTASIDENIB (FT-2102) ON COMPLETE REMISSIONS IN PATIENTS WITH RELAPSED/REFRACTORY MUTANT IDH1 ACUTE MYELOID LEUKEMIA. RESULTS FROM A PLANNED INTERIM ANALYSIS OF A PHASE 2 CLINICAL TRIAL

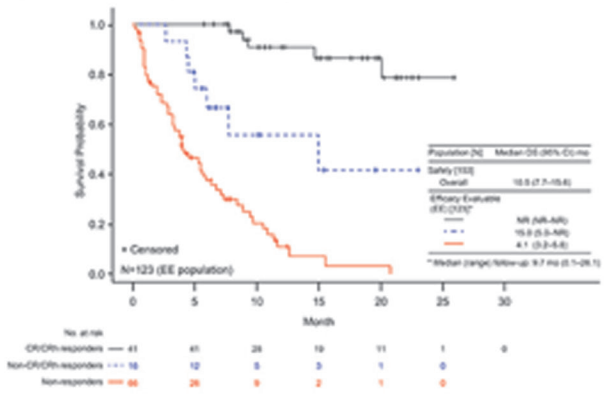
S. de Botton [1,*], K. Yee [2], R. Christian [3], A. Wei [4], P. Montesinos [5], D. Taussig [6], A. Pigneux [7], T. Braun [8], A. Curti [9], J. Esteve [10], C. Grove [11], B. A. Jonas [12], A. Khwaja [13], O. Legrand [14], P. Peterlin [15], M. Arnan Sangerman [16], W. G. Blum [17], D. Cilloni [18], D. K. Hiwase [19], J. G. Jurcic [20], J. Krauter [21], X. Thomas [22], J. M. Watts [23], J. Yang [24], O. Polyanskaya [25], J. Brevard [25], J. Sweeney [25], P. Henrick [25], H. Mohamed [25], J. Cortes [26], P. Fenaux [27]

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Background: Olutasidenib, a potent, selective, oral, small molecule inhibitor of mutant IDH1 (m*IDH1*), has exhibited favorable tolerability and clinical activity in high-risk acute myeloid leukemia (AML) patients (pts) in a phase 1 trial (Watts, *Blood* 2019).
Aims: Here, we present interim analysis results of a phase 2 trial (NCT02719574) in relapsed/refractory (R/R) m*IDH1* AML pts receiving olutasidenib monotherapy 150 mg twice daily.
Methods: The efficacy evaluable (EE) set comprised m*IDH1*^{R132X} pts whose first dose was ≥180 days before the data cut-off (18-JUN-20). The primary endpoint was CR + CRh (complete remission [CR] or CR with partial hematologic recovery [CRh] according to modified IWG 2003 criteria) rate. CRh was defined as bone marrow blasts <5%, absolute neutrophil count >0.5×10^9/L, *and* platelet count >50×10^9/L. Overall response rate (ORR) comprised CR + CRh + CR with incomplete recovery (CRi) + morphologic leukemia-free state (MLFS) + partial response (PR). Duration of treatment (DOT), duration of response (DOR), and overall survival (OS) were estimated using Kaplan-Meier methodology.
Results: This clinical trial met its pre-specified early enrollment-stopping criteria for efficacy. A total of 153 pts with R/R AML received olutasidenib; median DOT, 5.5 months (95% CI: 4.4–8.7). 43 pts (28%) remain on treatment and 110 pts (72%) discontinued, most commonly due to: disease progression (31%), AEs (14%), death (10%), and transplant (8%). For the EE set (123 pts), the median age was 71 y (range: 32–87) with a median number of prior therapies of 2 (1–7). The ORR was 46% with a median duration of ORR of 11.7 months. Notably, the CR + CRh rate was 33% including 30% of pts in CR. The median duration of CR + CRh was not reached (NR) but found to be 13.8 months based on a sensitivity analysis when HSCT or relapse was deemed end of response. Of responders who were transfusion-dependent at baseline, 56-day platelet transfusion independence (TI) and RBC TI were gained by 100% and 83%, respectively, of pts who achieved CR + CRh, and by 56% and 50% who did not. The median OS was 10.5 months. For patients with CR + CRh, the median OS was NR and the estimated 18-month OS was 87%; the median OS for non-CR/CRh responders was 15.0 months (Figure). TEAEs in ≥25% of pts were: nausea (38%), constipation (25%), and leukocytosis (25%). Grade 3/4 all-causality AEs in >10% of pts were: febrile neutropenia (20%), anemia (19%), thrombocytopenia (16%), and neutropenia (13%). TEAEs of QTc prolongation (all grades) were reported in 13 pts (8.5%) with one grade 3 event in 1 pt (<1%). No events led to dose reduction or discontinuation. Hepatobiliary TEAEs associated with liver enzyme abnormalities (all grades) were reported in 32 pts (21%) with grade 3/4 events in 16 pts (10%)/3 pts (2%). Most pts (n=25) had no dose modification or continued after a rechallenge; 7 pts with grade 3/4 events discontinued treatment (4 pts after positive rechallenge). There were no Hy's law cases. Investigator-assessed IDH1 differentiation syndrome (any grade) was observed in 21 pts (14%); most cases resolved with treatment interruption, dexamethasone, and/or supportive treatment; one case was fatal; 19 pts had concomitant leukocytosis.

Figure: Overall Survival by Response Category



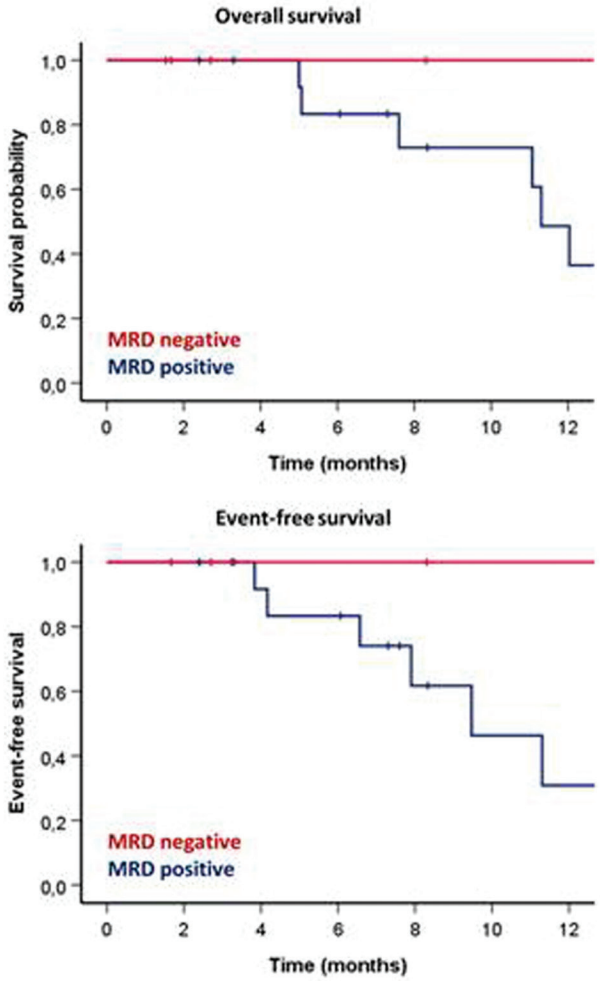
Summary/Conclusion: Olutasidenib induced durable CRs in a subset of high-risk R/R m*IDH1* AML pts. TI was achieved in all response groups, particularly in those achieving CR. Clinical benefit, as evidenced by DOR and OS, extended to pts who responded but didn't achieve CR/CRh. A favorable tolerability profile was observed; additional analyses of safety and efficacy will be presented.

S139 FLAVIDA CHEMOTHERAPY INDUCES MRD-NEGATIVE REMISSION IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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Background: Treatment options for relapsed and refractory (R/R) AML patients are limited. Here, we report safety and efficacy data of a novel combination therapy consisting of the BCL-2 inhibitor venetoclax (VEN) with fludarabine, cytarabine, and idarubicin in patients with R/R acute myeloid leukemia (AML).
Aims: To assess MRD response, event-free (EFS) and overall survival (OS) of a seven-day course of venetoclax in combination with standard intensive FLA-IDA chemotherapy (FLAVIDA) in patients with R/R AML reported to the venetoclax registry (NCT03662724; venreg.org).
Methods: In this retrospective controlled study, we included 30 patients aged 18 years or older with R/R AML previously treated with FLAVIDA. VEN dosing was 100 mg/day orally (days 1–7) due to comedication with posaconazole. Safety and efficacy analyses included all patients who received one cycle of FLAVIDA. The overall response rate (ORR) was defined by complete remission (CR) + CR with incomplete blood count recovery (CRi) + morphologic leukemia-free state (MLFS, defined as less than 5% blasts in an aspirate sample without hematologic recovery). MRD was determined by NGS-MRD with a sensitivity of 0.02% (Thol et al. Blood 2018). This study was approved by the local Ethics Review Committee in accordance with the Declaration of Helsinki. The data cut-off for this analysis was February 9th, 2021.
Results: Thirty patients with a median age of 54 years (range 19-70 years) received a maximum of 1 course FLAVIDA. 33% of patients had secondary or therapy-related AML. ELN risk was favorable, intermediate, and adverse in 13%, 57%, and 30% of patients. Patients received a median of 1 (range 1-5) prior lines of therapy and 27% of patients had prior allogeneic hematopoietic cell transplantation (alloHCT). ORR was 73% (22 of 30 patients), with 60% of patients (n=18) achieving a CR/CRi, while the 4 MLFS patients underwent alloHCT before blood count recovery and achieved CR only after alloHCT. Molecular MRD negativity was achieved in 8 of 17 (47%) responding patients with known molecular MRD markers. 75%, 71%, and 78% of patients with ELN favorable, intermediate and adverse risk disease achieved an overall response, respectively. One patient died before response assessment. Nineteen patients (63%) were consolidated with alloHCT, four received chemotherapy, three received donor lymphocyte infusions, and four patients received no additional treatment. After a median follow up of 13.3 months, median OS and EFS of the 30 patients was 12 months and 9.5 months, respectively. Median relapse-free survival in CR/CRi patients was not reached. In the 17 patients with available MRD data, the median OS and EFS were longer in patients who achieved a MRD negative response (OS: MRD- vs. MRD+: NR vs. 11.3 months, P= 0.048; EFS: MRD- vs. MRD+: NR vs. 9.5 months, P= 0.038, Figure 1). In patients who responded to FLAVIDA, the median time from the first day of chemotherapy to recovery of neutrophils (≥0.5x10^9/L) and platelets (≥50x10^9/L) was 33 (95% CI, 30-36) and 35 days (95% CI, 31-39), respectively. The most common grade 3/4 all-causality events were neutropenic fever (71%) and bacteremia (32%), while thrombocytopenia, anemia, and neutropenia were reported in all patients at nadir (100%).



Summary/Conclusion: Short-term VEN can be safely administered in combination with intensive chemotherapy in younger fit adults with AML with tolerable safety-profile, a high ORR rate of 73%, MRD negativity in 47% of responding patients, and promising survival in MRD negative patients.

New biological and translational insights in CLL

S140 CANCER STEMNESS ASSOCIATES WITH HIGH EXPRESSION LEVEL OF ROR1 AND VENETOCLAX RESISTANCE IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Although the BH3-mimetic venetoclax is highly cytotoxic for chronic lymphocytic leukemia (CLL) cells, some patients with CLL fail to clear their leukemia cells and develop progressive disease (PD) on venetoclax therapy. The persistence of measurable disease after at least 1 year of venetoclax therapy associates with the subsequent development of such drug resistance. The acquisition of BCL2 mutations has been noted in CLL cells of some patients who develop venetoclax resistance. However, such mutations apparently do not account for the only mechanism(s) of venetoclax resistance. Indeed recent studies found that CLL cells of refractory patients appeared more resistant to the cytotoxic effects of venetoclax when cultured with accessory cells found in the leukemia microenvironment. Moreover, factors provided by the leukemia microenvironment, such as Wnt5a, may enhance cancer stemness, which itself may mitigate the cytotoxicity of venetoclax.
Aims: We hypothesize that Wnt5a-induced ROR1 signaling may promote cancer stemness by activating genetic programs critical for embryonic stem-cell renewal that enhance resistance to cytotoxic drugs; a corollary of this hypothesis is that inhibition of ROR1-signaling may impair the cancer-cell's capacity for self-renewal and mitigate resistance to therapy. To this end, we examined the leukemia-cell expression of ROR1 and cancer stemness of patients who developed resistance to venetoclax.
Methods: ROR1 expression levels were assessed via flow cytometry. Negative isolation of CLL cells to ≥95% purity was performed prior to RNA extraction and sequencing. Sequencing depth was at least 30 million reads per sample to assure 90-95% sensitivity in detecting variants. GFP-tagged plasmids encoding either wild-type *BCL2* or mutant forms of *BCL2* found in CLL cells of patients resistant to venetoclax were transfected into MEC1 or MEC1-ROR1 cell lines using Neon Transfection System and cells were treated with DMSO or venetoclax (5μM). After 24 hours, for each plasmid, we determined the percentage of specific venetoclax-induced apoptosis of the transfected cells by flow cytometry. Viability of ROR1-high primary CLL cells cultured in serum-free media, with or without cirmtuzumab (20 μg/mL) with or without exogenous Wnt5a (200 ng/mL) and with venetoclax at concentrations ranging from 0.5nM to 4nM, was determined at 16h.
Results: We found that the CLL cells of six patients who developed resistance to venetoclax each used unmutated immunoglobulin heavy-chain-variable region genes (IGHV) and had high-level expression of ROR1 and a high-degree of cancer-stemness that increased after a year or more of venetoclax therapy. We found that high-level expression of ROR1 associates with cancer-stemness independent of IGHV mutation status or therapy. Transfection of the CLL-cell-line MEC1 to express *ROR1* enhanced its cancer-stemness and resistance to venetoclax, even when made to express mutant forms of *BCL2* found in CLL cells of patients resistant to venetoclax. Treatment of ROR1$^+$ CLL cells with Wnt5a enhanced venetoclax resistance, which could be offset by concomitant treatment with an anti-ROR1 mAb (UC-961, cirmtuzumab) that is capable of blocking Wnt5a-induced ROR1-signaling.
Summary/Conclusion: Collectively, these studies indicate that expression of ROR1 can enhance cancer-stemness and venetoclax resistance. Because the resistance of CLL cells to venetoclax can be enhanced by WNT5a-induced ROR1 signaling, strategies targeting ROR1 may enhance the efficacy of venetoclax-based regimens and/or mitigate the risk of developing PD on venetoclax therapy.

S141 SKEWED PRIMARY ANTIGEN-SPECIFIC RESPONSES AND CHROMATIN REMODELING OF T CELLS IN A COMBINED OT-I/TCL-1 ADOPTIVE TRANSFER MODEL

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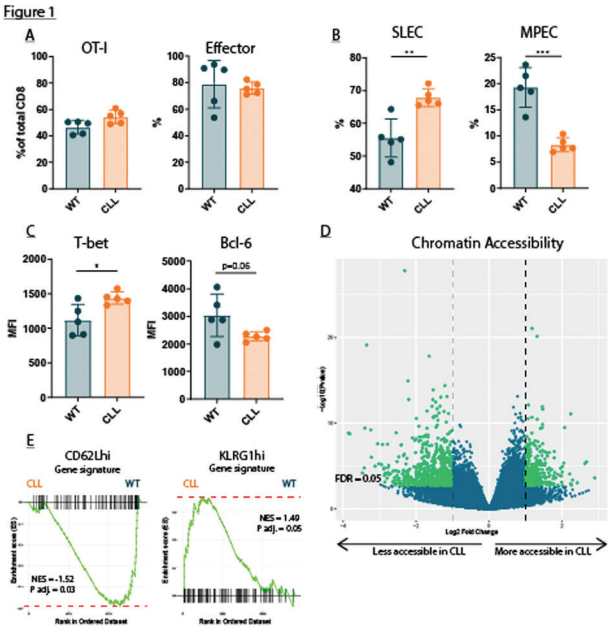
Background: Patients with chronic lymphocytic leukemia (CLL) develop an acquired T cell dysfunction during the disease, hampering efficacy of autologous-based T cell therapeutic strategies such as CAR-T (van Bruggen et al., 2019). Whilst the characteristics and functional capacity of these T cells can be analyzed *in vitro*, it remains to be studied how CLL affects antigen-specific T cell responses. Epigenetic features are increasingly recognized as key regulator, and therefore as therapeutic target, in the differentiation and function of T-cell subsets. By utilizing an adoptive transfer murine model of CLL that displays similar features of T cell dysfunction as in CLL patients (Hofbauer et al., 2011) we developed a model to study the impact of CLL on primary antigen-specific T cell responses.
Aims: To develop a model to study the impact of CLL on primary antigen-specific T cell responses.
Methods: Splenocytes from aged CD45.2$^+$*Eμ-T cell leukemia-1* (*TCL-1*) mice were adoptively transferred into wild-type (WT) mice to initiate CLL (CLL mice). Upon full CLL development, CLL mice and WT mice were injected with 50.000 OT-I splenocytes followed by infection with mCMV-OVA. At day 7 after infection the mice were killed and

spleen, liver and blood samples were analyzed by Flow Cytometry. In addition, 50,000 splenic OT-I cells were FACS-sorted and Assay for Transposase Accessible Chromatin (ATAC)-libraries were generated for sequencing.

Results: Seven days post-infection the percentages of total OT-I cells ($CD45.1^+CD8^+$) and OT-I effector cells ($CD62L^-CD44^+$) were not different between CLL and WT mice, indicating that the magnitude of response was not affected by CLL (Fig 1A). However, within these effector cells, CLL induced skewing towards short-lived effector cells (SLEC; $KLRG1^+CD127^-$) and a lower proportion of effector cells were of a memory precursor (MPEC; $KLRG1^-CD127^+$) phenotype in CLL compared to WT mice (Fig 1B). This was associated with increased expression of the effector-related transcription factor T-bet and reduced expression of the memory-related transcription factor Bcl-6 (Fig 1C).

Extensive chromatin remodeling of the OT-I cells was seen in CLL mice with > 3000 differentially accessible regions (Fig 1D). Among the regions with lower chromatin accessibility were memory associated genes such as *Bach2*, *Tcf7* and *Ccr7*, whilst effector-associated genes such as *Klrg1* and *Ifng* showed more accessible chromatin in CLL mice compared to WT. Accordingly, gene set enrichment analysis revealed enrichment of a $KLRG1^{hi}$ core gene signature (Johnnidis et al., 2021) in CLL and enrichment of a $CD62L^{hi}$ core gene signature (Johnnidis et al., 2021) in WT mice (Fig 1E).

Finally, we performed a restimulation of splenic OT-I cells with OVA-peptide *in vitro*. A decrease of effector cytokine production and degranulation was observed in CLL mice derived OT-I cells, indicating reduced functionality and memory capability upon restimulation.



Summary/Conclusion: These results suggest a CLL-antigen independent effect on an acute antigen-specific immune response, driving T cells towards a skewed and functionally impaired effector phenotype, impairing long-lived early memory formation. The altered chromatin accessibility indicates that presence of CLL majorly affects the epigenome of T cells and future studies will unravel the reversibility of these profiles and the potential of the T cells to regain their normal function.

S142 FOXO1-GAB1 AXIS REGULATES HOMING CAPACITY AND TONIC AKT ACTIVITY IN CHRONIC LYMPHOCYTIC LEUKEMIA: NOVEL THERAPEUTIC TARGET

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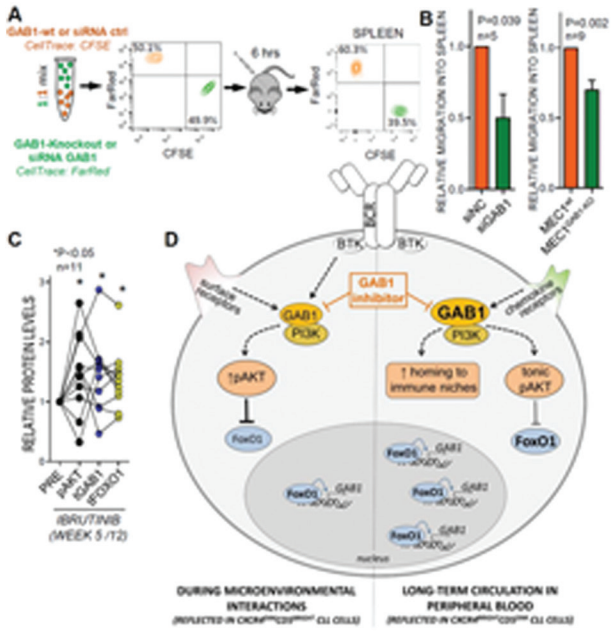
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Background: CLL cell recirculation between peripheral blood and immune niches plays an important role in CLL biology. However, it remains largely unknown how precisely CLL cells regulate their homing or how they balance survival in peripheral blood and the decision to return to immune niches.

Aims: We aim to identify and functionally characterize novel regulators of CLL cell migration.

Methods: We performed transcriptome profiling (RNAseq, Illumina) of CXCR4/CD5 intraclonal CLL cell subpopulations (n=20). GAB1 function was investigated by in vitro migration assays and in vivo migration in NSG mice (*GAB1*-knockout MEC1 cells or siRNA transfected CLL cells). The adaptation to BCR inhibitors was analyzed in CLL samples obtained before and during ibrutinib therapy (pre vs. week 5-12, n=22).

Results: CXCR4/CD5 subpopulations have been suggested as a model distinguishing CLL cells ready to re-enter immune niches ($CXCR4^{bright}CD5^{dim}$) versus recent emigrants from lymph nodes ($CXCR4^{dim}CD5^{bright}$) (Calissano et al. 2011). Indeed, intravenous injection of sorted CXCR4/CD5 subpopulations into NSG mice revealed increased migration capacity of $CXCR4^{bright}CD5^{dim}$ cells into the spleen (n=6, P=0,02). Analysis of CXCR4/CD5 subpopulations by RNAseq (n=20) identified 147 migration-related differentially expressed genes, among which we noted upregulation of *GAB1* (2-fold) in $CXCR4^{bright}CD5^{dim}$ cells. GAB1 has been previously suggested as a cell migration regulator in non-immune cells (Vasyutina et al. 2005). GAB1-knockout in MEC1 B cells largely inhibited their migration capacity towards chemokines SDF1, CXCL13, or conditioned media produced by bone marrow stromal cells (CM^{hMSC}). Similar results were obtained with siRNA against *GAB1* in CLL cells (all P<0.01). Importantly, *GAB1* knockout or silencing led to clearly impaired migration of malignant B cells to the spleen of NSG mice (P<0.05, n=14; Fig.A,B). Treating cells with SDF1, CXCL13, or CM^{hMSC} led to rapid (within minutes) GAB1 phosphorylation at activating tyrosines, suggesting that GAB1 is involved in response to multiple soluble factors. We have also identified another GAB1 function in the maintenance of "tonic" AKT phosphorylation via PI3K. Next, we demonstrated that transcription factor FoxO1 induces GAB1 by direct binding to its promotor. Altogether, increased FoxO1/GAB1 levels in $CXCR4^{bright}CD5^{dim}$ CLL cells are contributing to balancing CLL cell survival and their decision to migrate into the immune niches. Notably, administration of ibrutinib therapy in CLL patients induces FoxO1-GAB1, which leads to recovery of phospho-AKT within several days-weeks on ibrutinib (Fig.C, n=11). This "compensatory" AKT activation allows CLL survival but can be therapeutically targeted by novel GAB1 inhibitors tested herein. GAB1 inhibitors can be used to induce apoptosis, inhibit CLL migration, basal AKT activity, and adaptive AKT activation during ibrutinib therapy.



Summary/Conclusion: We described a novel FoxO1/GAB1-dependent regulatory mechanism of CLL homing and maintenance mechanism for "tonic" AKT signaling activity in an intraclonal CXCR4^{bright}CD5^{dim} CLL subpopulation (Fig.D). We showed for the first time that during ibrutinib therapy, CLL cells sustain AKT activity via the FoxO1-GAB1 axis and that this could be targeted by novel GAB1 inhibitors.

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S143 CLINICAL IMPACT OF RECURRENT GENE MUTATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: A RETROSPECTIVE, MULTI-CENTER COHORT STUDY BY ERIC, THE EUROPEAN RESEARCH INITIATIVE ON CLL, IN HARMONY

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Background: The introduction of next-generation sequencing (NGS) rapidly uncovered the genomic landscape of chronic lymphocytic leukemia (CLL). Using whole-genome and/or exome sequencing, a limited number of recurrently mutated genes was observed in more than 10% of patients, while a very long tail comprising hundreds of genes mutated only in a fraction of patients (<5%) has been demonstrated. Several of the more frequent gene mutations have been linked to worse outcomes with shorter time-to-first-treatment (TTFT) and overall survival.

Aims: To assess the prognostic strength of recurrent gene mutations, we collected a large, multi-center cohort including 4,674 well-characterized CLL patients [median age at diagnosis, 64.5 years; male/female, n=2,962 (63%)/n=1,712 (37%); Binet stage A (n=3,369, 74%), B (n=827, 18%), and C (n=387, 8%); IGHV-mutated (n=2,498, 56%) and IGHV-unmutated (n=1,927, 44%); del(13q) only (n=1,868, 41%), trisomy 12 (n=571, 13%), del(11q) (n=503, 11%), and del(17p) (n=249, 5.5%); treated (n=2,745, 59%) and untreated (n=1,929, 41%)].

Methods: We performed NGS and/or Sanger sequencing of 9 genes (*BIRC3, EGR2, NFKBIE, MYD88, NOTCH1, POT1, SF3B1, TP53,* and *XPO1*) on pre-treatment samples in order to study their clinical impact in CLL.

Results: Overall, mutations in any of these genes were detected in 1,720 of 4,674 patients (36.8%, using a variant allele frequency cutoff of 5% for NGS), while the remaining patients were wildtype; two mutations were seen in 361 patients (7.7%) and three or more mutations in 58 patients (1.2%). The mutation frequency for the individual genes was *TP53* (10.4%, including *TP53* mutations and/or del(17p)), *NOTCH1* (10.1%), *SF3B1* (9.3%), *XPO1* (3.9%), *POT1* (3.8%), *NFKBIE* (3.7%), *BIRC3* (3.0%), *EGR2* (2.5%) and *MYD88* (2.5%; Figure 1A). We observed that certain gene mutations appeared almost mutually exclusive, such as *BIRC3* and *SF3B1* mutations (10 *BIRC3*^{mut}/433 (2.3%) *SF3B1*^{mut} cases), and *TP53* aberrations and *XPO1* mutations (18 *XPO1*^{mut}/488 (3.7%) *TP53*^{abn} cases) or *BIRC3* mutations (14 *BIRC3*^{mut}/488 (2.9%) *TP53*^{abn} cases). Except for *MYD88*, mutations in each of the investigated genes were associated with significantly shorter TTFT in univariate analysis. On multivariable analysis (including all genes, unmutated IGHV genes, Binet stage B/C, age > median at diagnosis and male gender), *SF3B1* (Hazard Ratio 1.58; p<0.001), *EGR2* (HR 1.39; p=0.003), *XPO1* (HR 1.26; p=0.006), *BIRC3* mutations (HR 1.25; p=0.031) and *TP53* aberrations (HR 1.20; p=0.004), along with Binet stage B/C (HR 3.73; p-value <0.001) and unmutated IGHV genes (HR 2.95; p<0.001), remained as independent factors for shorter TTFT. As earlier studies have indicated different prognostic importance of genetic aberrations in IGHV-mutated (M-CLL) and IGHV-unmutated CLL (U-CLL), we next studied the impact of gene mutations in relation to IGHV gene mutation status. While *TP53* aberrations, *SF3B1* (Figure 1B) and *BIRC3* mutations were associated with a worse outcome in both U-CLL and M-CLL, *NOTCH1, POT1* and *XPO1* mutations were only linked to a worse outcome in M-CLL, whereas *EGR2* mutations correlated with a poor outcome only in U-CLL.

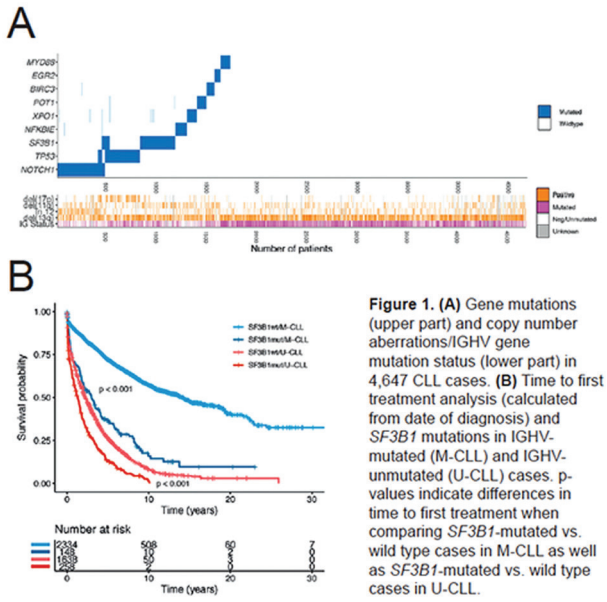


Figure 1. (A) Gene mutations (upper part) and copy number aberrations/IGHV gene mutation status (lower part) in 4,647 CLL cases. **(B)** Time to first treatment analysis (calculated from date of diagnosis) and *SF3B1* mutations in IGHV-mutated (M-CLL) and IGHV-unmutated (U-CLL) cases. p-values indicate differences in time to first treatment when comparing *SF3B1*-mutated vs. wild type cases in M-CLL as well as *SF3B1*-mutated vs. wild type cases in U-CLL.

Summary/Conclusion: Based on these results, we conclude that *SF3B1, EGR2, XPO1* and *BIRC3* mutations independently predicted short

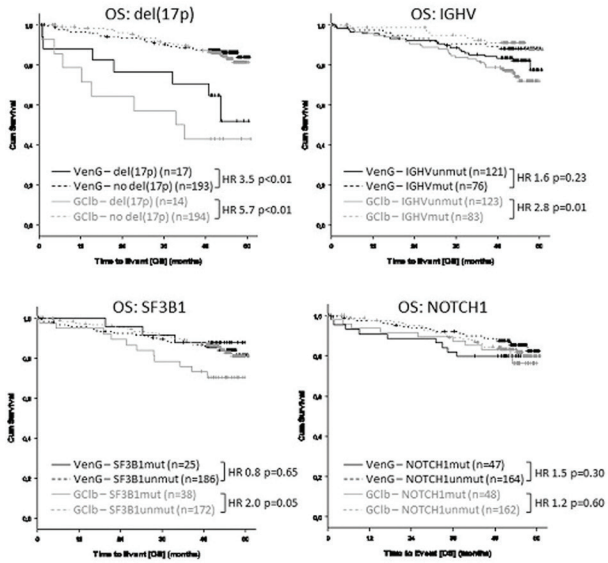
TTFT and should be considered for extended molecular testing in CLL. However, considering the different impact of gene mutations in M-CLL and U-CLL, the IGHV mutation status must be taken into account when constructing future prognostic models including recurrent gene mutations.

S144 GENETIC MARKERS AND OUTCOME IN FRONT LINE OBINUTUZUMAB PLUS CHLORAMBUCIL OR VENETOCLAX - UPDATED ANALYSIS OF THE CLL14 TRIAL

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Background: In 2019 we provided initial analyses of the prognostic and predictive value of genomic aberrations, IGHV mutation status and gene mutations in the CLL14 trial comparing obinutuzumab+chlorambucil (GClb) vs. obinutuzumab+venetoclax (VenG) in 432 patients (1:1) with CIRS>6 and/or creatinine clearance < 70 ml/min.
Aims: This update includes a) an extended follow-up at a median of 52 months, b) assessment of the prognostic value of minor mutations with a variant allele fraction (VAF) of 2-10% c) analysis of 113 samples at relapse for acquired gene mutation in candidate genes and specific resistance mutations such as BCL2 G101V.
Methods: Genomic aberrations were assessed by FISH, IGHV by sequencing with a threshold of 98% homology and mutations via amplicon-based targeted NGS for *TP53*, *NOTCH1*, *SF3B1*, *ATM*, *MYD88*, *FBXW7*, *POT1*, *BIRC3*, *XPO1*, *NFKBIE*, *EGR2*, *RPS15* and *BCL2* in 421 of 432 (94%) patients of the full trial cohort at baseline.
Results: The prevalence of genomic aberrations considering the hierarchical model was del(17p) 7%, del(11q) 18%, +(12q) 18% and del(13q) single 35%. IGHV was unmutated in 60% of patients. The prevalence of gene mutations with a VAF>10% was *NOTCH1* 23% (exon 34, 3'UTR), *SF3B1* 15%, *ATM* 13%, *TP53* 10%, *XPO1* 6%, *RPS15* 5%, *POT1* 5%, *BRAF*, *BIRC3*, *NFKBIE*, *EGR2*, *MYD88* and *FBXW7* (all <5%). Minor mutations (VAF 2-10%) occurred in *BIRC3* with an incidence of 5%, *NOTCH1* 5%, *SF3B1* 5%, *ATM* 4% and *TP53* 3%.
At a median follow-up of 52 months, 199 events for PFS and 75 for OS occurred in the ITT population.
VenG was superior to GClb regarding PFS in most genetic subgroups including del(17p) and mutated and unmutated IGHV (p<0.001).
For GClb del(17p) (HR 3.2, p<0.001), del(11q) (HR 1.84, p<0.01) and mutations in *ATM* (HR 1.8, p=0.01), *BIRC3* (HR 3.0, p<0.01), *NOTCH1* (HR 1.7, p<0.01) and *SF3B1* (HR 1.6, p=0.03) were associated with short PFS, while for VenG del(17p) (HR 3.2, p=0.001) and mutated *TP53* (HR 2.4, p<0.01) remained prognostic factors. Minor *TP53* mutations did not affect outcome, however, minor mutations in *NOTCH1* reduced PFS with GClb significantly (HR 2.1, p=0.02). Unmutated IGHV was prognostic with GClb (HR 3.1, p<0.001) and VenG (HR 2.1, p=0.02) treatment.
Overall survival (OS) was shorter with del(17p) and *TP53* mutation in both treatment arms (GClb: HR 5.7 and HR 3.1, VenG: HR 3.5 and HR 3.0, all p<0.01) and with mutated *SF3B1* (HR 2.0, p=0.05) and unmutated IGHV (HR 2.8, p=0.01) in the GClb arm, while none of the other factors were significantly associated with OS. In multivariate analysis, GClb therapy, high risk for tumor lysis (TLS), IGHV mutation status, del(17p), complex karyotype and *BIRC3* mutations were independent prognostic factors for PFS, while age, b2MG and del(17p) retained independent significance for OS.
Comparative analysis of 88 paired samples at baseline and relapse after GClb revealed acquisition of high risk variants such as *TP53* (n=4), *BIRC3* (5), *SF3B1* (3) and *RPS15* (1). Among 25 paired samples before and after VenG, a single variant was found each in *TP53* and *BIRC3*. Of note, none of the 25 relapse samples from the VenG treatment arm had acquired mutations in BCL2 at a detection limit of 2% VAF.



Summary/Conclusion: At a median follow up of 52 months, IGHV mutation status and del(17p) proved to be prognostic with VenG and GClb, while none of the other prognostic factors besides *TP53* affected outcome with VenG. After time limited VenG no BCL2 resistance mutations were identified at relapse supporting re-treatment concepts.

Clinical trials with targeted therapies in CLL

S145 FIRST RESULTS OF A HEAD-TO-HEAD TRIAL OF ACALABRUTINIB VERSUS IBRUTINIB IN PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib is more selective than ibrutinib, which may improve tolerability.
Aims: We conducted an open-label, randomized, noninferiority, phase 3 trial to compare acalabrutinib and ibrutinib in patients with previously treated chronic lymphocytic leukemia (CLL).
Methods: Patients with previously treated CLL who had del(17p) or del(11q) by central lab were randomized to receive acalabrutinib 100 mg orally twice daily or ibrutinib 420 mg orally once daily until progression or unacceptable toxicity. Randomization was stratified by del(17p) status, Eastern Cooperative Oncology Group performance status (2 vs ≤1), and number of prior therapies (1–3 vs ≥4). The primary endpoint was progression-free survival as assessed by independent review committee; secondary endpoints of all grade atrial fibrillation, grade ≥3 infection, Richter transformation, and overall survival were assessed in hierarchical order. Informed consent was obtained from all patients prior to trial enrollment.

Results: A total of 533 patients (acalabrutinib, n=268; ibrutinib, n=265) were randomized. Patients had a median age of 66 years and had received a median of 2 prior therapies; 45.2% of patients had del(17p), and 64.2% had del(11q). At a median follow-up of 40.9 months (range, 0.0–59.1), acalabrutinib demonstrated noninferiority to ibrutinib, with a median progression-free survival of 38.4 months in both arms (hazard ratio [HR], 1.00; 95% CI, 0.79–1.27). Acalabrutinib was statistically superior to ibrutinib in the incidence of all-grade atrial fibrillation (9.4% vs 16.0%; *P*=0.023). Among the other secondary endpoints, incidences of grade ≥3 infection (acalabrutinib: 30.8%, ibrutinib: 30.0%) and Richter transformation (acalabrutinib: 3.8%, ibrutinib: 4.9%) were comparable between the treatment arms. Median overall survival was not reached in either arm (HR, 0.82; 95% CI, 0.59–1.15), with 63 (23.5%) deaths in the acalabrutinib arm and 73 (27.5%) in the ibrutinib arm. Among any-grade adverse events occurring in ≥20% of patients in either arm, acalabrutinib was associated with a lower incidence of hypertension (9.4%, 23.2%), arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). Adverse events led to treatment discontinuation in 14.7% of acalabrutinib-treated patients compared with 21.3% of ibrutinib-treated patients. Among any-grade events of clinical interest, cardiac events, hypertension, and bleeding events were less frequent with acalabrutinib (Table).

Table. Selected events of clinical interest

	Acalabrutinib (n=266)		Ibrutinib (n=263)	
Events, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Atrial fibrillation[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events[c]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Second primary malignancies excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes preferred terms of atrial fibrillation and atrial flutter
[b]Includes preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased
[c]Any hemorrhagic event that was serious, grade ≥3, or a central nervous system hemorrhage (any grade)

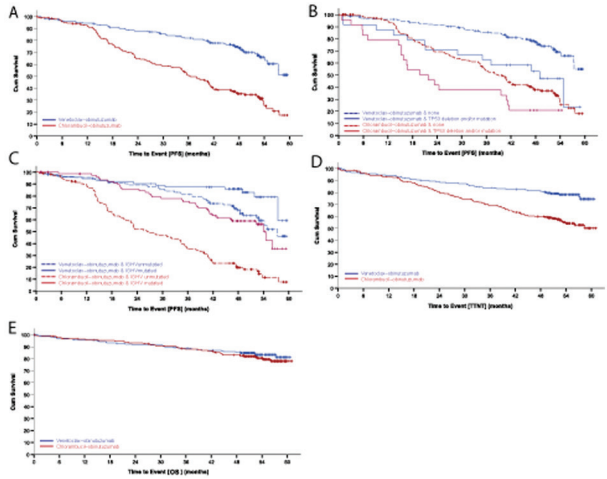
Summary/Conclusion: In this first head-to-head trial of BTK inhibitors in patients with previously treated CLL, acalabrutinib demonstrated non-inferior progression-free survival with less cardiotoxicity and fewer discontinuations due to adverse events compared with ibrutinib.

S146 VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 4-YEAR FOLLOW-UP ANALYSIS OF THE RANDOMIZED CLL14 STUDY

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Background: The CLL14 study showed significant improvement of progression-free survival (PFS) with venetoclax-obinutuzumab (Ven-Obi) as compared to chlorambucil-obinutuzumab (Clb-Obi) in patients (pts) with previously untreated chronic lymphocytic leukemia (CLL) and coexisting conditions. High rates of undetectable minimal residual disease (uMRD) have been observed after one year fixed-duration treatment with Ven-Obi, suggesting deep remissions and feasibility of the fixed-duration concept with targeted agents for CLL.
Aims: The aim of this report is to provide updated efficacy and safety data from the ongoing follow-up of the CLL14 study with now all pts being off study treatment for at least 3 years.
Methods: Pts with previously untreated CLL and coexisting conditions were randomized 1:1 to receive 12 cycles of venetoclax with 6 cycles of obinutuzumab or 12 cycles of chlorambucil with 6 cycles of obinutuzumab. Primary endpoint was investigator-assessed PFS. Key secondary endpoints were safety, response rates, rates of minimal residual disease (MRD)(measured every 3-6 months up to 5 years after last patient enrolment) and overall survival. Follow-up is ongoing, but all pts are off study treatment. This trial was registered with ClinicalTrials.gov, number NCT02242942.
Results: Of the 432 enrolled pts, 216 were randomly assigned to receive Ven-Obi and 216 to receive Clb-Obi. After a median follow-up of 52.4 months (interquartile range 49.5-56.2), PFS continued to be superior for Ven-Obi as compared to Clb-Obi (median not reached (nr) vs. 36.4 months; hazard ratio [HR] 0.33 [95% CI 0.25-0.45], p<0.0001)(Fig A). At 4 years after randomization, the estimated PFS rate was 74.0% in the Ven-Obi arm and 35.4% in the Clb-Obi arm. This improvement was observed across all clinical and biological risk groups, including pts with TP53 mutation/deletion (4-year PFS 53.0% vs 20.8%) and unmutated IGHV status (4-year PFS 68.0% vs 19.8%)(Fig B,C). Overall, 35 disease progressions in the Ven-Obi arm have been observed, compared to 122 in the Clb-Obi arm. Time to next treatment was significantly longer in the Ven-Obi arm (4-year TTNT 81.1% vs 59.9%; HR 0.46, 95% CI [0.32-0.65], p<0.0001)(Fig D). The majority of pts received and responded to BTK inhibitor monotherapy as a second-line treatment after progressive disease in both arms (57.1% in Ven-Obi arm, 55.6% in Clb-Obi arm).
Assessment of MRD by next-generation sequencing in peripheral blood 30 months after the end of treatment (EoT) showed that 26.9% of pts in the Ven-Obi arm still had uMRD ($<10^{-4}$), 21.8% had low (L)-MRD ($\geq 10^{-4}$ and $< 10^{-2}$) and 13.4% high (H)-MRD ($\geq 10^{-2}$), compared to 3.2% uMRD, 8.8%% L-MRD, 28.2% H-MRD in the Clb-Obi arm.
No difference in overall survival has been observed between the Ven-Obi and Clb-Obi arm; at 4 years 85.4% pts were alive in the Ven-Obi arm and 83.1% in the Clb-Obi arm (HR 0.85 [0.54-1.35], p=0.49)(Fig E). Second primary malignancies were reported in 40 (18.9%) pts in the Ven-Obi arm and 30 (14.0%) in the Clb-Obi arm. No new safety signals were observed.



Summary/Conclusion: The four-year follow-up confirms the superior efficacy with longer PFS and deep remissions after fixed-duration Ven-Obi compared to Clb-Obi. The majority of pts remains without relapse three years after completing Ven-Obi treatment. Although adverse features such as TP53 mutation/deletion were not fully mitigated, fixed-duration Ven-Obi continues to be an effective treatment for all pts with CLL and with coexisting conditions.

S147 PRIMARY ANALYSIS OF THE FIXED-DURATION COHORT FROM THE PHASE 2 CAPTIVATE STUDY OF FIRST-LINE IBRUTINIB + VENETOCLAX FOR CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Background: Ibrutinib (Ibr) + venetoclax (Ven) have synergistic and complementary antitumor activity that mobilizes and clears chronic lymphocytic leukemia (CLL) cells from multiple disease compartments, providing a rationale to evaluate time-limited treatment. We previously reported results from the Minimal Residual Disease (MRD) cohort of the multicenter phase 2 CAPTIVATE study of first-line Ibr + Ven in patients with CLL/small lymphocytic lymphoma (SLL). In that cohort, undetectable MRD (uMRD) was achieved in over two-thirds of patients (pts) with 12 cycles of Ibr + Ven; 30-month progression-free survival (PFS) rates were ≥95% irrespective of subsequent randomized treatment (Wierda, ASH 2020).
Aims: Here we present results from the fixed-duration (FD) cohort, evaluating fixed-duration treatment with Ibr + Ven.
Methods: Eligible patients were aged ≤70 y with previously untreated CLL/SLL. Patients received 3 cycles of Ibr lead-in followed by 12 cycles of Ibr + Ven (Ibr 420 mg/d orally; Ven ramp-up to 400 mg/d orally). The primary endpoint was complete response (CR) rate, including CR with incomplete recovery (CRi); secondary endpoints were overall response rate (ORR), duration of response, uMRD rate ($<10^{-4}$ by 8-color flow cytometry), PFS, overall survival (OS), tumor lysis syndrome (TLS) risk reduction, and adverse events (AEs).
Results: Overall,159 patients were enrolled; median age was 60 y. High-risk features included del(17p)/*TP53* mutation (17%), del(11q) (18%), complex karyotype (19%), and unmutated IGHV (56%). 147/159 (92%) patients completed planned treatment with Ibr, and 149/159 (94%) patients completed planned treatment with Ven. Median time on study was 27.9 months (range 0.8–33.2). With fixed-duration Ibr + Ven, 55% of patients in the overall population achieved a CR; the CR rate was consistent across high-risk subgroups. Of 88 patients who achieved CR, durable CR (duration ≥1 y from initial documentation of response) was confirmed in 78 patients (89%); an additional 9 patients (10%) were not yet evaluable with <1 y of post-CR follow-up and 1 pt died 7 months after achieving a CR. ORR was 96%. Best MRD response of uMRD was achieved in peripheral blood (PB) of 77% of patients and in bone marrow (BM) of 60% of patients. 24-month PFS and OS rates were 95% and 98%, respectively. Similar results were achieved in patients without del(17p) (n=136) (Table). In patients with del(17p)/*TP53* mutation (n=27), the CR rate was 56%, uMRD rates were 81% (PB) and 41% (BM), and the 24-month PFS rate was 84% (95% CI 63%–94%). Of 34 patients with high baseline TLS risk based on tumor burden, 32 (94%) shifted to medium or low risk after Ibr lead-in; no TLS occurred. AEs were primarily grade 1/2. The most common grade 3/4 AEs were neutropenia (33%), hypertension (6%), and decreased neutrophil count (5%). AEs led to discontinuation of Ibr in 4% of patients and to discontinuation of Ven in 2% of patients.

Table. Efficacy outcomes

	Patients without del(17p) n=136	All patients N=159
CR/CRi, n (%)	76 (56)	88 (55)
Durable CR/CRi ≥1 y, n/N (%)*	66/76 (87)	78/88 (89)
ORR, n (%)	130 (96)	153 (96)
uMRD in PB, n (%)	104 (76)	122 (77)
uMRD in BM, n (%)	84 (62)	95 (60)
24-month PFS rate, % (95% CI)	96 (91-98)	95 (90-97)
24-month OS rate, % (95% CI)	98 (93-99)	98 (94-99)

*Denominator is patients with CR/CRi.

Summary/Conclusion: First-line Ibr + Ven is an all-oral, once-daily, chemotherapy-free fixed-duration regimen that provides deep, durable responses in patients with CLL/SLL. Overall, CR, uMRD rates, PFS, and OS appear favorable, and benefit was observed regardless of genomic high-risk features. No new safety signals were identified, and the safety profile of Ibr + Ven was consistent with known safety profiles of each agent.

S148 ACALABRUTINIB ± OBINUTUZUMAB VS OBINUTUZUMAB + CHLORAMBUCIL IN TREATMENT-NAÏVE CHRONIC LYMPHOCYTIC LEUKEMIA: ELEVATE-TN 4-YEAR FOLLOW-UP

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Background: Early results from ELEVATE-TN (NCT02475681) at a median follow-up of 28.3 months demonstrated superior efficacy of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) (Sharman et al. Lancet 2020;395:1278-91).
Aims: To report the updated efficacy and safety results from the ELEVATE-TN study after a median follow-up duration of 4 years.
Methods: Patients received A±O or O+Clb. Crossover to A monotherapy was permitted in patients who progressed on O+Clb. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated. Informed consent was obtained from all patients prior to trial enrollment.
Results: A total of 535 patients (A+O, n=179; A, n=179; O+Clb, n=177) were randomized. The median patient age was 70 years; 63% of patients had unmutated IGHV and 9% had del(17p). At a median follow-up of 46.9 months (range, 0.0–59.4; data cutoff: Sept 11, 2020), the median PFS was not reached (NR) for A+O and A patients versus 27.8 months for O+Clb patients (both $P<0.0001$). In patients with unmutated IGHV, the median PFS was NR (A+O and A) versus 22.2 months among O+Clb patients (both $P<0.0001$). In patients with del(17p), the median PFS was NR (A+O and A) versus 17.7 months for O+Clb ($P<0.005$). Estimated 48-month PFS rates were 87% for A+O, 78% for A, and 25% for O+Clb. Median OS was NR in any treatment arm with a trend towards significance in the A+O group (A+O vs O+Clb, $P=0.0604$); estimated 48-month OS rates were 93% (A+O), 88% (A), and 88% (O+Clb). ORR was significantly higher with A+O (96.1%; 95% CI 92.1–98.1) versus O+Clb (82.5%; 95% CI 76.2–87.4; $P<0.0001$); ORR with A was 89.9% (95% CI 84.7–93.5; $P=0.035$ vs O+Clb). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates were higher with A+O (26.8%/3.9%) versus O+Clb (12.4%/0.6%); 10.6%/0.6% had CR/CRi with A. Common adverse events (AEs) and AEs of interest are shown in the Table. Overall treatment discontinuation rates were 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb); the most common reasons were AEs (12.8%, 12.3%, 14.7%, respectively) and progressive disease (4.5%, 7.8%, 1.7%). Most patients (77.4%) completed O+Clb treatment.

	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any grade	G≥3	Any grade	G≥3	Any grade	G≥3
Common AEs (in ≥30% of patients [any grade] in any group), n (%)						
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	71 (39.9)	2 (1.1)	68 (38.0)	2 (1.1)	20 (11.8)	0
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	76 (45.0)	70 (41.4)
Nausea	41 (23.0)	0	41 (22.9)	0	53 (31.4)	0
Infusion-related reaction	25 (14.0)	5 (2.8)	0	0	68 (40.2)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0

Summary/Conclusion: With a median follow-up of 46.9 months (~4 years) in the ELEVATE-TN study, the efficacy and safety of A+O and A monotherapy was maintained, with an increase in CR since the interim analysis (from 21% to 27% [A+O] and from 7% to 11% [A]) and low rates of discontinuation.

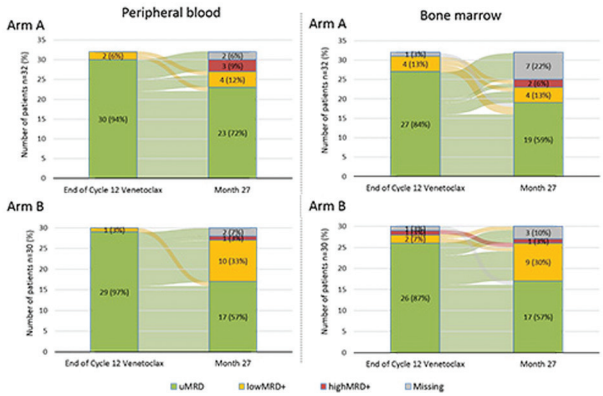
S149 MRD-GUIDED OR FIXED 12 CYCLES OF VENETOCLAX CONSOLIDATION AFTER VENETOCLAX PLUS OBINUTUZUMAB TREATMENT IN FIRST-LINE FCR UNFIT PATIENTS WITH CLL: PRIMARY ENDPOINT ANALYSIS OF THE HOVON 139/GIVE TRIAL

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Background: Fixed duration treatment of chronic lymphocytic leukemia (CLL) patients with venetoclax (V) combined with anti-CD20 antibody both in 1st-line (12 cycles) and relapsed / refractory (RR) (24 cycles) results in high rates of undetectable minimal residual disease (uMRD) and prolonged PFS. The benefit of consolidation treatment in 1st-line patients after Obinutuzumab (O)-V is currently unknown.
Aims: Primary endpoint analysis of a phase 2 randomized trial in 1st-line FCR unfit CLL patients treated with standard O-V, randomized to standard or MRD-based addition of V for 12 cycles.
Methods: FCR-unfit treatment naïve CLL patients with treatment indication according to IWCLL were eligble. Treatment consisted of 4 treatment phases: two cycles of O; 6 cycles of O+V (IND-1); 6 cycles V (IND-2); and a 1:1 randomization phase: maintenance with 12 cycles of V irrespective of MRD (arm A) or MRD guided V maintenance (treatment limited to patients with no uMRD after IND-2 with 12 cycles of V, arm B). MRD was centrally assessed by flow cytometry in bone marrow (BM) after 12 and 24 cycles and in blood (PB) at screening, cycle 6 and 12 and every 3 months thereafter until month 27. Complex genotype (CG), ≥ 3 CNV, was assessed by CGH-array. The primary endpoint was uMRD (<1:10.000 leukocytes by flowcytometry) in BM and no progression after a maximum of 24 cycles of V.

Results: In total, 70 patients were enrolled, of whom 3 were post-hoc excluded because of not fulfilling the diagnosis of CLL. Baseline characteristics were 70% male, median age 71 years (range 57-89 years), 49% unmutated IgVH, 13% del 17p/TP53 and 22% CG. The primary endpoint was reached in 53% and 57% of patients in arm A and arm B, respectively, therefore both arms reached the pre-set requirements. In PB, uMRD and no progression was established in 59% and 57% of patients, respectively. After 2 cycles of O ORR was 43% which improved to 94% (31% CR) after IND-2 (no PD). At the primary endpoint ORR was 88% (16 CR, 3 PD) in arm A versus 97% (19 CR, 1 PD) in arm B. Grade 2, 3, 4 and 5 AE were established 14, 35, 17, 1 times before randomization; 14, 6, 2, 0 times in arm A and 7, 4, 0, 0 in arm B, mainly hematological and infections. Two cycles of O reduced the TLS risk from 28 and 60% to 1 and 15% (high and medium TLS risk, respectively). O was stopped in 4 patients during IND-1 because of mainly hematologic toxicity and 4 patients stopped V, while 22 patients received G-CSF and 17 patients rasburicase. During IND-2 1 patient stopped V, while 14 patients received G-CSF. Five patients were not randomized due to death (1), refusal to continue (1) and excessive toxicity (3). Finally 62 patients underwent randomization, 32 to fixed V and 30 to MRD-guided V treatment (of whom only 2 patients received V due to no uMRD). uMRD in BM was found in 79% after IND-2; and at primary endpoint in arm A 59% and 57% in arm B. uMRD in PB was found in 88% after IND-2, and at primary endpoint 72% and 57% in arm A and arm B, respectively (Figure 1). Estimated overal survival at 48 months was 94%. MRD positive disease was not found more frequently in patients with high-risk baseline characteristics (unmutated IGVH, del17p/TP53mut, CG).



Summary/Conclusion: In this phase 2 study we confirm that treatment with O-V is well tolerated in FCR-unfit patients and both fixed duration V and MRD-guided V consolidation resulted in > 50% of patients with uMRD and without progression after a maximum of 24 cycles of V, which warrants further study of MRD-guided or fixed consolidation treatment after O-V induction.

Response, resistance and treatment-free remission in CML

S150 LOSS OF G0/G1 SWITCH GENE 2 (G0S2) IN CML PROMOTES TKI RESISTANCE BY DEREGULATING THE MITOCHONDRIAL ELECTRON TRANSPORT CHAIN.

M. Gonzalez [1,*], A. Bencomo-Alvarez [1], A. Rubio [1], S. Dang [2], C. Barreto-Vargas [3], I. Olivas [2], S. Glovier [2], J. Lara [4], D. Yan [5], A. Senina [5], J. Ahman [5], K. Varley [5], C. Mason [5], C. Eide [6], B. Druker [6], A. Eiring [1,2,4]

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Background: Chronic myeloid leukemia (CML) was turned from a fatal to a chronic disease with the use of tyrosine kinase inhibitors (TKIs) targeting BCR-ABL1. Despite these advances, clinical resistance is a problem, as TKIs do not target the CML leukemic stem cell (LSC), which are independent from BCR-ABL1 kinase activity. Microarray data on TKI-naïve versus TKI-resistant CML patients, after 12 months of therapy,

revealed that mRNA encoding G0/G1 switch gene 2 (G0S2) is downregulated in TKI resistance (>3-fold, p<0.02).
Aims: Identify the mechanism by which G0S2 is downregulated in CML and how it contributes to TKI resistance.
Methods: To assess the functional role of G0S2 in CML and TKI resistance, we used ectopic G0S2 expression and shRNA-mediated G0S2 knockdown in CML cell lines and CD34$^+$ cells from chronic phase (CP-CML) and blast phase (BP-CML) CML patients. The consequence of altered G0S2 expression was measured using colony formation assays, apoptosis assays, and subcutaneous injection into immunocompromised mice. The effect of G0S2 on mitochondrial respiration was identified with RNA sequencing (RNAseq) and metabolomics analyses.
Results: G0S2 mRNA and protein were downregulated in CML CD34$^+$ cells compared with normal cord blood CD34$^+$ cells (p=0.0043), and further downregulated in samples from BP-CML (p=0.0079) and TKI-resistant (p=0.0357) patients. Low levels of *G0S2* correlated with a worse overall survival (n=35, p=0.036) in CP-CML. We observed lower *G0S2* mRNA expression in primitive, TKI-resistant CD34$^+$38$^-$ LSCs compared with more committed CD34$^+$38$^+$ progenitor cells in CML (n=6, p<0.01), and in granulocyte-macrophage progenitors (GMPs) from CML versus normal CD34$^+$ cells (p=0.044). Loss of G0S2 expression in CML was not affected by TKI treatment, and thus occurs in a BCR-ABL1-independent manner. G0S2 ectopic expression significantly reduced colony formation of TKI-sensitive and TKI-resistant K562 cells, and in CD34$^+$ cells from both CP-CML and BP-CML patients. While ectopic G0S2 alone did not alter apoptosis, it restored imatinib-mediated apoptosis in BP-CML CD34$^+$ cells (p<0.05). Consistently, ectopic G0S2 reduced *in vivo* subcutaneous tumor growth of K562 cells injected into nude mice. ShRNA-mediated G0S2 knockdown, conversely, enhanced survival of CML cell lines in the presence and absence of imatinib. DNA bisulfite conversion and patch PCR sequencing on primary CML CD34$^+$ cells revealed that G0S2 downregulation was not due to promoter hypermethylation. Rather, ChIP-PCR revealed the presence of MYC/MAX at the *G0S2* promoter in CML, suggesting MYC-mediated transcriptional repression. Accordingly, ectopic MYC resulted in rapid downregulation of G0S2 mRNA and protein in CML cell lines. G0S2 has been shown to inhibit adipocyte triglyceride lipase (ATGL), the rate-limiting enzyme in intracellular lipolysis. However, ectopic G0S2 impaired survival even in the presence of ATGL knockdown. RNAseq and metabolomics data suggest that reduced G0S2 expression in CML results in deregulation of the mitochondrial ETC. This has implications for TKI response, as CML LSCs were shown to be more dependent on oxidative phosphorylation than their normal counterparts, which could serve as a novel target for therapy.
Summary/Conclusion: Altogether, our data suggest that MYC-mediated G0S2 downregulation contributes to TKI resistance and blastic transformation of CML. Restoring G0S2 expression could have clinical utility by reestablishing TKI sensitivity in TKI-resistant patients and altering mitochondrial metabolism.

S151 MITOCHONDRIAL DNA MUTATIONS ARE ASSOCIATED WITH RESPONSE TO IMATINIB IN CHRONIC MYELOID LEUKAEMIA PATIENTS

I. S. Pagani [1,2,3,*], C. H. Kok [3], P. Dang [3], K. Lim [2], V. A. Saunders [3], M. Hughes [3], M. M. Kutyna [3], D. K. Hiwase [4], D. T. Yeung [4], D. Thomas [2], T. P. Hughes [3], D. M. Ross [4]

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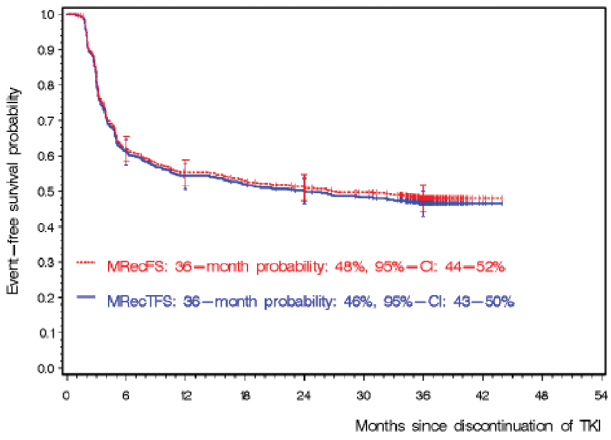
Background: More than 20% of chronic myeloid leukaemia (CML) patients are resistant to first-line therapy with tyrosine kinase inhibitors (TKIs), with some of them developing fatal blast crisis. Even when treatment is effective most patients require lifelong TKI therapy. New therapies are therefore needed. Metabolic reprogramming is one of the earliest hallmarks of cancer and the identification of deregulated metabolic pathways offers new approaches to target cancer cells. Mitochondrial (mt) metabolism, in particular, may play a key role in controlling survival and proliferation of cancer stem cells and conferring resistance to apoptosis.
Aims: We hypothesize that mtDNA mutations could affect mt function, leading to reduced respiration (oxidative phosphorylation, OXPHOS) and increased sensitivity to TKIs. The role of mutations in mitochondrial-encoded electron transport chain genes has not been elucidated in CML. Therefore, the aim of our work was to investigate the genomic landscape of mtDNA mutations in CML and their association with response to TKIs.
Methods: We sequenced the mt genome of 80 CML patients from the ALLG Tidel I and II trials. Follow-up samples after 12 months of imatinib therapy were used as the inferred germline to identify mtDNA somatic mutations at diagnosis (*Pagani IS, et al 2016*). Patients not achieving major molecular response (*BCR-ABL1* <= 0.1% IS) at 12 months were defined as poor responders (PR). The oxygen consumption rate of primary CML CD34+ cells was measured using the Seahorse XF96 analyser to evaluate OXPHOS function.
Results: We identified 142 mtDNA somatic point mutations in 31/41 (78%) good responders (GR) at diagnosis (median 3 per patient, range 1-21), and 49 mutations in 30/39 (77%) PR (median 1 per patient, range 1-3) (P=0.041). Interestingly, 4 GR patients showed hypermutated sites with a larger number of mtDNA somatic mutations (>11) than expected from the background distribution. The median variant allele frequency (VAF) was 96.6% (range 3.5-100%), with 2 patients carrying 29 homoplasmic mutations (VAF>98%). The remaining GR patients had mutations with a median VAF of 8% (range 2.1-90.8%). All mtDNA somatic point mutations found in PR were heteroplasmic (median 6.6%, range 2-87.2%). Patients with 3 or more mtDNA somatic point mutations more often achieved MMR (90% vs 68%, P=0.0038) and MR$^{4.5}$ (*BCR-ABL1*<0.0032% IS; 63% vs 37%, P=0.011) at 24 months of therapy than did patients with <3 mutations. There was no correlation between Sokal or EUTOS score and the number of mutations.
A limited number of patients had cryovials available for analysis of the mt respiration in CD34+ cells. Four GR had a range of 1-12 mtDNA mutations per patient with median VAF 61.8% (range 5.8-97.1%), and 5 PR had 0-2 mtDNA mutations per patient with median VAF of 5.5% (range 4.2-6.1%). GR had lower maximal respiration (median 115.9 pmol/min, range 76.6-149.7) than PR (median 199.7 pmol/min, range 170.9-222.4; P=0.0055).
Summary/Conclusion: A greater number of mtDNA mutations was associated with a better molecular response in imatinib-treated patients. In a small number of patients we found that mtDNA mutations with a higher VAF were associated with impaired OXPHOS in CD34+ cells at diagnosis. We hypothesize that reduced OXPHOS may sensitize the leukemic cells to imatinib. Functional studies are ongoing.

S152 FINAL ANALYSIS OF A PAN EUROPEAN STOP TYROSINE KINASE INHIBITOR TRIAL IN CHRONIC MYELOID LEUKEMIA: THE EURO-SKI STUDY

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Background: With the introduction of tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukaemia (CML), treatment cessation has become a realistic therapy goal for some CML patients. Around 40-60% of patients with stable DMR [deep molecular response, corresponding to <0.01% BCR-ABL (IS)] can stop the TKI successfully, e.g. in accordance with the recommendations given by the European LeukemiaNet. In the interim analysis of the first 200 patients of the EURO-SKI (European stop TKI) trial, 62% were in major molecular response (MMR: <0.1% BCR-ABL1 IS) or better at 6 months. DMR duration prior to TKI stop was most predictive for maintenance of MMR. Here we present the final analysis of the EURO-SKI trial after 3 years of follow-up.
Aims: The EURO-SKI trial was set up to define prognostic markers to increase the rate of patients in durable deep MR after stopping TKI. Further aims are the evaluation of harmonized methods of molecular monitoring, and assessment of prognostic factors.
Methods: Adult CML patients in chronic phase CML on TKI treatment in confirmed DMR for at least one year (>4 log reduction on TKI therapy for >12 months confirmed by three consecutive PCR tests) and under TKI treatment for at least 3 years were eligible. DMR confirmation was performed in standardized laboratories. Primary endpoint was maintenance of MMR after stopping TKI. According to protocol, a 36 months follow-up was planned. The null hypotheses were that MMR maintenance at 6 and 36 months was less or equal 40% and less or equal 35%, respectively.
Results: Between May 30, 2012 and December 03, 2014, 868 CP CML patients were pre-registered by 61 European centres from 11 countries. 140 pts were excluded (consent withdrawal n=1, protocol violation n=38, not eligible n=74 DMR not confirmed n=11, atypical or unknown transcript n=15, missing data n=1) resulting in 728 eligible patents.
Of the eligible 728 patients, 46.8% were female. Median age at diagnosis was 51 years (range, 11 to 85 years). Median duration of TKI treatment was 7.6 years (range, 3.0-14.1 years) and median duration of MR4 before TKI cessation was 4.7 years (range, 1.0-13.3 years).
Nine patients died without MMR loss (none CML related), 15 patients restarted TKI without prior MMR loss.
At 6 months 713 patients were available (without molecular test at 6 months n=6, TKI restart without relapse n=9). Since 434 patients (61%) [95% CI: 57–64] remained without relapse in the first 6 months, the null hypothesis could be rejected (p<0.0001).
At 36 months, 678 patients could be analysed (TKI restart without relapse n=17, no molecular test at 36 months n=33). 309 patients were in MMR or better corresponding to 46% [95% CI: 42–49]. The null hypothesis of 35% or lower was rejected (p<0·0001).
Molecular recurrence-free survival (MRecFS) at 36 months resulted in 48% (CI: 44-52%) and MRecTFS (molecular treatment-free survival) in 46% (CI 43-50%) (s. Fig 1).
No Blast crisis was documented.
Prognostic factors for early (up to 6 months) and late (> 6 months) MMR relapses will be updated and presented.



Summary/Conclusion: With this final analysis we confirm the MRecFS and MRecTFS rate at 6 months from the interim analysis. However, late relapses (15% between 6 and 36 months) occurred. Nevertheless, with 46%, almost half of the patients stayed at least in MRecTFS.

S153 OPTIC PRIMARY ANALYSIS: A DOSE-OPTIMIZATION STUDY OF 3 STARTING DOSES OF PONATINIB (PON)

J. E. Cortes [1,*], J. Apperley [2], E. Lomaia [3], B. Moiraghi [4], M. Undurraga Sutton [5], C. Pavlovsky [6], C. Chuah [7], T. Sacha [8], J. H. Lipton [9], J. K. McCloskey [10], A. Hochhaus [11], P. H. Rousselot [12], G. Rosti [13], H. De Lavallade [14], M. J. Mauro [15], T. Hall [16], V. Lu [16], S. Srivastava [16], M. W. Deininger [17]

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Background: PON, a third-generation tyrosine kinase inhibitor (TKI), demonstrated deep and long-lasting responses and survival in patients (pts) with chronic-phase chronic myeloid leukemia (CP-CML) resistant/intolerant to second-generation TKI therapy (PACE; NCT01207440); post hoc analysis suggested a relationship between dose and both adverse events and response. Here we present the primary analysis of OPTIC (NCT02467270), an ongoing, randomized, phase 2 trial with a novel response-based dosing regimen of PON in pts with resistant/intolerant CP-CML.
Aims: Evaluate the safety and efficacy of ponatinib response–based dosing regimens in patients with resistant/intolerant CP-CML.
Methods: Informed consent was obtained and pts with CP-CML resistant/intolerant to ≥2 TKIs or with the *BCR-ABL1* T315I mutation were randomized to PON starting doses of 45 mg (cohort A; 45 mg → 15 mg), 30 mg (B; 30 mg → 15 mg), and 15 mg (C) once daily. Doses were reduced to 15 mg with achievement of ≤1% *BCR-ABL1*^{IS} in cohorts A and B. The primary endpoint is ≤1% *BCR-ABL1*^{IS} at 12 mo; secondary endpoints include cytogenetic and molecular responses and safety outcomes. AOEs were adjudicated prospectively by an independent review committee.
Results: 283 pts were randomized (A/B/C: n=94/95/94) and had the following baseline characteristics: median age 48 y (18–81 y); 98% received ≥2 (55% ≥3) TKIs; 99% had resistant disease; 40% had ≥1 baseline mutations (23% T315I). At the primary analysis with 32 mo median follow-up, 134 pts (47%; n=50/41/43) remained on treatment and 204 pts (72%) had PON exposure ≥12 mo. At 12 mo, 44% (41/93) in A, 29% (27/93) in B, and 23% (21/91) in C achieved ≤1% *BCR-ABL1*^{IS} (Table); primary endpoint was met by cohort A. Dose reductions to 15 mg after achieving response (A/B) were 48/30%.
Most common grades ≥3 TEAEs were thrombocytopenia, 27%; neutropenia, 17%; and anemia, 7%. AOEs/serious AOEs were reported in cohorts A (10%/4%), B (5%/4%), and C (3%/3%). Dose reductions or discontinuations for TEAEs (A/B/C) were 46/35/32% and 19/16/14%, respectively.

Response*	Cohort A 45 mg	Cohort B 30 mg	Cohort C 15 mg
BCR-ABL1^{IS} ≤1% at 12 mo, % (n/N)	44 (41/93)	29 (27/93)	23 (21/91)
BCR-ABL1^{IS} ≤1% by 12 mo by mutation status at baseline, % (n/N)	52 (48/93)	35 (33/93)	25 (23/91)
Response in pts with T315I mutation	60 (15/25)	25 (5/20)	11 (2/19)
Response in pts without T315I mutation	48 (32/66)	38 (28/73)	30 (21/71)
Survival probability at 36 mo, % (95% CI)			
PFS	73 (58, 84)	66 (48, 80)	70 (55, 80)
OS	89 (79, 95)	89 (77, 95)	92 (82, 96)

*Includes all pts who are randomized and with measurable *BCR-ABL1*^{IS} at BL.

Summary/Conclusion: The OPTIC primary analysis demonstrates the optimal benefit:risk profile for PON was achieved with a response-based dosing regimen starting with 45 mg/d, followed by dose reduction to 15 mg/d upon achieving ≤*1% BCR-ABL1*^{IS}; 30 mg →15 mg and 15 mg cohorts may provide benefit, especially in pts without T315I mutation (Table). The observed ≤1% *BCR-ABL1*^{IS} responses are supported by robust survival outcomes in pts with CP-CML resistant to second-generation BCR-ABL1 TKI therapy, both with and without *BCR-ABL1* mutations.

S154 COVID-19 INFECTION IN CHRONIC MYELOID LEUKEMIA AFTER 1 YEAR OF THE PANDEMIC IN ITALY. A CAMPUS CML ANALYSIS

M. Breccia [1,*], E. Abruzzese [2], V. Accurso [3], I. Attolico [4], S. Barulli [5], M. Bergamaschi [6], G. Binotto [7], M. Bocchia [8], M. Bonifacio [9], G. Caocci [10], I. Capodanno [11], F. Castagnetti [12], F. Cavazzini [13], E. Crisà [14], M. Crugnola [15], M. S. De Candia [16], C. Elena [17], C. Fava [18], S. Galimberti [19], A. Gozzini [20], G. Gugliotta [12], T. Intermesoli [21], A. Iurlo [22], G. La Barba [23], R. Latagliata [24], S. Leonetti Crescenzi [25], L. Levato [26], G. Loglisci [27], A. Lucchesi [28], L. Luciano [29], F. Lunghi [30], D. Luzi [31], A. Malato [32], M. C. Miggiano [33], M. Pizzuti [34], P. Pregno [35], D. Rapezzi [36], G. Rege-Cambrin [37], G. Rosti [28], S. Russo [38], R. Sancetta [39], A. R. Scortechini [40], F. Sorà [41], P. Sportoletti [42], F. Stagno [43], A. Tafuri [44], M. Tiribelli [45], R. Foà [1], G. Saglio [46]

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Background: An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019 in the province of Hubei in China. Italy was one of the most affected countries with many cases diagnosed already in February 2020 and a lockdown was declared on March 9th. Limited information has been reported with regard to the impact of the pandemic on chronic myeloid leukemia (CML) patients.
Aims: To observe the temporal course of Covid-19 infection and the characteristics of positive patients.
Methods: The Campus CML Italian group carried out a first survey on the management of CML patients during the lockdown. We launched a second survey during the pandemic phases 2 and 3, between May 2020 and January 2021.

Results: We collected retrospective information on 8665 CML patients followed at 46 centers throughout the country. Within this cohort, we recorded 217 Covid-19-positive symptomatic patients (2.5%). Most patients (57%) were diagnosed as having Covid-19 infection between September 2020 and January 2021; 30% were diagnosed in phase 1 (March-April 2020) and only 13% between May and August. Most of the positive patients were between 50 and 65 years (35%), while 26% had less than 50 years, 18.8% were between 65 and 75 years, and 11% had more than 75 years. A male prevalence was observed (73%). The median time from CML diagnosis to Covid-19 infection was 6 years (3 months-18 years). Fifty-six percent of patients presented concomitant comorbidities at the time of infection. When Covid-19 was diagnosed, 27% of patients were receiving imatinib, 26% nilotinib, 18% dasatinib, 8% ponatinib, 8% bosutinib, 2% asciminib, while 11% were not receive treatment. At the time of the infection, 74% of patients were in molecular remission, 6% in complete cytogenetic remission, 3% in partial cytogenetic remission, 6% in complete hematological response and 11% in treatment-free remission. At diagnosis, 28% of patients presented fever and respiratory symptoms, 13% cough, 10% isolated fever, 13% ageusia, 12% anosmia, 4% had more than 1 symptom, while 20% were completely asymptomatic. Twenty-one patients (9.6%) required hospitalization without the need of respiratory assistance, 18 (8.2%) were hospitalized for respiratory assistance, 8 (3.6%) were admitted to an ICU, while 150 patients (69%) were only quarantined. Twenty-three percent of patients discontinued TKI therapy during the infection. The source of contagion was familiar in 49% of patients, 18% due to work, 3% in healthcare professionals, whereas in 30% was not known. Twelve patients died due to Covid-19 infection with a mortality rate of 5.5% in the positive cohort and of 0.13% in the whole cohort. Five patients reported consequences post-infection: 1 patient reported a Guillan-Barrè syndrome, 1 patient a maculopapular rash, 1 patient a pulmonary fibrosis, 1 patient a bacterial endocarditis and 1 patient was diagnosed as having alterations of the microcirculation.
Summary/Conclusion: This study reports the 1-year of data on the Covid-19 infection in a specific hematological malignancy in the European country first hit by the pandemic. A longer follow-up is needed to further define the impact of Covid-19 infection sequelae in CML patients.

Population based studies in myeloid disorders

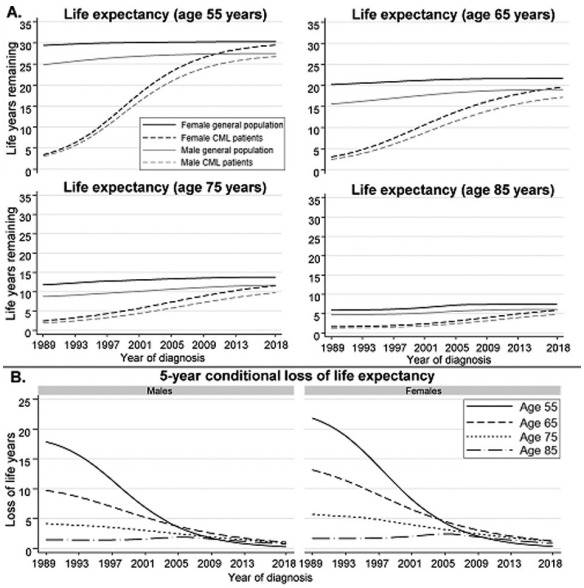
S155 THE LOSS OF LIFE EXPECTANCY IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: A POPULATION-BASED STUDY IN THE NETHERLANDS, 1989-2018

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Background: The treatment of chronic myeloid leukemia (CML) was transformed around the early-2000s with the advent of the first-generation BCR-ABL tyrosine kinase inhibitor (TKI) imatinib. This seminal milestone, along with the introduction of subsequent generations of BCR-ABL TKIs, markedly improved the population-level survival of CML patients. The overall 5-year relative survival rate (RSR) of CML patients in the TKI era is around 80%. While the RSR has an abiding history in population-based cancer research, it does not capture the magnitude of a cancer diagnosis on the life expectancy of cancer patients. At present, only one study assessed trends in CML patients' life expectancy in Sweden during 1973-2013 (Bower et al. *J Clin Oncol* 34, 2016).
Aims: To complement and extend this Swedish study, we assessed how the life expectancy and loss of life expectancy (LOLE) have evolved among CML patients diagnosed in the Netherlands during 1989-2018. In addition to the Swedish study, we estimated the 5-year conditional LOLE to assess time trends in the average number of life-years lost among CML patients who survived five years post-diagnosis.

Methods: We identified 3,353 CML patients aged ≥50 years and diagnosed between 1989-2018—with survival follow-up through December 31, 2019—from the Netherlands Cancer Registry. The age selection was chosen to align with the Swedish study. Flexible parametric relative survival models were used to estimate the LOLE that quantifies the difference between the life expectancy of patients and the general population, of which the latter is matched to the patients by age, sex, and calendar year. The LOLE reflects the average number of life-years lost due to a cancer diagnosis. Also, the 5-year conditional LOLE was estimated, a concept that portrays the patients' LOLE after having survived five years post-diagnosis. The survival measures were presented by year of diagnosis for four ages at diagnosis (i.e. 55, 65, 75, and 85 years), stratified by sex.
Results: The life expectancy of CML patients increased between 1989 and 2018, irrespective of age and sex, especially among patients aged 55 and 65 years (Figure 1A). Consequently, there was a marked decrease in the LOLE, particularly among younger patients since younger individuals have more remaining life-years than older individuals (Figure 1A). For example, a 55-year-old male patient diagnosed in 1990 loses, on average, 21.5 (95% CI: 20.7; 22.3) life-years, whereas a 55-year-old male patient diagnosed in 2018 on average loses 0.7 (95% CI: -0.1; 1.5) life-years. The corresponding estimates for an 85-year-old male patient were 3.4 (95% CI: 3.2; 3.7) and 1.3 (95% CI: 0.8; 1.9) life years, respectively. While the LOLE was low among CML patients diagnosed in 2018, small excess mortality prevailed for patients aged 65, 75, and 85 years. Encouragingly enough, as of 2010, the life expectancy of CML patients who survived five years post-diagnosis came close to the general population's life expectancy, regardless of age (Figure 1B).



Summary/Conclusion: The life expectancy of CML patients improved over time, particularly among younger patients between the 1990s and mid-late-2000s. The most reassuring finding was that the life expectancy of CML patients across all age groups ultimately approached that of the general population. This finding among contemporary diagnosed patients can essentially be attributed to the introduction of several TKIs across various therapy lines. Collectively, CML patients can look forward to a near-normal life expectancy in an era with modern approaches to manage CML.

S156 ELTROMBOPAG FOR MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA WITH NO EXCESS BLASTS AND THROMBOCYTOPENIA: A FRENCH MULTICENTER RETROSPECTIVE REAL-LIFE STUDY.

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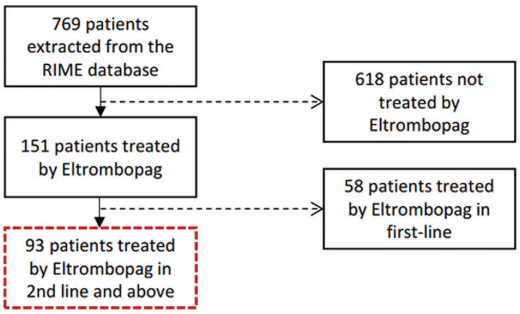
Background: Anemia is generally the predominant cytopenia in Low-Risk Myelodysplastic syndromes (LR-MDS) but thrombocytopenia may predominate in 10 to 15% of these patients. Options to improve thrombocytopenia are limited but recently, two thrombopoietin receptor agonists, romiplostim and eltrombopag (ELT) have been evaluated in clinical trials and yield 30 to 50% platelet responses in relatively selected LR-MDS patients. Only two clinical trials, have been performed in LR-MDS with ELT monotherapy and one in CMML.
Aims: The main objective of this study was to assess the efficacy and safety profile of ELT in thrombocytopenia related to MDS and CMML with no excess blasts (EB), in a "real life" context.
Methods: We collected data from MDS and CMML patients treated by ELT between January 2011 and January 2019 and included in the 'Groupe Francophone des Myélodysplasies' (GFM) registry of MDS patients. Inclusion criteria were (1) MDS or chronic myelo-monocytic leukemia with leucocytes < 13 G/L (according to WHO 2016 classification)(2) less than 5% bone marrow blasts (3) treatment with ELT outside of a clinical trial (4) platelet count ≤ 50.10^9/L at the onset of ELT. The primary endpoint was platelet response (HI-P), according to International Working Group (IWG 2006) response criteria. We also reported other hematological responseswhen available, safety and tolerability, bleeding and thrombotic events. This study has been approved by institutional review board, in accordance with the French data protection authority (MR004, Commission Nationale de l'Informatique et des Libertés, CNIL)
Results: Platelet response occurred in 38 (76%) MDS patients and 9 (82%) CMML. Median (IQR) duration of response was 13 (4-24) months and 6 (4-11) months in MDS or CMML patients respectively. Three MDS and 3 in CMML were still responders 6 to 23 months after ELT discontinuation. Although 34% MDS and 46% CMML were anticoagulated or anti aggregated, only 10% patients experienced ≥ grade 3 bleeding events (6% in responders vs 21% in non-responders). Thrombotic events were observed in 6 (12%) MDS patients, who all but one had a medical history of arterial or venous thrombosis. Progression to AML occurred in 4 (7%) patients.
Summary/Conclusion: We reported for the first-time real-life data about ELT in LR-MDS and CMML patients with thrombocytopenia. We confirmed that ELT is effective with a sustained effect on platelet counts reduction in the platelet transfusion burden and in severe bleeding. The effect of ELT was often prolonged after drug discontinuation. The tolerance profile was favorable in this population with no excess of blast, but previous history of thrombosis remains a major risk factor for thrombotic events on treatment.

S157 EVALUATION OF THE IMPACT OF THE USE OF ELTROMBOPAG IN A REAL-LIFE SETTING IN FRANCE BASED ON DATA IN THE NATIONAL OBSERVATORY FOR MEDULLAR INSUFFICIENCY (RIME): THE REVEPI STUDY

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Background: Aplastic anaemia (AA) is characterised by bone marrow failure (BMF), and acquired AAs represent 70% of cases. Eltrombopag (ELT) is indicated in adult patients with acquired severe AA refractory to prior immunosuppressive treatment (IST) not eligible for hematopoietic stem cell transplantation, alone or associated with IST. To date, clinical data about the use of ELT are scarce.
Aims: The aim of this study is to describe patients treated by ELT and to evaluate the impact of ELT use in real-life in terms of survival, clinical benefit, hospitalization, quality of life, tolerance and clonal evolution.
Methods: This study was based on the RIME Observatory whose purpose is to collect prospectively and retrospectively standardised clinical information related to the management of French patients with BMF. The study population was all AA patients included in this observatory, between February 27th 2017 and December 24th 2019, and treated with ELT in second line and above. Adverse events were coded according to MedDRA and detailed by SOC and PT. The quality of life data were collected with QLQ-C30 questionnaires.
Results: A total of 93 AA patients used ELT in second line and above (median age 54 years and 58% women). Most patients were included in the APHP Saint-Louis Center. The median follow-up was 37.2 months from diagnosis and 9.4 months between AA diagnosis and start of ELT. According to the Camitta score, 46% of patients had severe aplastic anemia at diagnosis and 25% at the initiation of ELT. At the initiation of ELT, among patients receiving concomitant treatment (n=65), half used an association cyclosporine/ATGAM®; among patients receiving an adjuvant (n=29), most used an iron chelator.
Regarding ELT discontinuation, 82% (n=76) of patients stopped it at least once and 76% (n=71) permanently. Among these 71 patients, 65% (n=46) stopped for treatment failure and 14% (n=10) for safety concerns. A total of 18% of patients (n=17) died during follow-up, mainly from infection or haemorrhage. The median survival after ELT initiation was 74.4 months and the probability of survival at 20 months was around 90%. Among the 62 patients exposed to ELT in second line and above for at least 6 months, 66% (n=41) were responders of which 42% (n=26) had a complete response. The median response time was 27.5 months. Among the 79 patients having received a transfusion during the study, 59% (n=47) achieved transfusion independence. After the initiation of ELT, 43% of patients (n=40) were hospitalized mainly in conventional hospitalization. The main reasons for hospitalization were scheduled hospitalization and complication (30% and 43% respectively). Quality of life data were collected for 6 patients and cannot be interpreted. Among the 93 patients, 63% (n=59) experienced at least one adverse event during treatment, and the main adverse events reported were infections, hepatobiliary disorders, pain, asthenia and bleeding. Lastly, 11% of patients (n=10) had a clonal evolution (myelodysplastic syndrome (n=9) and acute myeloid leukemia (n=1)).



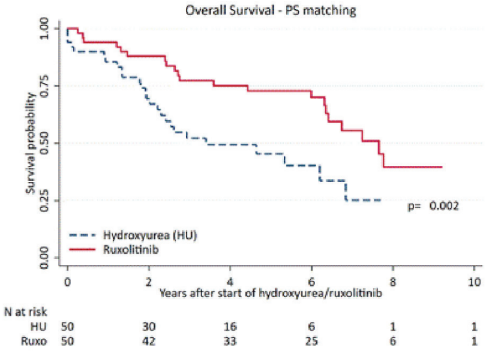
Summary/Conclusion: This study evaluated the impact of ELT use in real-life in AA. Two-thirds of the patients were responders to ELT. Two years after starting ELT, 42% had a complete response (cumulative incidence). More than half of the patients achieved transfusion independence. Clonal progression was identified in 11% of patients, which is comparable to the data in literature. The safety profile was similar to the one observed in ELT clinical studies. The results of this real-life study confirm the positive benefit-risk ratio of ELT in these patients.

S158 IMPACT OF RUXOLITINIB ON SURVIVAL OF PATIENTS WITH MYELOFIBROSIS IN REAL WORLD – UPDATE OF ERNEST (EUROPEAN REGISTRY FOR MYELOPROLIFERATIVE NEOPLASMS) STUDY

P. Guglielmelli [1,*], A. Ghirardi [2], A. Carobbio [2], A. Masciulli [2], C. Maccari [1], B. Mora [3], E. Rumi [4], A. Triguero [5], M. C. Finazzi [6], H. Pettersson [7], C. Paoli [8], F. Mannelli [8], D. Vanni [4], A. Rambaldi [6], F. Passamonti [9], A. Alvarez-Larràn [5], B. Andreasson [7], A. M. Vannucchi [1], T. Barbui [2]

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Background: Ruxolitinib (RUXO) is a JAK1/2 inhibitor approved for the treatment of patients (pts) with primary (PMF) and secondary myelofibrosis (sMF). In randomized controlled trials, RUXO was effective in controlling symptoms and splenomegaly, while survival improvement, reported in post-hoc analysis, is still debated. In 2013 the ERNEST registry was activated to prospectively enroll MF patients receiving ruxolitinib.
Aims: The aim of the ERNEST project was to collect estimates of clinical outcome of contemporary MF pts in real-life settings.
Methods: Current study describes updates with cut-off deadline at dec 31, 2018 of those ERNEST patients who were reported already as alive and/or in active surveillance at Nov 2014 (Blood 2014; 124:1849). Italy, Spain and Sweden participated in the Registry update. The chi-square test or Fisher's exact test (categorical variables) and t-test or Wilcoxon-Mann-Whitney test (continuous variables) were used. Kaplan-Meier analysis was used for OS. To avoid immortal time bias, only pts exposed to cytoreductive therapy were included and followed from the start of treatment until death or censoring (last contact/study-end fixed at Dec 31, 2018), whichever came first. A multivariable Cox proportional-hazard model was used to investigate predictors of mortality. To assure comparability between patients treated with Hydroxyurea (pts-HU) and RUXO (pts-RUXO), we conducted a propensity score (PS) matching analysis. The PS included age at first administration, gender, type of MF, DIPSS at first administration, year of diagnosis, palpable spleen at first administration and time to first administration. 2-tailed p-values <0.05 were considered significant.
Results: At cut-off, the data of 1,010 pts were analyzed; there were 68% PMF, 20% PET-MF, 22% PPV-MF (median age at diagnosis: 64y). 23%,37% and 40% of diagnosis were performed between 2001-2004, 2005-2008 and 2009-2012. After a median follow-up of 5.2y (2.3–8.2), 625 deaths occurred with a mortality rate (per 100 person-years) of 10.9 (95%CI 10.1-11.8). Median OS: 6.2y (95%CI 2.8-12.6), with no significant difference according to diagnostic categories (P=0.4). Among pts treated with cytoreduction during follow-up (59.2% of total), at first administration pts-RUXO were significantly younger (64.yrs vs 67.0 yrs, p=0.02), with massive splenomegaly (≥20cm from LCM; 37% vs 6.0%, p<0.001) and higher incidence of constitutional symptoms (80% vs 49%;p=0.03) compared to pts-HU. Time to first treatment with HU (median time 0.0y, range 0-1.2y) was significantly shorter than RUXO (median 4.5y range 2.2-6.7y; p<0.001); 64% of pts-RUXO had been previously treated with HU, in 2 cases with interferon. OS was significantly longer in pts-RUXO compared to pts-HU (6.7y vs 5.1y; P=0.001); for those in higher DIPSS category OS was 6.4y for pts-RUXO vs 3.0 for pts-HU (p=0.003). Multivariable analysis identified the following factors that negatively affected OS: age (linear covariate, HR 1.03,p<0.001), male gender (HR 1.58, p<0.001), high DIPSS category (HR 2.96,p<0.001). Conversely, protective variables were more recent diagnosis (2009-2012 vs 2001-2004; HR 0.47,p<0.01) and exposure to ruxolitinib (HR 0.62,p=0.029). After PS matching (n=50 in each group), median OS was 7.7y in pts-RUXO vs 3.4y in pts-HU, respectively (p=0.002;Fig.1), and was not statistically different in those who used RUXO as first line or after HU (6.4y vs 7.8y, p=1.00).



Summary/Conclusion: Within the limitations of an observational study, these real-life data support an overall survival benefit of RUXO over HU alone in pts with PMF and sMF

S159 CLONAL HEMATOPOIESIS, ELEVATED BLOOD CELL COUNTS, AND DECREASED RENAL FUNCTION – A GENERAL POPULATION STUDY

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Background: The Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are acquired stem-cell diseases. The molecular basis for MPNs includes the *JAK2*V617F, *CALR* -and *MPL*-mutations. MPNs evolve from clonal hematopoiesis of indeterminate potential (CHIP), which is characterized by an age-dependent acquisition of mutations. In recent years, chronic inflammation has been increasingly recognized as an important pathogenetic mechanism for MPN development – which may even in the CHIP phase be important for clonal evolution and development of comorbidities. Several studies have described a progressive reduction in estimated glomerular filtration rate (eGFR) among MPN patients, hence termed MPN-related nephropathy. However, no studies have focused upon the impact of CHIP mutations on eGFR.
Aims: We investigated the association between CHIP mutations and elevated blood counts on eGFR in a Danish general population study.
Methods: In total, 19,958 participants were included from the General Suburban Population Study, with 645 (3.2%) participants being positive for either the *JAK2V617F* (N=613) or *CALR* (N=32) mutation. All participants with MPN or other hematological malignancy at baseline were excluded from the analysis. eGFR (mL/min pr. 1.73m^2) was calculated by the EPI-CKD formula using plasma-creatinine levels and adjusted for age and gender as recommended for use. Neutrophil/lymphocyte – ratio (NLR) and thrombocyte/lymphocyte– ratio (PLR) were calculated as proxies for chronic inflammation. A composite binary variable for cytosis was calculated, including hemoglobin concentration, hematocrit, erythrocyte, thrombocyte, leukocyte, neutrophil, eosinophil, basophil, and lymphocyte cell counts adjusted for gender. We assessed the impact of CHIP (*JAK2V617F* or *CALR)* on eGFR using inverse-probability weighting (IPW) regression analysis to estimate potential outcome mean (95%CI) differences. The IPW regression was adjusted for age, gender, blood pressure, BMI, smoking status, ischemic heart disease, NLR, and PLR.
Results: Using IPW-regression analysis, CHIP (*JAK2*V617F & *CALR*) had an adjusted mean (95%CI) difference in eGFR of -0.3 (-1.5 - -0.86), *p=0.6* with a -0.39% (-1.8% - 1%) reduction in eGFR compared with non-mutated participants. *JAK2*V617F positive individuals had an adjusted mean(95%CI) difference in eGFR of -0.2 (-1.4 - -0.1), *p=0.7* with a -0.2 % (-1.6% - 1.1%) reduction in eGFR compared with non-mutated participants. *CALR* positive individuals, had an adjusted mean(95%CI) difference in eGFR of -9 (-13.7 - -4.3), *p <0.0001* with a -10.3% (-15.6% - -4.9%) reduction in eGFR compared with non-mutated participants. Cytosis in the general population was associated with an adjusted mean(95%CI) difference in eGFR of -0.5 (-0.9 - -0.04), *p=0.03* with a -0.5% (-1% - -0.04%) reduction in eGFR compared with participants with no cytosis. CHIP participants had a significantly elevated NLR and PLR compared to non-mutated participants with a mean (95%CI) difference of 0.1 (0.03 – 0.17), *p=0.008* and 9.8 (5.6 – 13.7), *p=3.8x10^{-6}*, respectively. NLR was negatively associated with eGFR among CHIP individuals with coefficient (95%CI) -2.2 (-3,6 - -0.78), adjusted R^2=0.04, *p=0.002*).
Summary/Conclusion: This study shows that CHIP *CALR*-mutations in a general population study associate with a significant reduction in eGFR as a proxy for renal function. Furthermore, cytosis is associated with a significant decrease in eGFR. Chronic inflammation and MPN-associated mutations may contribute to a decrease in eGFR even in the very early stage of MPN-development.

Correlating mutations with phenotype in MDS

S160 CONCURRENT MUTATIONS IN ZRSR2 AND TET2 DISRUPT MYELOID AND ERYTHROID DIFFERENTIATION AND CAUSE ABNORMALITIES COMPATIBLE WITH MDS DISEASE IN MICE

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Background: Splicing factor (SF) and epigenetic genes mutations are the most frequent genetic alterations found in patients with myelodysplastic syndromes (MDS). About 25% of patients present concurrent mutations in such pathways, suggesting a cooperative role in the pathogenic mechanism of MDS. Inactivating mutations in the minor spliceosome factor *ZRSR2* and alterations in the epigenetic regulator *TET2* are frequently found together and are associated with higher blast percentage in bone marrow (BM), higher risk of AML transformation, and shorter overall survival. The underlying molecular mechanism of disease remains, however, unclear.
Aims: To investigate the functional role of *ZRSR2* and *ZRSR2-TET2* mutations in hematopoiesis and MDS.
Methods: We generated a *Zrsr2* mutant mouse model (*Zrsr2*^{mut}) by CRISPR/Cas9. A *Zrsr2-Tet2* double mutant model (*Zrsr2*^{mut}*Tet2*^{mut}) was generated by crossing *Zrsr2*^{mut} mice with a *Tet2* knock-out model (*Tet2*^{mut}) previously established in our laboratory. Hematopoietic cell immunophenotype was analyzed by flow cytometry. Peripheral blood (PB) smears were stained for morphologic evaluation. To study hematopoietic stem and progenitor cells (HSPCs) functionality we conducted competitive BM transplantation and colony-forming unit (CFU) assays. Whole transcriptome sequencing of LSK cells was performed to study gene expression and to identify changes in splicing patterns.
Results: *Zrsr2*^{mut}*Tet2*^{mut} mice immunophenotyping indicated a global alteration of hematopoiesis. In BM, Lin$^-$ Sca-1$^+$ c-kit$^+$ (LSK) cell compartment was expanded, being CD48$^+$CD150$^+$ (HPC2) cells significantly increased and CD48$^-$CD150$^-$ (MPP) significantly reduced. Myeloerythroid differentiation was disrupted, showing an increase in the myeloid pre-GM progenitors accompanied by a sharp decrease in GMP. Erythroid progenitors showed a similar behavior, having a significant increase of pre-CFU-E cells and a reduction of CFU-E. CFU assays confirmed a significant increase in myeloid progenitors and an increase of erythroid progenitors in double-mutant mice. Notably, a subset of *Zrsr2*^{mut}*Tet2*^{mut} mice (30%) showed a more striking phenotype, including PB anemia and thrombocytopenia, leukocytosis, splenomegaly, and extramedullary hematopoiesis. Morphologically, peripheral blood cells showed dysplastic features including red blood cell abnormalities and giant platelets.
Transplantation experiments indicated an impairment of *Zrsr2*^{mut} cell capacity to repopulate the receptor BM. Conversely, transplantation of *Zrsr2*^{mut}*Tet2*^{mut} cells revealed an enhanced engraftment capacity when compared to WT BM. Immunophenotypic analysis of *Zrsr2*^{mut}*Tet2*^{mut} recipients recapitulated the erythroid phenotype observed in steady-state animals. One out of the five analyzed mice (20%) showed a more marked phenotype, similarly to what happened in non-transplanted mice.
RNA-seq analysis from *Zrsr2*^{mut}*Tet2*^{mut} cells revealed 2952 differentially expressed genes and 43272 differential alternative splicing events in comparison to controls. Exon skipping (ES) was the most common alternative splicing (AS) event (71%) while intron retention (IR) was less common (7%).
Summary/Conclusion: Here we report that co-occurring mutations in *Zrsr2-Tet2* disturb normal hematopoiesis and cause abnormal myeloid and erythroid differentiation. Thirty percent of these mice displayed some MDS-like abnormalities. Transcriptome analysis revealed an important dysregulation in gene expression accompanied by aberrant mRNA splicing. This study provides new insights into the biology of this MDS subtype and opens the possibility to more in-depth interrogate its molecular disease mechanism.

S161 ACTIVATION OF DISTINCT INFLAMMATORY PATHWAYS IS DRIVEN BY GENETICS IN MDS

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Background: Myelodysplastic syndromes (MDS) lie on a continuum of myeloid neoplastic progression between clonal hematopoiesis of indeterminate potential (CHIP) and myeloid leukemia. Innate immune signalling in the marrow has been identified as a determinant of progression, particularly in low-risk (LR)-MDS, suggesting that it may be possible to prevent or delay progression by suitably targeted anti-inflammatory therapy. However, while early data point to a pivotal role for the NLRP3-inflammasome, little is known about the extent or functional relevance of patient-specific variations in inflammatory network activity.
Aims: Our objective was to assess the diversity of pre-treatment bone marrow inflammation in LR-MDS compared to non-CHIP, CHIP, high-risk (HR)-MDS and CMML patients and to investigate associations with phenotype, genotype and outcome in LR-MDS.
Methods: We analyzed a total of 102 bone marrow samples (15 non-CHIP; 12 CHIP; 47 LR-MDS; 14 HR-MDS; 14 CMML) collected under informed consent as part of the MDS registry and the BoHemE Study (NCT02867085) at the University Hospitals in Dresden and Leipzig. BM-MNC RNA was analyzed by qPCR TaqMan® Array for the expression of 12 genes encoding inflammasome-related proteins (*NLRP3*, *PYCARD*, *CASP1*, *IL1B*, *IL18*, *S100A9*, *NLRP1*, *NLRC4*, *AIM2*, *CASP3*, *CASP4*, *CASP5*). In parallel, we measured the levels of 14 circulating inflammatory mediators (e.g. IL1B, IL18, S100A9) in paired plasma samples by Luminex™ and conventional ELISA. Inflammasome data were then correlated with mutation status and clinical parameters.
Results: Inflammasome gene expression was generally higher in LR-MDS than in either CHIP or HR-MDS. In LR-MDS samples selected inflammatory biomarkers such as *NLRP3*, *IL1B*, *IL18*, and *S100A9* were differentially expressed and correlated, indicating the presence of distinct patterns of inflammation within this cohort. A principal component analysis (PCA) performed in order to identify consistent subgroups in the gene expression separated the LR-MDS cohort into three defined clusters based predominantly on the levels of *PYCARD*, *IL18*, *S100A9* and *NLRC4*. Re-examination of these groups for NLRP3-related gene expression confirmed low, medium and high levels (Figure 1).
Low NLRP3-inflammasome state (LR-MDS 1) associated with the presence of SF3B1 mutation/ring sideroblasts, hypercellular bone marrow, transfusion dependence and expanded erythropoiesis, as well as low IL1B mRNA and protein expression. High NLRP3-inflammasome state (LR-MDS 2) associated with del(5q), hypocellular bone marrow and transfusion independence, as well as high IL1B mRNA and protein expression. Medium NLRP3-inflammasome state (LR-MDS 3) associated with fewer mutations, hypocellular bone marrow and expanded erythropoiesis, as well as high IL1B mRNA and protein expression.

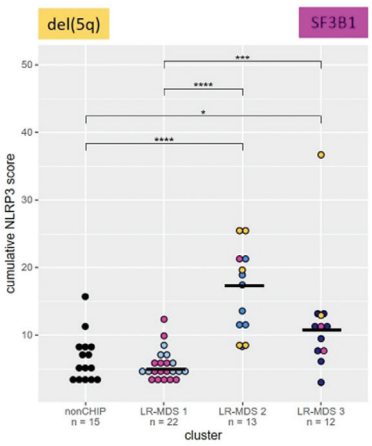


Figure 1. Cumulative NLRP3-score of LR-MDS PCA clusters.
Cumulative NLRP3 score = ∑ *NLRP3, PYCARD, CASP1, IL1B, IL18*; Mann Whitney test: * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, **** p ≤ 0.0001; black bold bar depicts median

Summary/Conclusion: We demonstrate the presence of distinct inflammasome activation states in LR-MDS and identify associated biomarkers (IL1B, SF3B1mut, del(5q)) of potential relevance for patient stratification to anti-inflammatory therapies. We are currently analyzing gene expression in sorted cell populations to further increase the resolution of our analysis, which will be validated in the prospective CANFIRE trial investigating the IL1B antibody canakinumab in LR-MDS.

S162 TET2 MUTATIONS IN MYELODYSPLASTIC SYNDROME PATIENTS DISRUPTS NATURAL KILLER CELL'S BIOLOGY

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Background: Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders essentially occurring in elderly individuals and associated with a high risk of progression to acute myeloid leukemia (AML). A majority of MDS patients harbors somatic mutations including in genes encoding for epigenetic regulators such as TET2 and IDH1 and 2. Those mutations have been also found in individuals with clonal hematopoiesis of indeterminate potential (CHIP), a preleukemic state. However, mechanisms of disease progression remain largely unknown and may implicate defects in the anti-leukemic immunosurveillance. Among immune cells, Natural Killer (NK) cells are key players in charge of eliminating tumor cells. At diagnosis of AML and MDS, we and others showed impaired NK cell's phenotype and function with a reduction of cytotoxicity and cytokine release (Khaznadar *et al.* 2015 *J Immunol*, Carlsten *et al.* 2010 *Leukemia*). However no data are yet available on the impact on NK-cells of the mutation status in MDS patients at diagnosis.
Aims: We hypothesized that MDS patients with *TET2*/*IDH* mutations could show particular defective NK cell profile leading to the disruption of their anti-leukemic activity, by contrast to other MDS-related mutations.
Methods: Bone marrow (BM) and blood samples from 63 patients with MDS were collected, from the Hematological Departments of Saint Louis Hospital at diagnosis prior any treatment. Next generation sequencing (NGS) using a 80 genes panel was performed on sorted blood NK and T cells. NK cells phenotype was analyzed by flow-cytometry and NK-cell mediated cytotoxicity against the leukemic K562 cell-line was evaluated in calcein-release assays. The NK-cell methylation landscape has been assessed by representation bisulfite sequencing (RRBS). Finally, NK-cells treated *in vitro* with HMA have been analyzed for NK receptor expression before and after HMA exposure.
Results: Phenotyping of NK cells in blood and BM of MDS patients showed a strong reduction of KIR2D receptors expression counterbalanced by the increase of NKG2A at the NK-cell surface in patients harboring *TET2* or *IDH1/2* mutations (Figure 1A). The NGS analysis revealed a shared mutation profile between blasts and NK cells, but not T lymphocytes, in the MDS patients (Figure 1B). Interestingly, KIR expression correlated with the Variation of Allele Frequency (VAF) of *TET2* mutations in NK cells (Figure 1C). Chromatin immuno-precipitation experiments in primary NK cells unveiled the direct binding of TET2 on the KIR promoter region. In parallel, RRBS analysis showed DNA hypermethylation of the KIR locus and other genes involved in NK cell physiology, including *PRF1* and *IFNG*, in the $TET2^{MUT}$ NK-cells by comparison to $TET2^{WT}$ NK-cells. Importantly, *in vitro* HMA treatment of NK-cells restores KIR2D cell-surface expression (figure 1D).

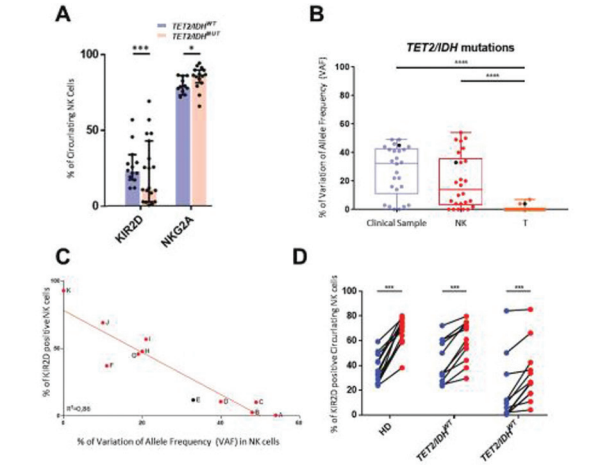


Figure 1 : Impact of *TET2/IDH* mutations in NK cells phenotype
(A) Circulating NK cells phenotyping of KIR2D and NKG2A receptors in *TET2/IDH* WT (n=13) and MUT (n=19) patients
(B) Variation of Allele Frequency (VAF) of *TET2/IDH* mutations at diagnosis and in NK/T sorted cells.
(C) Correlation between VAF of *TET2/IDH* mutations in NK cells and KIR2D expression.
TET2 mutated patients are depicted in red and IDHMUT patient in black.
(D) KIR2D expression at the surface of NK cells after PBMC treatment with 5-Aza-2'deoxycytidine (DEC) at 0,5 µM (in red). DMSO treatment was used as CTRL (in blue).

Summary/Conclusion: Altogether, our findings showed that mutations in *TET2* altered NK-cell biology in MDS patients. This study highlights the potential dual role of mutations in the emergence of MDS and immune defects, which could lead to progression to AML by associating oncogenic mechanisms and tumor escape to immunosurveillance.

S163 E-CADHERIN CONTROLS ERYTHROPOIESIS: A NOVEL AVENUE TO ANEMIA TREATMENT

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Background: In Western world aging-associated bone marrow (BM) dysplasia's, such as Myeloid Dysplastic Syndrome (MDS), increasingly contribute to anaemia incidence. One major goal of MDS-treatment is to treat anaemia with the aim of avoiding or delaying chronic transfusional support, to decrease the risk of transfusion–related complications and improve quality of life. When serum erythropoietin (EPO) is low, MDS-patients are treated with EPO and/or Sotatercept, displaying a ~50% response rate in terms of erythroid hematological improvement. Anaemia-treatment in MDS therefore urgently requires development of novel options to promote erythropoiesis.
Aims: A fundamental requirement to develop novel treatment opportunities that promote erythropoiesis is to obtain improved understanding of the erythroid homeostatic responses in BM to anaemia.
Methods: We analyzed human healthy and MDS BM by flow cytometry to supplement our exploit of existing genomic and proteomic databases. Additionally, we performed functional experiments using genomic knockout of our gene of interest, CDH1, using CRISPR-cas9.
Results: We here identify Epithelial cadherin (E-cadherin) to selectively mark the erythroid lineage in human BM. This is striking, because E-cadherin is well-established to mediate epithelial integrity, as key component in adherens junctions. In the epithelium, E-cadherin functions as mechanosensor and transduction cascades, such as the Wnt pathway. It has been reported that Wnt signaling is aberrantly active in myeloid dysplastic syndrome. We here report our observation that E-cadherin membrane expression is reduced in MDS erythroid progenitors. We hypothesize that consequently, MDS erythroid progenitors lack the gatekeeper function that E-cadherin has on β-catenin signaling.
In our CRISPR-Cas9 KO experiments, we show that E-cadherin in erythroblasts cross talks with the Wnt pathway by stabilizing β-catenin, key Wnt signal transducer, at the cytoplasmic membrane. In addition, we show inhibition of the β-catenin destruction complex results in further accumulation of β-catenin and hampering of erythroid differentiation.
Importantly, we find that E-cadherin expression is not conserved in mouse erythroid progenitors. Erythropoiesis is an evolutionary conserved process and has been extensively studied in vivo using mouse models. Despite many homologies, stress erythropoiesis, the erythroid homeostatic response to anemia, is differently controlled in mice as compared to humans. Stress erythropoiesis in mice is mainly driven extramedullary, in the spleen, and not in BM as seen in humans. The underlying mechanism of stress erythropoiesis in human BM is mostly elusive.
Summary/Conclusion: Due its control on cell adhesion, survival and differentiation we hypothesize that E-cadherin in fact may display an unanticipated BM-specific control on (stress) erythropoiesis in human BM that cannot be uncovered by exploring the anemic response in mouse models. We suggest E-cadherin to function as double edged sword, on the one hand stabilizing, but also sequestering β-catenin at the cytoplasmic membrane. Hereby, E-cadherin links cell adhesion between (pro) erythroblasts in erythroblastic islands with Canonical Wnt signaling. In extension, we suggest deficient E-cadherin to underlie inefficient stress erythropoiesis and anemia as we observe reduced protein expression in the erythroid lineage in MDS patient BM.
Overall, E-cadherin signaling may underlie (stress) erythropoiesis by controlling differentiation of erythroid progenitors in human BM, and is an interesting candidate for targeted treatment of inefficient erythropoiesis.

S164 RVU120/SEL120 CDK8/19 INHIBITOR - A DRUG CANDIDATE FOR THE TREATMENT OF MDS CAN INDUCE ERYTHROID DIFFERENTIATION IN TRANSFORMED CD34+ HEMATOPOIETIC PROGENITOR CELLS

T. Rzymski [1,*], U. Pakulska [1], K. Goller [1], E. Adamczyk [1], K. Dziedzic [1], K. Wiklik [1], M. Combik [1], M. Mikula [2], M. Obacz [1], M. Mazan [1], K. Keska [1], M. Masiejczyk [1], P. Juszczynski [3], J. Flygare [4], K. Brzozka [1]

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Background: Myelodysplastic syndrome (MDS) is a disorder of hematopoietic cells that as a result of genetic and epigenetic changes do not give rise to mature blood cells. Production and accumulation of dysplastic cells leads to cytopenias and can often evolve to acute myeloid leukemia (AML). Primary clinical goals in MDS are to achieve remissions, alleviate symptoms associated with cytopenias and to minimize the transfusion burden. While supportive red blood cell transfusions and erythropoiesis-stimulating agents may lead to clinical improvement, frequent transfusions may lead to iron overload and decreased quality of life. Several additional therapeutics are now available for the treatment of symptomatic anemia, however there is a need for novel agents as majority of patients eventually develop resistance. RVU120 (formerly known as SEL120) is a specific, selective inhibitor of CDK8 and its paralog CDK19. A first- in- human phase Ib clinical trial with RVU120 in patients with AML or HR-MDS is currently ongoing. Preclinical studies indicated strong antileukemic potential of RVU120 that was often associated with multilineage commitment of CD34+ AML cells. Moreover, RVU120 could improve proliferation and induce erythroid differentiation of CD34+ cells derived from Diamond-Blackfan anemia patients.
Aims: Primary aim was to evaluate erythroid differentiation potential of RVU120 in transformed lineage depleted (Lin-) CD34+ blood cells characterized with the early block in erythroid differentiation.
Methods: Primary cellular model was based on cord blood cells transduced with TLS-ERG - a fusion gene generated from t(16;21)(p11;q22) translocation associated with primary AML and secondary AML associated MDS. Transformed cells displayed increased capacity for self-renewal, proliferation and altered erythroid differentiation. Cells were treated with RVU120 and global transcriptional changes and chromatin status were analyzed by RNAseq, ATACseq and ChIPseq. Cell cycle, proliferation and lineage specific markers were studied by flow cytometry in liquid and semi-solid methylcellulose-based media.
Results: RVU120 treatment leads to transcriptional reprogramming of transformed (Lin-) CD34+ cells. The most profound changes included decreased CDK8 occupancy and increased RNA Pol II loading. RVU120 could repress many genes associated with stem cells and importantly induce the expression of genes involved in erythroid commitment, including regulators of erythroid/megakaryocytic fate, such as RGS18,

KLF1, FLI1, INHBA, GATA1/2 and hemoglobin genes. Detailed analysis by flow cytometry at early and late time points reflected sequential changes in the expression of lineage-specific surface markers, leading to differentiation and the presence of GlyA+/CD71+ erythroblasts. Observed effects on differentiation towards erythroid cells were independent of erythropoietin.
Summary/Conclusion: Presented results indicate strong erythroid differentiation potential of RVU120 in (Lin-) CD34+, that acquired genetic abnormalities resulting in arrested erythroid commitment, characteristics of many MDS and AML subtypes. Observed differentiation phenotype strikingly resembles effects of RVU120 in DBA cells caused by disruption of genes encoding ribosomal proteins. Detailed transcriptomic profiling strongly associated differentiation with enrichment of genes representing regulators of erythroid commitment and hemoglobin metabolism. Further studies are warranted to investigate efficacy of RVU120 in anemias associated with bone marrow failures in AML and MDS patients.

Novel targets in MDS

S165 A PHASE 1, DOSE ESCALATION TRIAL WITH NOVEL ORAL IRAK4 INHIBITOR CA-4948 IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA OR MYELODYSPLASTIC SYNDROME – INTERIM REPORT

G. Garcia-Manero [1,*], S. Tarantolo [2], A. Verma [3], J. Dugan [4], E. S. Winer [5], A. Giagounidis [6], C. Talati [7], C. Lieberman [8], E. Martinez [9], R. von Roemeling [9], U. Platzbecker [10]

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Background: Interleukin-1 receptor-associated kinase 4 (IRAK4) plays a critical role in toll-like receptor (TLR) or interleukin-1 receptor (IL-1R) signaling pathway activation. This results in stimulation of NFκB, triggering inflammatory responses, oncogenesis and survival mechanisms of malignant cells. Genetic mutations of myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) include SF3B1 and U2AF1 affecting spliceosomes in 50% of cases that lead to expression of a longer, highly active isoform of IRAK4 (IRAK4-L) [1,2]. CA-4948 is a novel oral inhibitor of IRAK4 and FLT3 signaling.
Aims: Assessment of safety, tolerability and recommended phase 2 dose (RP2D).
Methods: This is an ongoing, phase 1 dose escalation trial (NCT 042787688). In a 3+3 design, enrolling adult patients with relapsed or refractory high-risk MDS or AML, CA-4948 is orally administered at dose level (DL) cohorts of 200, 300, 400, and 500 mg bid given continuously in 28-day cycles until limiting toxicity or disease progression. Primary objective: Safety and RP2D. Secondary: Early efficacy (ORR; evaluable: patients with baseline- and at least 1 follow-up malignancy assessments); pharmacokinetics (PK). Exploratory: Pharmacodynamic (PD) mechanism-of action (MoA) related biomarkers.
Results: As of February 8, 2021, 15 patients (10 males, 5 females; median age 72, range: 32-84) have been enrolled with higher risk MDS by IPSS-R (N=8), and 7 with AML. Median number of prior therapies was 2 (range 1- 4). Most patients were transfusion dependent at baseline. Three dose levels of 200, 300, and 400 mg bid have been completed for DLT evaluation; DL 4 at 500 mg bid is open for enrollment. Treatment duration ranged from <1 to 7 months with enrollment ongoing.
Safety: Treatment was generally safe and tolerable. No DLT was reported at the first 3 dose levels incl. 400 mg bid. One treatment-related dose reduction (Grade 3 dizziness) resulted in no toxicity-related discontinuation.
Pharmacokinetics/Pharmacodynamics: Drug is rapidly absorbed with a half-life of 6 hours supporting bid dosing. Exposure increased dose proportionally. No major accumulation and no CYP450 inhibition or induction were observed. Pharmacodynamic results are pending, results will be included in presentation.
Efficacy: Bone marrow blast reductions were observed at all tested dose levels in 8 of 9 (89%) evaluable patients with elevated blast counts at baseline. Responses included 1 CR with full hematologic recovery, 1 CRi with negative minimal residual disease, and 2 bone marrow CRs. Three patients had a spliceosome mutation, and all 3 patients achieved a marrow CR or better. Patients with objective responses also saw signs of hematologic recovery.
Summary/Conclusion: CA-4948 monotherapy is so far well tolerated and with signs of clinical activity in this group of patients with advanced disease. Three of 3 patients with spliceosome mutations achieved a marrow CR or better. The study continues to define RP2D and to obtain definitive PK and PD profile.
References 1) Smith MA. et al., 2019 Nat Cell Biol. 21(5): 640–650
2) Choudhary G et al., 2019. Blood 134 (Suppl 1): 4224

S166 LOWER RESIDUAL MUTATION LOAD FOLLOWING TREATMENT WITH PEVONEDISTAT+AZACITIDINE VERSUS AZACITIDINE ALONE: COMPARATIVE ANALYSIS OF STUDY ARMS IN P-2001, A RANDOMIZED PHASE 2 TRIAL

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Background: Pevonedistat (PEVO), a first-in-class small-molecule inhibitor of the neural-precursor-cell-expressed developmentally down-regulated protein 8 activating enzyme, disrupts proteasomal degradation of selected proteins, leading to cancer cell death. In P-2001 (NCT02610777), overall response rate (ORR) among response-evaluable patients (pts) was 70.9% with PEVO + azacitidine (AZA) vs 60.4% with AZA alone.[1] Among pts with higher risk myelodysplastic syndromes (MDS), event-free survival (EFS; defined as time to transformation to acute myeloid leukemia [AML] or death, whichever occurred first) was longer, time to transformation was delayed, CR rate nearly doubled, and median duration of response was almost tripled with PEVO+AZA vs AZA.[1,2] Among pts with low-blast (LB)-AML, OS was numerically longer with PEVO+AZA vs AZA.[1] A highly-sensitive duplex sequencing method was developed to detect low variant allelic fraction (VAF <0.01%) of residual somatic mutation load after treatment and the emergence of new clones as a way to augment clinical observations at a molecular level.
Aims: Based on the clinical findings in P-2001, we hypothesized that PEVO+AZA would induce deeper and more persistent molecular responses than AZA alone. To test this hypothesis, we conducted a pre-specified comparative analysis in which the abundance of mutant allele burden in each study arm was measured over time using ultra-sensitive duplex sequencing.
Methods: In all, 96 bone marrow aspiration samples (55 higher-risk MDS; 15 higher-risk chronic myelomonocytic leukemia [CMML]; 26 LB-AML) were collected at screening and subjected to DNAseq. A custom TruSeq Hybrid Capture panel, incorporating 123 myeloid genes, was utilized to characterize the mutation profile of the baseline samples. Fifty eight longitudinal samples (33 higher-risk MDS; 7 higher-risk CMML; 18 LB-AML) collected at selected timepoints (Day 22 of Cycle [C] 2, C4, and C7, and at relapse) underwent duplex sequencing of a 54-myeloid gene targeted panel to ensure variant bases were identified with support from both DNA strands and to allow for ultra-deep sequencing coverage. Mutations identified at baseline were followed longitudinally to evaluate patterns of clearance over time.
Results: In accordance with the clinical efficacy observed in P-2001, the **Figure** below shows significantly less expansion of treatment-emergent mutations (defined as either newly detected or significantly increased VAF after treatment) in the PEVO+AZA arm compared with the AZA alone arm (29.3% vs 49.6%, respectively; p=0.002), particularly in genes associated with disease progression and leukemic transformation (including Ras-mitogen-activated protein [MAP] kinase signaling and myeloid transcription factors). This is consistent with the significantly larger percentage of mutations with low VAF (<0.01%) in PEVO+AZA vs AZA alone arms (34% vs 21%, respectively; p=0.03).

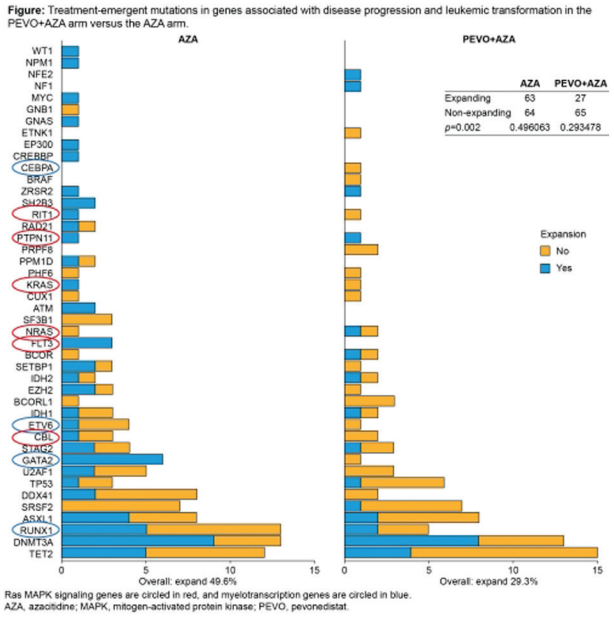


Figure: Treatment-emergent mutations in genes associated with disease progression and leukemic transformation in the PEVO+AZA arm versus the AZA arm.
Ras MAPK signaling genes are circled in red, and myelotranscription genes are circled in blue.
AZA, azacitidine; MAPK, mitogen-activated protein kinase; PEVO, pevonedistat.

Summary/Conclusion: These data suggest that the combination of PEVO+AZA reduces mutation burden and the likelihood of treatment-emergent resistance or progression mutations vs AZA, thereby maintaining response for a longer period. The combination of PEVO+AZA may be beneficial in higher-risk MDS and LB-AML, and potentially as a maintenance treatment in AML. This will be further assessed in the ongoing randomized Phase 3 trial (NCT03268954).

1. Sekeres MA, et al. *Leukemia* 2021. https://doi.org/10.1038/s41375-021-01125-4.
2. Sekeres MA, et al. The 62nd Annual Meeting and Exposition of the American Society of Hematology; Dec 5–8, 2020. Abstract 653.

S167 PHASE II STUDY OF THE IDH2-INHIBITOR ENASIDENIB IN PATIENTS WITH HIGH-RISK IDH2-MUTATED MYELODYSPLASTIC SYNDROMES (MDS)

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Background: Isocitrate dehydrogenase 2 (*IDH2*) mutations occur in 5% of patients (pts) with MDS. Enasidenib (ENA) is a selective oral inhibitor of the mutant IDH2 enzyme with single-agent activity in relapsed/refractory acute myeloid leukemia (AML).
Aims: An open label phase II study designed to evaluate the efficacy and tolerability of ENA, as monotherapy or in combination with azacitidine (AZA) in pts with higher-risk *IDH2*-mutated MDS. (NCT03383575)
Methods: Pts with higher-risk [Revised International Prognostic Scoring System risk > 3 or high molecular risk (HMR)] MDS/CMML or LB AML naïve to hypomethylating agents (HMA) received ENA100 mg orally daily for 28 d of each 28-d cycle + AZA 75 mg/m2 IV or SC on d 1-7 of each cycle (ENA+AZA), and pts with refractory or progressive MDS to prior HMA therapy received ENA alone (ENA), in 28-d cycles until unacceptable toxicity, relapse, transformation to AML, or progression. The primary endpoint was overall response rate (ORR) [complete remission (CR), marrow CR (mCR), partial remission (PR) and hematologic improvement (HI)]. Other endpoints include safety, and survival outcomes.
Results: 48 pts received ENA+AZA (n = 26) or ENA (n = 22). The median age was 73 yrs (range, 46-83). Most pts (72%) had HMR: *ASXL1* (39%), and *RUNX1* (17%). Median number Tx cycles was 4 (2–32) in the ENA+AZA, and 7 (1–23) in the ENA arm. Common Tx-related grade 3–4 AEs in the ENA+AZA arm were neutropenia (64%), thrombocytopenia (28%), and anemia (8%); these occurred in 10%, 0%, and 5%, in the ENA arm. Grade 3–4 infections occurred in 32% (ENA+AZA) and 14% (ENA). IDH differentiation syndrome occurred in 3 pts (12%) in the ENA+AZA and 5 pts (24%) in the ENA arm. Two deaths occurred during the initial 60 d, both unrelated to study and due to COVID. In response-evaluable pts (n=46), ORR was 84% (n = 21/25; 24% CR + 8% PR+44% mCR+ 8% HI] in the treatment naïve ENA+AZA and 43% (n = 9/21; 24% CR+5%PR+5% mCR+10% HI) in the HMA failure ENA arm (Table). Most common reason for Tx discontinuation was disease progression (ENA+AZA 20%, ENA 33%).5 pts (20%) received HCT in the ENA+AZA and 1 (5%) in the ENA arm. 7 pts in the ENA+AZA and 5 in the ENA arm were ongoing at data cutoff (Dec 31, 2020). After a median follow up of 12.6 mo, median OS was 32.2 mo in the ENA+AZA and 21.3 mo in the ENA arm.

	Response Evaluable (N = 46)	Arm A (Untreated) ENA+AZA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Overall response rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)
No response (NR), n (%)	**16 (35)**	**4 (16)**	**12 (57)**
Stable disease (SD)	14 (30)	4 (16)	10 (48)
Progressive disease (PD)	2 (4)	0 (0)	2 (10)

Summary/Conclusion: ENA is well tolerated and shows promising efficacy in *IDH2*-mutated higher risk MDS. Follow up and accrual is ongoing to better define duration and biomarkers of response.

S168 SABATOLIMAB PLUS HYPOMETHYLATING AGENTS (HMAS) IN PATIENTS (PTS) WITH HIGH-/VERY HIGH-RISK MYELODYSPLASTIC SYNDROME (HR/VHR-MDS) AND ACUTE MYELOID LEUKEMIA (AML): SUBGROUP ANALYSIS OF A PHASE 1 STUDY

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Background: Novel therapies providing improved and durable outcomes with a favorable safety profile are needed in higher-risk MDS and AML. Sabatolimab (MBG453) is a novel immuno-myeloid therapy targeting TIM-3, an immune regulator expressed on immune and myeloid leukemic cells but not on normal hematopoietic stem cells. In a Ph 1b study (NCT03066648), sabatolimab+HMA showed promising overall response rates in pts with HR/vHR-MDS (64%) and newly diagnosed (ND)-AML (41%). Response durability was encouraging, with an estimated 84% and 79% still in response after 6 mo. Treatment-emergent AE profile was consistent with that reported for HMA alone (Brunner ASH 2020).
Aims: To further explore safety/tolerability, efficacy in pt subgroups, and biomarkers with sabatolimab+HMA.

Methods: Study design/eligibility criteria have been reported. Pts with HR/vHR-MDS (per IPSS-R) or ND-AML who were HMA-naïve and ineligible for intensive chemotherapy received sabatolimab (1-2 infusions/mo) + decitabine or azacitidine. Primary objectives were safety/tolerability; secondary objectives included PK and preliminary efficacy. Data cutoff 22 Sep 2020; updated data will be presented.
Results: To explore sabatolimab+HMA safety/tolerability, sabatolimab dose interruption (>7 d delay), reduction, and discontinuation due to AE/death were assessed in 89 pts with HR/vHR-MDS (n=41) and ND-AML (n=48). Of 89 pts, 36 (40%) had sabatolimab dose interruption, 1 (1%) had sabatolimab dose reduction, 2 (2%) had dose interruption and reduction, 5 (6%) discontinued, and 3 (3%) had dose interruption and discontinued. Dose interruption rate in first 2 cycles was low (21% [19/89]). Of 8 discontinuations, 4 were due to AE (1/4 related to study treatment) and 4 to death. Of 22 pts with gr 4 neutropenia/thrombocytopenia at baseline (BL), 4 (18%) had dose interruption, 2 (9%) discontinued, 1 (5%) had dose interruption and discontinued, and none had dose reduction.
In analyses of remission rates (CR+mCR/CRi+PR) by BL factors, response was independent of BM blast burden in pts with HR/vHR-MDS or ND-AML. Remission rates were similar in pts ≥75 and 65-74 y: 50% (6/12) and 65% (11/17) with HR/vHR-MDS and 42% (8/19) for both groups with ND-AML. Response durability in pts ≥75 and 65-74 y was encouraging: an estimated 83% and 86% with HR/vHR-MDS and 69% and 88% with ND-AML remained in remission after 6 mo. In pts with *TP53* mutation or pts with ≥1 mutation conferring ELN high risk (*TP53*, *RUNX1*, *ASXL1*), respectively, remission rates were 55% (6/11; 4/6 in remission >200 d) and 59% (13/22; 8/13 in remission >200 d) for HR/vHR-MDS and 25% (1/4; in remission 129 d) and 50% (6/12; 2/6 in remission >200 d) for ND-AML. 6/7 responders with *TP53* mutation had complex karyotype.
Biomarker analyses identified IL-1β, a proinflammatory cytokine reported to promote expansion of AML progenitor cells, as one of the most differentially expressed genes in BM of responders vs nonresponders to sabatolimab+HMA, with expression levels inversely correlated with remission. Single-cell RNA sequencing showed sabatolimab+HMA downregulated IL-1β in blast cells but, consistent with prior observations in TIM-3 deficient pts, it upregulated IL-1β in myeloid cells.
Summary/Conclusion: Sabatolimab+HMA showed favorable tolerability in MDS/AML, including in pts with gr 4 cytopenias at BL. Promising remission rates were seen irrespective of BL blast burden and in older pts and pts with adverse risk mutation. This supports development of sabatolimab+HMA in the STIMULUS trial program in MDS/AML.

S169 CLINICAL CHARACTERISTICS AND SURVIVAL OF GATA2-MUTATED MYELOID NEOPLASMS: SINGLE INSTITUTION EXPERIENCE

A. Nanaa [1,*], D. Viswanatha [2], Z. Xie [1], D. Jevremovic [2], P. Nguyen [2], M. Salama [2], P. Greipp [3], K. Bessonen [2], N. Gangat [1], M. Patnaik [1], A. Pardanani [1], H. B. Alkhateeb [1], M. Shah [1], W. Hogan [1], A. Tefferi [1], M. Litzow [1], R. He [1], A. Al-Kali [1]

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Background: The *GATA2* gene, a DNA binding transcription factor with two zinc finger domains, is crucial for the regulation of hematopoietic stem cell proliferation, differentiation and maintenance (Wlodarski et al. Semin Hematol 2017). *GATA2* mutations are seen in myeloid neoplasms (MN) with different domains being associated with different leukemogenic
Aims: To describe patients (pts) with *GATA2*-mutated MN.
Methods: In this study, we included pts with *GATA2* mutations diagnosed with MN between 2015 and 2020 at Mayo Clinic. Pts characteristics were obtained from medical records. Our institution's next-generation sequencing (NGS) panel (OncoHeme) was analyzed to detect mutations in 42 genes recurrently mutated in MN. JMP® Pro 14.1.0 Software was used for statistical analysis
Results: Out of 3,872 pts who underwent NGS testing, a total of 54 pts were identified harboring 64 *GATA2* mutations in four diagnostic groups; 15 (27.7%) myelodysplastic syndromes (MDS), 16(29.6%) myelodysplastic/myeloproliferative neoplasms overlap (MDS/MPN), 9 (16.6%) myeloproliferative neoplasms (MPN) and 14 (25.9%) acute myeloid leukemia (AML). The median age was 67 years, 67% were males (Table 1).
A) *GATA2 mutations characteristics and co-mutations*: Median *GATA2* mutation VAF was 31% in the total cohort (range 5-74%), with 28%, 37%, 34%, and 39% (p= .6) seen in MDS, MDS/MPN, MPN, and AML, respectively. 31 (57%) mutations clustered in the zinc finger 2 domain (ZF2), 9 (17%) in the ZF1 domain and 14 (26%) were outside the ZF domains (non-ZF). ZF1-mutated pts had lower mean VAF compared to ZF2 pts (22% vs. 38%, p=.03), and the majority occurred in AML cases (6/9, 67%), with the most common mutation type being missense (78%). There was a significant association between mutation type and location (p <.0001). The median number of mutations per pts was 4. We identified 28 co-mutations in 52 (96%) pts. *ASXL1* (60%), *SRSF2* (33%) and *RUNX1* (19%) were the most common co-mutations. *ASXL1* was frequently co-mutated with *GATA2*-ZF2 (74%) and non-ZF (22.6%) (only 1 co-mutated with *GATA2*-ZF1). *ASXL1* was also more commonly co-mutated in chronic MN compared to AML (94% vs. 6%, p=.0001). *KIT*, *CEBPA* and *PTPN11* were co-mutated only in ZF1-mutated pts. *KIT, FLT3*, *PTPN11, CEBPA* were co-mutated only in AML, whereas *CALR* was co-mutated only in MPN.
B) *Survival outcome*: After a median follow-up time of 26.4 months, 34 (63%) pts died with a median OS of 23.9, 22.4, 20.6, and 5.6 months in MDS, MDS/MPN, MPN, and AML pts; respectively. After excluding AML pts for survival analysis, we found that pts with several *GATA2* mutations had poorer median OS (4.9 vs. 24.5 months, p=0.03) compared to those with single *GATA2* mutation. MDS pts with chromatin modification co-mutations (*BCOR, EZH2, ASXL1, KDM6A*) (17 vs. 30 months, p=.04) or frameshift (FS) mutation (10.3 vs. 27.3 months, p=.05) had worse median OS compared to those without chromatin modification co-mutation or non-FS mutation, respectively. MDS/MPN overlap pts with *RUNX1* co-mutation had worse median OS (2.2 vs. 25.7 months, p=.0004) than their un-mutated counterparts. There was no difference in median OS between *GATA2*-ZF1, ZF2, and non-ZF (30 vs. 20.6 vs. 22.4 months, p= .7).

Table1. Characteristics and hematological features of GATA2 patients.

Variable	Value
No. of patients	54
Age years, median(range)	67 (26 – 89)
Sex (male), n (%)	36 (67)
Hemoglobin G/DL, median (range)	8.6 (5.8 – 13)
Leukocytes 109/L, median (range)	12.9 (0.3 – 186)
Thrombocytes 109/L, median (range)	53 (1.5 – 873)
MCV median (range)	93 (77 – 119)
ANC , median (range)	6.64 (0.17 – 96.7)
AMC , median (range)	0.39 (0 – 44.5)
ALC , median (range)	1.44 (0.37 – 38.8)
RDW, median (range)	17.7 (13.1 – 26.8)
Number of mutations, median (range)	4 (1 - 6)

Summary/Conclusion: We describe the spectrum and characteristics of *GATA2* mutations across myeloid neoplasms. There was an impact of different *GATA2*-mutation types, single vs several *GATA2* mutations, and co-mutations pattern on survival. Our work was limited by the small number of patients and inability to completely rule out germline mutation possibility.

New directions in aplastic anemia and PNH

S170 GATA2 HAPLOINSUFFICIENCY REDUCES AGED HEMATOPOIETIC STEM CELL FUNCTIONALITY IN MULTIPLE LINEAGES

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Background: Mutations in the *GATA2* transcription factor cause immunodeficiency syndromes, which can present with monocytopenia, B cell, NK cell and dendritic cell deficiencies and an increased lifetime risk for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) of 80% at 40 years of age. The role of GATA2 haploinsufficiency in the MDS/AML progression is still poorly understood.
Aims: Because patients with *GATA2* mutations have increased lifetime risk of developing MDS/AML, we hypothesize that aging has a

contributing factor in the development of MDS/AML in Gata2 haploinsufficiencies. Therefore, we have analysed *Gata2*$^{+/-}$ mice in aging to reveal the Gata2 dependent mechanisms in leukemic progression.
Methods: We aged *Gata2*$^{+/-}$ and WT mice and performed primary and secondary transplantations of the aged bone marrow to young, lethally irradiated, WT recipients. We have also performed transcriptome analysis on HSCs of the adult, aged and transplanted *Gata2*$^{+/-}$ and WT mice.
Results: We found that HSCs in *Gata2*$^{+/-}$ mice have lost their quiescence. 2 months after transplantation of the aged cells, *Gata2*$^{+/-}$ mice developed B cell cytopenia, which represents the most common feature of GATA2 haploinsufficiency in patients. B cell cytopenia was persistent also after the secondary transplantation. We observed a significantly reduced blood chimerism in *Gata2*$^{+/-}$ mice after secondary transplantation, which suggested HSC exhaustion. 5 months after the secondary transplantation, *Gata2*$^{+/-}$ mice developed neutropenia and monocytopenia in addition to B cell cytopenia.
Summary/Conclusion: These results indicate a reduced functionality of aged and transplanted *Gata2*$^{+/-}$ HSCs in multiple lineages. Currently, we are working on the identification of Gata2 haploinsufficiency phenotype and the analysis of transcriptomic changes in Gata2 haploinsufficient HSCs observed in our aged *Gata2*$^{+/-}$ mouse model. Additionally, we are working on understanding the clonality of HSCs in the aged *Gata2*$^{+/-}$ mice.

S171 GLYCOSYLPHOSPHATIDYLINOSITOL-ANCHORED PROTEIN DEFICIENCY CONFERS RESISTANCE TO ANTIGEN-SPECIFIC T CELLS ON HEMATOPOIETIC STEM PROGENITOR CELLS IN APLASTIC ANEMIA PATIENTS WITH HLA-DR15

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Background: Glycosylphosphatidylinositol-anchored protein-deficient (GPI[-]) cells are often detected in patients with acquired aplastic anemia (AA) and are thought to represent immune pathogenesis of bone marrow (BM) failure; however, little is known what kind of immune responses favor the proliferation of *PIGA*-mutated hematopoietic stem progenitor cells (HSPCs) over GPI(+) HSPCs to induce an increase in GPI(-) cells in peripheral blood (PB) of AA patients. We recently identified HLA-DR lacking HSPCs in four AA patients with HLA-DR15 whose hematopoietic function depended on cyclosporine (CsA, ASH2020 abstract #933). Since DR15 has been implicated in the development of PNH and all these patients possessed GPI(-) granulocytes, CD4$^+$ T-cell attack that allows DR15(-) HSPCs to survive may also contribute to the survival advantage of GPI(-) HSPCs.
Aims: To test this hypothesis, we analyzed the HLA-DR expression on GPI(+) and GPI(-) HSPCs in PB of patients with AA or PNH in remission, and determined which HSPC population underwent the HLA-DR loss.
Methods: We determined the HLA-DR expression on HSPCs defined as lineage$^-$CD45^{dim}CD34$^+$CD38$^+$ cells in 52 AA patients (38 with GPI[-] granulocytes and 14 without) and 5 with hemolytic PNH (37 with DR15 and 20 without DR15) as well as 20 healthy individuals using flow cytometry with anti-pan-HLA-DR antibodies. All patients were in remission after immunosuppressive therapy or anabolic steroids, although 20 required low-dose CsA to maintain remission. Nineteen (33%) had HLA-class I allele-lacking (HLA-class I[-]) leukocytes due to 6pLOH and/or allelic mutations.
Results: Eight (14.0%, 6 with AA and 2 with PNH) of the 57 patients had DR(-) cell populations accounting for 11.1% to 56.0% (median 39.8%) of HSPCs, and these cells were not detected among either monocytes or B lymphocytes of the same patients or among HSPCs of any healthy individuals. All 8 of these patients possessed either *HLA-DRB1*15:01* (n=5), *DRB1*15:02* (n=2), or *DRB1*15:01/15:02* (n=1), with the other DRB1 alleles differing among individuals. In addition to HSPCs completely lacking DR, these patients also possessed HSPCs partially lacking DR, findings that were not detected in the other 49 patients or healthy individuals. Of particular interest, DR(-) cells were exclusively detected in GPI(+) HSPCs in four patients (two with AA and two with PNH) whose HSPCs were able to be analyzed separately for GPI(+) and GPI(-) HSPCs. In one patient whose HSPCs were serially evaluable over 6 years, the DR(-) cell proportion increased from 29.2% to 57.1% following temporary discontinuation of CsA, during which period the proportion of GPI(-) granulocytes in PB increased from 0.037% to 3.78%. Only 1 of the 8 patients possessed HLA-class I(-) leukocytes, which were detected in 19 (39%) of 49 patients not possessing DR(-) HSPCs.
Summary/Conclusion: HLA-DR-lacking HSPCs were exclusively detected in AA/PNH patients with DR15, suggesting that CD4$^+$ T cells specific to autoantigens presented by DR15 are involved in the development of BM failure. The presence of HSPCs partially lacking DR in these patients suggests the presence of HSPCs that lack DR15 but retain the other DR allele. Given that DR(-) cells were only detected in GPI(+) HSPCs and the expansion of DR(-) cells occurred concomitantly with the expansion of GPI(-) clones after CsA cessation, the antigen-specific CD4$^+$ T-cell attack against HSPCs is likely responsible for the survival advantage of GPI(-) HSPCs in AA/PNH.

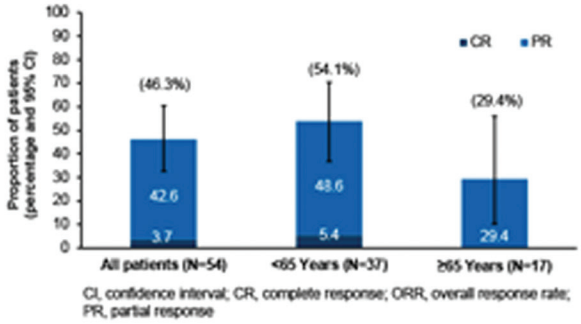
S172 AN INTERVENTIONAL, PHASE 2, SINGLE-ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF ELTROMBOPAG COMBINED WITH CYCLOSPORINE AS FIRST-LINE THERAPY IN ADULTS WITH SEVERE ACQUIRED APLASTIC ANEMIA (SOAR)

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Background: Severe aplastic anemia (SAA) is a life-threatening bone marrow failure disorder characterized by pancytopenia and a hypocellular bone marrow. The standard of care for patients that are ineligible for hemopoietic stem cell transplant is immunosuppressive therapy (IST), comprising antithymocyte globulin (ATG) and cyclosporine A (CsA). Horse (h-) ATG is considered more effective than rabbit ATG; however, lack of response, relapse, and clonal evolution remain significant limitations. Expense, individual intolerance, and a lack of global availability of h-ATG also leave many patients (pts) with more limited treatment options and poorer outcomes. Eltrombopag (ETB) is indicated for use in patients with SAA who have had an insufficient response to IST (FDA PI, 2014) or are refractory to IST (EMA SmPC, 2015). More recently in the USA, ETB may also be used in combination with IST as first-line treatment (FDA PI, 2018).
Aims: To assess the efficacy and safety of an ATG-free regimen (ETB + CsA) in treatment-naïve pts with SAA.
Methods: SOAR (NCT02998645) is a Ph2, single-arm, multicenter, open-label study. Adult pts with SAA received ETB + CsA as first-line therapy for 6 months; responders continued CsA therapy for an additional 24 months (subsequently reduced to 18 months). The primary efficacy endpoint was overall response rate (ORR) by 6 months. ORR was defined as the proportion of pts with complete response ([CR] = absolute neutrophil count [ANC] ≥1000/μL AND platelet count ≥100,000/μL AND hemoglobin ≥10 g/dL) plus the proportion of pts with partial response ([PR] = any 2 of the following counts: ANC ≥500/μL; platelet count ≥20,000/μL; automated reticulocyte count ≥60,000/μL, but not sufficient for a CR). CR and PR were confirmed by 2 assessments ≥7 days apart; transfusion restrictions were applied. Based on historical data, an ORR of ≥30% was considered clinically meaningful.
Results: A total of 54 pts were enrolled. The median (interquartile range [IQR]) age was 55.0 (40.0-67.0) years, 63.0% were male, and the majority of pts were White (40.7%) or Asian (40.7%). The median (IQR) duration of exposure to ETB and CsA were 5.7 (2.5-5.8) months and 5.7 (2.4-8.1) months, respectively, and the median (IQR) daily ETB dose was 150.0 (100.0-150.0) mg/day. In the full analysis set, the primary endpoint was met with an ORR by 6 months of 46.3% (25/54); 95% CI, 32.6-60.4% (Fig. 1). Of the 25 responders, 2 (3.7%) achieved CR by 6 months. ORR by 6 months is also shown by age group (<65 and ≥65 years) (Fig. 1). Secondary endpoints included ORR by 3 months (40.7% [22/54]; 95% CI, 27.6-55.0%), and ORR at 6 months (ie, patients with confirmed response at 6-month visit: 37.0% [20/54]; 95% CI, 24.3-51.3%). Adverse events (AEs) occurred in 52/54 pts; 45 (83.3%) pts experienced treatment-related AEs (TAEs), 23 (42.6%) of whom had a grade ≥3 TAE. The most common all-grade AEs were increased blood bilirubin (40.7%), nausea (29.6%), increased alanine aminotransferase (22.2%), and diarrhea (22.2%). Seven (13.0%) pts discontinued study due to AEs. There were 8 on-treatment deaths (aplastic anemia [n=3]; COVID-19, hemorrhage, multi-organ dysfunction syndrome, pyrexia, and thrombosis [all n=1]); no deaths were considered treatment-related.

Figure 1: ORR by 6 months (full analysis set)



CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response

Summary/Conclusion: Data from the SOAR study indicate that ETB + CsA therapy may be beneficial as first-line treatment for SAA pts who cannot use ATG. The ORR is particularly notable, given the median age of this pt cohort (55.0 years). No new safety signals were identified.

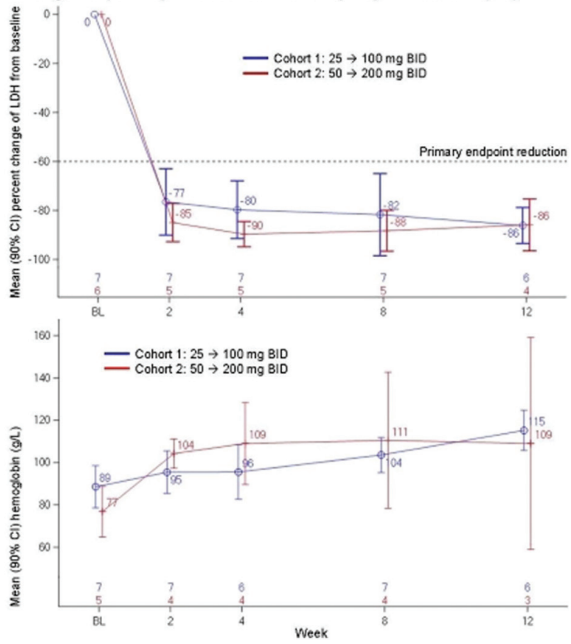
S173 FIRST-LINE TREATMENT OF PNH PATIENTS WITH IPTACOPAN LEADS TO RAPID AND DURABLE HEMOGLOBIN INCREASE BY CONTROLLING BOTH INTRA- AND EXTRAVASCULAR HEMOLYSIS

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a severe hematological disease caused by an acquired PIGA mutation in hematopoietic stem cells, leading to loss of regulatory proteins affecting the complement alternative pathway, of which factor B is an essential component. The only regulatory approved treatment for hemolytic PNH is based on antibodies targeting complement component 5 (C5), controlling intravascular hemolysis, reducing thromboembolic events, and eventually improving long-term survival. However, 20-50% of patients remain transfusion-dependent due to persistent extravascular hemolysis, and an additional 20-40% exhibit varying degrees of residual anemia. Iptacopan (LNP023) is a new, oral, selective and potent first-in-class factor B inhibitor, designed to block both intra- and extravascular hemolysis.
Aims: The trial presented here investigates the effect of first-line iptacopan monotherapy on intra- and extravascular hemolysis, the extent of red blood cell (RBC) C3 opsonization, and changes in hemoglobin levels in anti-C5 naive PNH patients with active hemolysis.
Methods: CLNP023X2204 (NCT03896152) is a multi-national, randomized Phase 2 efficacy, safety, pharmacokinetics/-dynamics study assessing four iptacopan doses in two separate cohorts with two treatment periods each in treatment-naive adult PNH patients with active hemolysis. The primary objective is to assess the effect of iptacopan on the reduction of PNH-associated hemolysis. Additional objectives include assessing the effect on hemoglobin levels, the dose-response effect, and the effect on markers associated with a risk of thrombosis.
Results: A total of N=13 patients (ages 20-62; n=7 female) were randomized to either Cohort 1 (iptacopan 25-to-100 mg dose increase at Week 4; N=7) or Cohort 2 (50-to-200 mg; N=6). Median (range) lab values at baseline were: Hb 86.5 (68-107) g/L, reticulocytes 209 (30-352) x10E9/L, LDH 1686 (1008-3761) U/L, bilirubin 27.0 (20.0-51.0) umol/L; haptoglobin was below lower limit of detection for all patients. The primary endpoint of lowering LDH by at least 60% was reached for all patients. Mean LDH levels declined by 79.7 and 86.2% in Cohort 1 and by 89.7 and 85.9% in Cohort 2 at weeks 4 and 12, respectively [Figure 1]. Importantly, all patients remained transfusion-free up until week 12, with the exception of one patient who received a single RBC transfusion on study day 3; Hb levels spontaneously increased by a mean of 23.4 and 37.1 g/L at week 12 in Cohorts 1 and 2, respectively [Figure 1]; and no thromboembolic events were reported. In addition, reticulocyte counts decreased by a mean of 93.0 and 84.9 x10E9/L, and bilirubin decreased by a mean of 21.6 and 23.2 umol/L in Cohorts 1 and 2, respectively. Iptacopan was well tolerated (n=1 discontinued from the trial at Day 2 due to headache); no fatal events and no serious adverse events were reported during the 12-week treatment period.

Figure 1: Mean percent change of LDH from baseline (top) and mean hemoglobin (bottom) over time for cohort 1 (blue) and cohort 2 (red)



Summary/Conclusion: Iptacopan is a new, well-tolerated oral factor B inhibitor that blocks both intra- and extravascular hemolysis in patients with hemolytic PNH. 12-week study results demonstrate that, in anti-C5 naive patients with active hemolysis, iptacopan therapy ≥50 mg BID results in normalization of various hemolytic markers and resolution of anemia. Maximal effects on various efficacy parameters were obtained at 200 mg BID. These results demonstrate that proximal inhibition of the complement cascade parallel and further improve the hematological benefit seen with anti-C5 therapies, with iptacopan eventually offering an alternative first-line therapy for patients with PNH.

S174 FORTY-EIGHT WEEK EFFICACY AND SAFETY OF PEGCETACOPLAN IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND SUBOPTIMAL RESPONSE TO PRIOR ECULIZUMAB TREATMENT

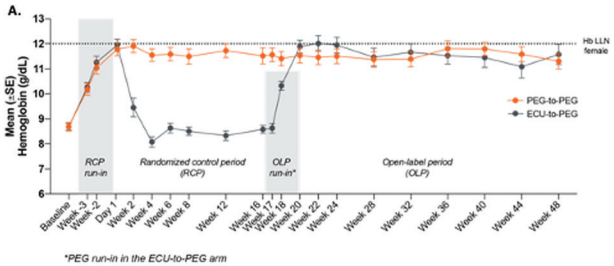
R. Peffault de Latour [1,*], J. Szer [2], I. Weitz [3], A. Röth [4], B. Höchsmann [5], J. Panse [6], K. Usuki [7], M. Griffin [8], J. -J. Kiladijan [9], C. M. de Castro [10], H. Nishimori [11], L. Tan [12], M. Al-Adhami [13], P. Deschatelets [13], C. Francois [13], F. Grossi [13], A. Risitano [14,15], P. Hillmen [16]

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United Kingdom, [13]Apellis Pharmaceuticals, Inc, Waltham, MA, United States, [14]Hematology and BMT Unit, AORN San Giuseppe Moscati, Avellino, [15]Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy, [16]Department of Haemotology, St James University Hospital, Leeds, United Kingdom

Background: Pegcetacoplan (PEG), a PEGylated peptide targeting proximal complement protein C3, can control both intravascular and extravascular hemolysis. In the PEGASUS trial (NCT03500549), a phase 3, randomized, open-label, active-comparator controlled study, PEG was shown to be superior to eculizumab (ECU) after 16 weeks in improving hemoglobin levels (Hb) and clinical outcomes in patients with paroxysmal nocturnal hemoglobinuria (PNH) *(Hillmen P et al, EHA 2020)*.
Aims: We report on the efficacy and safety of PEG through 48 weeks of treatment.
Methods: This study is a continuation of the PEGASUS trial. Eighty patients ≥18 years with PNH, and Hb levels <10.5 g/dL despite stable ECU treatment for ≥3 months, were enrolled. Patients completed a 4-week run-in period with both ECU and PEG before 1:1 randomization to PEG (n=41; 1080 mg subcutaneously twice weekly) or ECU monotherapy (n=39; continued dosing regimen). The primary endpoint was the change from baseline (CFB) in Hb levels to Week 16. After the randomized control period (RCP), patients could continue to an open-label period (OLP), which included a 4-week run-in period for ECU patients (ECU-to-PEG), followed by PEG monotherapy (same dosage as in RCP) for all patients for a 48-week total study period. Key secondary endpoints included blood transfusion avoidance, CFB in absolute reticulocyte count (ARC), CFB in lactate dehydrogenase (LDH), CFB in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, and adverse events (AEs).
Results: Three patients discontinued PEG during the 16-Week RCP due to hemolysis; the remaining 77 patients entered the OLP. PEG demonstrated superiority to ECU with a mean Hb level improvement of 2.7 g/dL at Week 16, which was sustained throughout the OLP in all patients receiving PEG monotherapy. ECU-to-PEG patients demonstrated Hb improvement with mean Hb levels of 11.6 g/dL at Week 48 (CFB: 2.9 g/dL), while PEG-to-PEG patients maintained high Hb levels through the OLP with a mean Hb level of 11.3 g/dL at Week 48 (CFB: 2.6 g/dL) (Figure A).
Seventy-three percent of PEG-to-PEG patients remained transfusion free for the 48-week study, and 72% of the ECU-to-PEG patients were transfusion free during the OLP through Week 48. Improvements in ARC (PEG-to-PEG: 80.0×10^9 cells/L; ECU-to-PEG: 94.0×10^9 cells/L), LDH (PEG-to-PEG: 222.7U/L; ECU-to-PEG: 224.1 U/L), and FACIT-fatigue score (PEG-to-PEG: 40.6; ECU-to-PEG: 42.5) were also observed at Week 48 (Figure B).
The most common AEs by physician-reported preferred term throughout the study for all patients who received PEG were injection site reactions (36%), hemolysis (24%), and diarrhea (21%). Of all study patients, 30% experienced serious AEs with 6% possibly related to PEG. No cases of meningitis were reported. One death was reported due to COVID-19, unrelated to study treatment. Six patients discontinued due to hemolytic events: 5 classified by the treating physician as "hemolysis" and 1 as "hemolytic anemia." Overall, 12 patients (15%) discontinued PEG: 3 in RCP, 8 in OLP due to TEAEs (6 in ECU-to-PEG, 2 in PEG-to-PEG), and one during follow-up; one patient withdrew due to physician decision.

A.



*PEG run-in in the ECU-to-PEG arm

B.

	PEG			ECU		
	Baseline	Week 16	Week 48 PEG-to-PEG	Baseline	Week 16	Week 48 ECU-to-PEG
Hb level, g/dL; NRR, 12.0-18.0 g/dL Mean (SD)[a]	8.7 (1.1)	11.5 (2.0)	11.3 (1.8)	8.7 (0.9)	8.6 (1.0)	11.6 (2.2)
Transfusion Transfusion avoidance, n (%)	N/A	35 (85)	30 (73)	N/A	6 (15)	28 (78)
ARC, ×10^9 cells/L; NRR, 30-120×10^9 cells/L Mean (SD)	217.5 (75.0)	77.1 (26.6)	80.0 (26.8)	216.2 (69.1)	221.8 (88.7)	94.0 (50.1)
LDH, U/L; NRR, 113-226 U/L Mean (SD)	257.5 (97.7)	189.1 (78.1)	222.7 (141.1)	308.6 (284.8)	353.2 (477.5)	224.1 (133.5)
FACIT-Fatigue Score; population norm (43.6) Mean (SD)	32.2 (11.4)	41.8 (9.6)	40.6 (10.1)	31.6 (12.5)	30.6 (11.8)	42.5 (8.7)

ARC, absolute reticulocyte count; ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin, LDH, lactate dehydrogenase; N/A, not applicable; NRR, normal reference range; PEG, pegcetacoplan; PNH, Paroxysmal Nocturnal Hemoglobinuria; PRBC, packed red blood cell; SD, standard deviation. [a]Observed values by group differ from the combined PEG monotherapy mean CFB described in the text.

Summary/Conclusion: Adult patients with PNH with suboptimal response on prior ECU treatment received PEG in this continuation of the PEGASUS trial and experienced durable treatment effect in all efficacy parameters at Week 48. The safety profile of PEG was consistent with previously reported data. The results suggest that PEG represents a new effective therapeutic option for patients with PNH.

Basic and translational myeloma research

S175 SINGLE AND DOUBLE HIT EVENTS IN GENES ENCODING FOR IMMUNOTHERAPY TARGETS IN MULTIPLE MYELOMA

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Background: BCMA targeting CAR T-cells or T-cell engaging bispecific antibodies (TCE) show high response rates in relapsed/refractory (RR) multiple myeloma (MM). Beyond BCMA, a number of other plasma cell targets such as SLAMF7, FCRH5, and GPRC5D are currently under investigation with promising preliminary results. Yet, patients continue to relapse and no survival plateau after CAR T-cells or TCEs has been observed so far. Recently, we described the first tumor-intrinsic resistance mechanism to BCMA-directed CAR T-cell therapy, unraveling biallelic loss of the *BCMA* gene as the cause of antigen escape after anti-BCMA CAR T therapy. Whether this mechanism of resistance is also relevant for TCE therapy, is currently unknown.
Aims: (1) To elucidate the mechanism of resistance to BCMA-directed TCE treatment. (2) To analyze genomic alterations in genes encoding for plasma cell targets in MM patients prior to immunotherapy by WGS and RNA sequencing (RNAseq).
Methods: WGS was performed in 100 MM patients (50 newly diagnosed, 50 RR) with WGS libraries prepared from CD138 purified cells and 2x150bp paired-end sequences generated on NovaSeq6000 with 100x coverage. For RNAseq of 72 patients stranded RNA libraries were produced and 2x100bp paired-end reads were sequenced on NovaSeq6000 with a median of 64 million reads per sample. BCMA protein expression was determined by immunohistochemistry (AF193, R&D systems) on paraffin embedded bone marrow sections.
Results: We report on a RRMM patient who experienced homozygous *BCMA* gene deletion after relapse from CD3xBCMA TCE therapy. Initially, the patient responded well to TCE therapy and achieved a CR, but relapsed after 6 months of treatment. Retrospective immunohistochemistry on bio-banked trephine biopsies showed strong and consistent BCMA expression prior to TCE therapy but a complete loss of BCMA expression at relapse. Without knowing about BCMA loss at relapse at that time, belantamab mafodotin was administered, to which the patient was primary refractory. Together, irreversible antigen loss and failure of subsequent BCMA-directed therapy, highlights targeted immunotherapies to present an evolutionary bottleneck in MM progression.
To further explore the relevance of this resistance mechanism, we screened for genomic alterations in *BCMA* and other immunotherapy targets. Indeed, we found heterozygous deletions in *GPRC5D* (15%), *CD38* (10%), *SDC1* (5%), *TNFRSF17* (4%) and *NCAM1* (3%). Overall, heterozygous deletions occurred in 30% of patients, and some patients showed deletions in up to three different immunotarget genes. As expected, we observed a clear trend for more deletions in pretreated patients. Notably, single nucleotide variants (SNV) in genes encoding for immune targets were only found at low frequency. Gains, heterozygous deletions, and SNV in genes encoding for immunotherapy targets did not result in significant changes of gene expression by transcriptome analysis in 72 patients, suggesting that expression of these genes is not solely regulated by their copy number and that antigen loss requires a biallelic event.
Summary/Conclusion: (1) Biallelic *BCMA* gene deletion may be a key immune-evasion mechanism to BCMA targeting T-cell therapies. (2) This mechanism of resistance to immunotherapies may affect alternative antigens as we detected genomic vulnerability in their encoding genes in a significant number of treatment naïve patients. (3) Combination of different immunotargets, e.g. multi-specific CAR T-cells, might be an approach to overcome drug resistance caused by loss of a single antigen.

S176 DISCOVERY OF A SELECTIVE INHIBITOR OF THE SETD2 HISTONE METHYLTRANSFERASE WITH POTENT IN VITRO AND IN VIVO ACTIVITY IN PRECLINICAL MODELS OF MULTIPLE MYELOMA

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Background: Multiple myeloma (MM) is a heterogeneous disease of monoclonal plasma cells. Nearly 50% of MM patients harbor translocations of the immunoglobulin heavy chain (IgH) gene on chromosome 14q32 leading to overexpression of putative oncogenes (Kuehl, 2002). One of the most common translocations in MM (15-20%) juxtaposes IgH control elements with two genes on chromosome 4, fibroblast growth factor receptor 3 and multiple myeloma SET domain (MMSET). This (4;14) (p16; q32) translocation is associated with poor prognosis and less effective treatment with standard of care (SOC) therapy. MMSET expression has been confirmed as a driver in t(4;14) MM pathogenesis (Keats, 2003), but MMSET remains undruggable. SETD2 is currently the only known histone methyltransferase (HMT) capable of catalyzing H3K36 trimethylation, utilizing MMSET-catalyzed H3K36me2 as its substrate. To date, a gain of function role for SETD2 in oncogenesis and tumor survival has not been demonstrated. Our data suggests that the overexpression of MMSET and subsequent increase in H3K36me2 in t(4;14) MM leads to a dependency on SETD2 for MM cell growth and survival.
Aims: Characterization of a small molecule SETD2 inhibitor exhibiting potent *in vitro* anti-proliferative activity and a pharmacokinetic profile that supports *in vivo* efficacy in preclinical models of MM.
Methods: Biochemical selectivity assays performed in a panel of HMTs and a 14-day cellular proliferation assay determined IC_{50}'s in MM cell lines of diverse genetic subtypes. Combinatorial potential of SETD2 inhibition with anti-MM SOC agents was evaluated in 7-day cotreatment *in vitro* cellular assays. Mouse xenograft studies in MM models assessed tumor growth inhibition. H3K36me3 levels determined by western blot and ELISA to evaluate target engagement by SETD2 inhibitor.
Results: A small molecule inhibitor of SETD2 methyltransferase enzymatic activity was characterized demonstrating an IC_{50} value of 5.3 nM in biochemical assays with greater than 10,000-fold selectivity against a panel of 14 HMTs. Inhibition of SETD2 results in potent inhibition of proliferation in 6 of 7 t(4;14) MM cell lines *in vitro* with an average IC_{50} of 0.14 uM and resulted in marked reduction of H3K36me3. Isogenic t(4;14) cell lines containing allele-specific knock-out of MMSET demonstrated sensitivity to SETD2 inhibition only in the presence of the overexpressed MMSET allele. *In vivo* efficacy studies in the KMS11 t(4;14) cell line-derived xenograft model resulted in robust tumor growth inhibition (TGI) in a dose-dependent manner with maximal TGI of 95% achieved at the top doses administered and corresponding reduction in intratumoral H3K36me3 levels. Interestingly, *in vitro* anti-proliferative activity was also demonstrated in 13 of 15 non-t(4;14) MM cell lines tested with an average IC_{50} of 1.8 uM. SETD2 inhibition in xenografts from the two most sensitive non-t(4;14) MM cell lines resulted in strong TGI with maximal inhibition of 92% at the top dose administered. Lastly, *in vitro* synergy was observed with MM SOCs, supporting a rationale to combine SETD2 inhibition with current MM therapies.
Summary/Conclusion: To our knowledge, these are the first preclinical data to show successful targeting of the underlying oncogenic mechanism driven by MMSET overexpression in t(4;14) MM and the first demonstration of SETD2 as an oncogenic driver. Importantly, this work validates the targeting of SETD2 with a small molecule inhibitor in MM and presents a promising potential therapeutic option for the high-risk t(4;14) MM patient population.

S177 REGULATED MEMBRANE BOUND IL-15 INCREASES BCMA CAR-T EXPANSION, POTENCY, AND DURABILITY OF RESPONSE IN A XENOGRAFT MODEL OF MULTIPLE MYELOMA

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Background: B cell maturation antigen (BCMA) is a promising immunotherapy target for patients with multiple myeloma (MM). Although BCMA CAR-T therapies have delivered high overall and complete response rates in heavily pretreated patients, a majority of patients continue to relapse and MM remains incurable, supporting the need for more potent and durable therapies.
Aims: To develop a more potent and persistent BCMA therapy, we engineered BCMA CAR-Ts with membrane bound IL-15 (mbIL15) to determine whether IL15 could improve BCMA CAR-T performance, enabling greater *in vivo* expansion potential and antigen-independent CAR-T persistence following tumor clearance. To engender this potent product with titratable, drug-like properties, we also coupled mbIL15 to Obsidian's regulated cytoDRiVE™ technology, providing superior efficacy and safety for patients with MM.
Methods: Obsidian's cytoDRiVE™ platform consists of small, fully human protein sequences called drug responsive domains (DRD)s that enable regulated expression of a fused target protein under control of FDA-approved, orally bioavailable small molecule ligands. BCMA CAR-T cells were engineered with mbIL15 fused to a carbonic anhydrase 2 (CA2) DRD that facilitates regulation of mbIL15 expression via acetazolamide (ACZ) administration. *In vitro* mbIL15 activity was assessed in an assay of CAR-T expansion and survival in the absence of antigen or exogenous cytokines and by immunophenotyping. CAR-T function was assessed *in vitro* using cytotoxicity and cytokine production assays. We also evaluated IL15-driven antigen-independent BCMA CAR-T cell expansion in non-tumor-bearing NSG mice, as well as anti-tumor efficacy in a $BCMA^+$ MM xenograft tumor model.
Results: mbIL15-BCMA CAR-T cells retained equivalent CAR activity compared with standard BCMA CAR-Ts not expressing mbIL15, as evidenced by cytotoxicity against, and IFNγ and IL2 cytokine production in response to, $BCMA^+$ RPMI8226 MM cells *in vitro*. In the presence of ACZ, functional levels of mbIL15 were expressed on the cell surface of the mbIL15-BCMA CAR-Ts, which supported *in vitro* antigen independent survival, expansion, and development of a $CD45RO^-$, $CCR7^+$, $CD95^+$, $CD27^+$ memory stem cell phenotype. Two weeks after adoptive cell transfer into non-tumor-bearing mice, animals receiving daily ACZ displayed elevated numbers of CAR-Ts in the peripheral blood, and mbIL15 was specifically expressed on CAR-Ts from ACZ- but not vehicle-dosed animals. In RPMI8226 tumor-bearing mice, regulated mbIL15 increased expansion of BCMA CAR-T cells, promoting anti-tumor activity at lower cell doses than BCMA CAR-Ts without mbIL15. Upon tumor rechallenge, regulated mbIL15 prevented tumor growth, demonstrating CAR-T persistence for up to 72 days post initial cell transfer. Regulation of mbIL15 expression on BCMA CAR-Ts also resulted in modulation of inflammatory cytokines detected in the plasma of MM tumor-bearing mice.
Summary/Conclusion: Regulated mbIL15 resulted in BCMA CAR-Ts marked by a memory stem cell phenotype with increased anti-tumor activity and enhanced response duration, even at suboptimal CAR-T cell doses. Regulating mbIL15 levels with our novel DRD control system supports improved antigen-independent T cell expansion and survival, translating to more potent and persistent BCMA CAR-Ts. Thus, Obsidian's cytoDRiVE™ technology confers drug-like properties to CAR-Ts, providing physicians with potentially greater control of CAR-T expansion and survival to optimize durable CAR-T efficacy and safety for patients with MM.

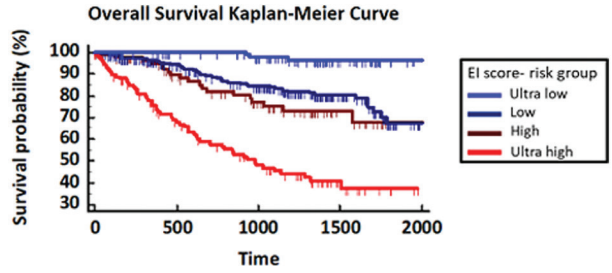
S178 IMPROVING THE RISK STRATIFICATION OF MULTIPLE MYELOMA WITH A BASE EDITORS/INFLAMMATION-BASED SCORING SYSTEM

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Background: Current clinical prognostication of newly diagnosed MM (NDMM) patients relies on clinical parameters and/or recurrent genetic changes, which mainly reflect early events in the development of MM. However, recent insights into the pathogenesis of MM highlighted

genome/transcriptome editing through APOBEC/ADAR genes as well as inflammation as drivers for the onset and progression of MM.
Aims: To build a superior base editors/inflammation-based risk scoring system reflecting biological processes that drive the progression of MM.
Methods: We hypothesized that a prognostic score reflecting biological processes as well as clinical features is superior to the currently used classification systems for MM patients, such as ISS, R-ISS and the Mayo clinic classification. The Multiple Myeloma Research Foundation CoMMpass study genomics dataset, combining mRNA Seq and clinical data from more than 700 patients, allowed us to evaluate the prognostic value of demographic and clinical parameters, cytogenetics, and gene expression levels of ADAR and the APOBEC family as well as inflammation-modulating cytokines of MM patients. We calculated hazard ratios and Kaplan-Meier survival estimates for all extracted features. Combining clinical variables that were significantly associated with PFS and OS, we then applied machine learning approaches to identify the most accurate classification model to define a new risk score that is easy to compute and able to stratify NDMM patients more accurately than cytogenetics-based classifiers.
Results: Based on our machine learning models, we defined a weighted OS/PFS risk score (*E*ditor-*I*nflammation score) based on expression of *APOBEC2, APOBEC3B, APOBEC3C, APOBEC3D, ADAR1, IL10, IL11, IL27, TGFB1, TGFB2,* as well as ß-2-microglobulin, hemoglobin, LDH and creatinine serum levels, that achieved the best classification outcome and showed superior performance compared to ISS and R-ISS. Of note, cytogenetic abnormalities did not proof relevant have therefore not been included in the EI score. Besides superior overall risk stratification, the EI score further allowed to identify subgroups of MM patients with very good prognosis and an "ultra high risk" group of patients who do not benefit from bone marrow transplantation maintenance therapy.



Number at risk				
Group: High				
91	61	43	14	1
Group: Low				
284	200	157	58	5
Group: Ultra high				
108	61	39	11	0
Group: Ultra low				
112	95	80	31	6

Summary/Conclusion: Our findings support the adoption of molecular biomarkers, reflecting dynamic biological processes rather than cytogenetics for a more accurate risk classification of MM. Considering that mRNA-seq is as cost effective as FISH and is being increasingly adopted by diagnostic centres, the EI score is a unique approach to shed light on underlying molecular mechanisms that drive disease progression and the development of true risk-adapted treatment strategies.

S179 MULTIPLE MYELOMA DERIVED MITOCHONDRIAL DAMPS PROMOTE A PRO-INFLAMMATORY SIGNATURE WITHIN THE MYELOMA BONE MARROW MICROENVIRONMENT

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Background: Multiple myeloma (MM) is a malignancy of the antibody secreting plasma cells, that is characterized by the accumulation and localisation of tumour cells within the bone marrow microenvironment (BMM). The mitochondrial genome belongs to a group of mitochondrial damage associated molecular patterns (mtDAMPs) and contains islands of unmethylated CpG nucleotide motifs, which have been shown to activate and promote memory B cell antibody secretion and proliferation. Studies have indicated that mitochondrial DNA (mtDNA) is elevated in the circulation of trauma and cancer patients.
Aims: Here we aim to explore the hypothesis that multiple myeloma cells secrete mitochondrial DNA and other mitochondrial DAMPs into the bone marrow microenvironment, leading to the promotion of a state of chronic inflammation that supports multiple myeloma disease progression and expansion.
Methods: Immunocompromised NSG mice were engrafted with human myeloma cell line (MMIS), blood serum samples were taken and analysed using real-time PCR (RT-PCR) to detect the presence of human mtDNA. We established syngeneic mouse models of multiple myeloma using the murine 5TGM1 myeloma cell line, flow cytometry was used to analyse the haematopoietic stem and progenitor cell (HSPC) and macrophage populations within the bone marrow. Bone marrow derived macrophages were sorted from these mice and RT-PCR was used to analyse pro-inflammatory gene expression. To further investigate the role of mtDNA in HSPC expansion, C57BL/6 mice were treated with multiple doses of CpG oligodeoxynucleotides to mimic the mtDNA released by MM. *in vitro*, BMDM were treated with CpG and mtDNA and pro-inflammatory gene expression was analysed via RT-PCR. To further understand the role of mtDAMPs in regulating proinflammatory signals in the MM microenvironment, we used an inhibitor to block TLR9 (toll-like receptor), the key mtDNA sensing receptor.
Results: We detected elevated levels of MM derived mtDNA in the blood serum of immunocompromised NSG mice engrafted with human myeloma cell line (MM1S). Flow cytometry analysis of the HSPC populations showed that 5TGM1 induced an expansion of the stem cell niche, and real-time PCR analysis of the blood serum showed an elevated level of cell free mtDNA in 5TGM1 engrafted mice. Moreover, the frequency of tumour associated macrophages (TAM) was increased in 5TGM1 engrafted mice and RT-PCR analysis of sorted BMDM showed a pro-inflammatory phenotype. Flow cytometry analysis of CpG treated mice revealed an expansion of HSPC populations similarly found in 5TGM1 engrafted mice. Furthermore, *in vitro* analysis of BMDM treated with mtDNA and CpG showed increased expression of pro-inflammatory cytokines including IL-6. Lastly, blocking of the TLR9 receptor resulted in reduced MM tumour burden in 5TGM1 engrafted mice treated with TLR9 inhibitor compared to untreated mice.
Summary/Conclusion: Here we ascertain that MM releases mtDNA into the microenvironment and show the involvement of mtDAMPs in promoting the disease progression of MM via a pro-inflammatory BMM. This data proposes targeting potential receptor signalling pathways as a novel therapeutic intervention for multiple myeloma.

New treatment strategies for newly diagnosed multiple myeloma

S180 DARATUMUMAB MAINTENANCE VS OBSERVATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE ± DARATUMUMAB AND ASCT: CASSIOPEIA PART 2 RESULTS

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Background: Daratumumab in conjunction with bortezomib, thalidomide, and dexamethasone (D-VTd) and autologous stem cell transplantation (ASCT) is approved for the treatment of transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) based on results from CASSIOPEIA part 1.
Aims: To assess daratumumab maintenance vs observation (OBS) in patients with partial response or better (≥PR) in part 1, regardless of induction/consolidation treatment (CASSIOPEIA part 2 prespecified interim analysis).
Methods: CASSIOPEIA is a 2-part, open-label, randomized, phase 3 study in transplant-eligible patients with NDMM. Written informed consent was obtained from all patients. In part 1, patients received 4 cycles of induction and 2 cycles of consolidation with D-VTd or VTd alone. All responders in part 1 (≥PR; n=886) were rerandomized in part 2 to receive maintenance (intravenous daratumumab 16 mg/kg every 8 weeks for ≤2 years [n=442]) or OBS (n=444) until disease progression (IMWG criteria). Patients were stratified by induction (D-VTd vs VTd) and depth of response (minimum residual disease [MRD] status and ≥PR post consolidation). Progression-free survival (PFS) after rerandomization was the primary endpoint. The efficacy and safety were assessed after 281 PFS events. Key secondary endpoints (preplanned hierarchical order) were time to progression, complete response or better (≥CR), MRD negativity rates by next-generation sequencing, and overall survival (OS).
Results: Median PFS was not reached with daratumumab vs 46.7 months for OBS (median follow up, 35.4 months; hazard ratio [HR] 0.53 [95% CI 0.42–0.68]; $P<0.0001$). Daratumumab showed consistent PFS advantage across most subgroups, except for a significant interaction with induction/consolidation treatment arm ($P<0.0001$; prespecified analysis). The daratumumab vs OBS PFS HR was 0.32 (95% CI 0.23–0.46) in the VTd arm and 1.02 (0.71–1.47) in the D-VTd arm. The median time to progression was not reached for daratumumab vs 46.7 months for OBS (HR 0.49 [0.38–0.62]; $P<0.0001$). Compared with OBS, more patients with daratumumab maintenance achieved ≥CR (60.8% vs 72.9%; odds ratio [OR] 2.17 [1.54–3.07]; $P<0.0001$). In patients with ≥CR at 10^{-5}, the MRD negativity rate was 58.6% with daratumumab maintenance vs 47.1% with OBS (OR 1.80 [1.33–2.43]; $P=0.0001$). Median OS was not reached in either arm. Most common (≥2.5%) grade 3/4 adverse events (AEs) reported with daratumumab maintenance vs OBS were lymphopenia (3.6% vs 1.8%), hypertension (3.0% vs 1.6%), and pneumonia (2.5% vs 1.4%). Serious AEs were reported in 22.7% of patients with daratumumab maintenance vs 18.9% with OBS; the most common (≥2.5%) being pneumonia (2.5% vs 1.6%). Thirteen patients (3.0%) discontinued daratumumab due to an AE. The rate of infusion-related reactions (90% were grade 1/2) was 54.5% in daratumumab-naive patients and 2.2% in daratumumab-pretreated patients. Second primary malignancies occurred in 5.5% of patients with daratumumab maintenance vs 2.7% with OBS.
Summary/Conclusion: CASSIOPEIA part 2 interim analysis showed a significantly longer PFS with daratumumab maintenance vs OBS in transplant-eligible patients with NDMM. The maintenance PFS benefit appeared only in patients treated with VTd as induction/consolidation. Patients who received D-VTd induction/consolidation ± daratumumab maintenance achieved similar PFS; longer follow up is needed for OS and PFS2. Compared with OBS, daratumumab maintenance significantly increased deeper response and MRD negativity rates, and it was well tolerated with no new safety signals.

S181 DEPTH OF RESPONSE AND MRD STATUS IN ULTRA HIGH-RISK MYELOMA AND PLASMA CELL LEUKEMIA TREATED WITH DARA-CVRD AND AUGMENTED AUTOLOGOUS TRANSPLANT: RESULTS OF THE RISK-STRATIFIED UK OPTIMUM/MUKNINE TRIAL

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Background: Patients with ultra high-risk (UHiR) newly diagnosed multiple myeloma (NDMM) as well as patients with plasma cell leukemia (PCL) continue to have dismal outcomes and are underrepresented in clinical trials. Recently, improved and deepened responses with anti-CD38 monoclonal antibody combination therapy have been reported for NDMM patients. We report here outcomes for NDMM UHiR and PCL patients treated in the OPTIMUM/MUKnine (NCT03188172) trial with daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (Dara-CVRd) induction, augmented high-dose melphalan (HDMEL) and ASCT. With final analysis follow-up surpassed in Feb 2021, we report here early protocol defined endpoints from induction to day 100 post ASCT.
Aims: To demonstrate response and MRD-negativity rate in UHiR NDMM and PCL prospectively identified by central molecular screening and treated in a risk-stratified trial with Dara-CVRd and augmented ASCT.
Methods: Between Sep 2017 and Jul 2019, 107 patients with UHiR NDMM by central trial genetic (≥2 high-risk lesions (double-hit): t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p)) or gene expression SKY92 (SkylineDx) profiling, or with PCL (circulating plasmablasts >20%) were included in OPTIMUM across 39 UK hospitals. Patients received a maximum of 6 cycles of Dara-CVRd induction, HDMEL and ASCT augmented with bortezomib, followed by Dara-VR(d) consolidation for 18 cycles and Dara-R maintenance. Primary trial endpoints are minimal residual disease (MRD) status post ASCT and progression-free survival. Secondary endpoints include response, safety and quality of life. Data is complete but subject to further data cleaning prior to conference.
Results: Median follow-up for the 107 patients in the safety population was 22.2 months (95% CI: 20.6 – 23.9). Median age was 60 (range 35 to 78) years, 59.8% of patients were male. Ninety eight patients (92%) were included based on UHiR status by central tumour molecular analysis, and 9 because of PCL (8%). At baseline, 22.4% of patients were ISS stage I, 37.4% stage II and 26.2% stage 3 with 14.0% missing data. Two patients died during induction due to infection. Bone marrow aspirates suitable for MRD assessment by flow cytometry (10^{-5} sensitivity) were available for 81% of patients at end of induction and 78% at D100 post ASCT. Responses in the intention-to-treat population at end of induction were 94% ORR with 22% CR, 58% VGPR, 15% PR, 1% PD, 5% timepoint not reached (withdrew, became ineligible or died) and at D100 post ASCT 83% ORR with 47% CR, 32% VGPR, 5% PR, 7% PD, 10% timepoint not reached. MRD status was 41% MRD-negative, 40% MRD-positive and 19% not evaluable post induction and 64% MRD-negative, 14% MRD-positive and 22% not evaluable at D100 post ASCT. Responses at D100 post ASCT were lower in PCL with 22% CR, 22% VGPR, 22% PR, 22% PD, 12% timepoint not reached. Most frequent grade 3/4 AEs during induction were neutropenia (21%), thrombocytopenia (12%) and infection (12%). Grade 3 neuropathy rate was at 3.7%.
Summary/Conclusion: We report, to our knowledge for the first time, on a trial for UHiR NDMM and PCL investigating Dara-CVRd induction and augmented ASCT. Response rates and MRD-negativity were high in this difficult-to-treat patient population, with toxicity comparable to other induction regimens. However, some early progressions highlight the need for innovative approaches to UHiR NDMM and PCL.

S182 EFFICACY OF CARFILZOMIB-BASED INDUCTION/CONSOLIDATION WITH OR WITHOUT AUTOLOGOUS TRANSPLANT AND LENALIDOMIDE OR CARFILZOMIB-LENALIDOMIDE MAINTENANCE IN HIGH-RISK PATIENTS IN THE FORTE TRIAL

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Background: Cytogenetic abnormalities (CA) are powerful prognostic factors in multiple myeloma (MM). In the FORTE trial, carfilzomib-lenalidomide-dexamethasone induction/consolidation with ASCT (KRd_ASCT) significantly improved progression-free survival (PFS) vs KRd without ASCT (KRd12, HR 0.64) or carfilzomib-cyclophosphamide-dexamethasone plus ASCT (KCd_ASCT, HR 0.53). KR maintenance significantly improved PFS vs R (HR 0.63).
Aims: The primary aim of this analysis was the impact of treatment on PFS and 1-year sustained MRD negativity (1y-MRD neg) rates according to patient (pt) risk.
Methods: Newly diagnosed MM pts were randomized to KRd_ASCT vs KCd_ASCT vs KRd12 and, thereafter, to KR vs R maintenance. Subgroup analyses according to FISH assessed the impact of each single high-risk (HiR) CA [del17p, t(4;14), t(14;16), del1p and 1q gain (3 copies) or amp1q (≥4 copies)] and that of combined HiR CA, defining HiR by the presence of ≥1 HiR CA and double hit (DH) by the presence of ≥2 HiR CA. Standard risk (SR) was defined by the absence of all the CA.
Results: 396 out of 474 enrolled pts were included in the analysis with complete FISH data: 243 HiR, 105 DH and 153 SR. Among HiR pts, 60 had del17p, 65 t(4;14), 20 t(14;16), 44 del1p, 126 1q gain and 49 amp1q. SR pts benefited from intensification with KRd_ASCT vs KRd12 (HR 0.47, p=0.05) and KCd_ASCT (HR 0.38, p=0.01), with a 4-year PFS of 80%, 67% and 57%, respectively. In the overall HiR population, KRd_ASCT improved PFS vs KRd12 (HR 0.6, p=0.04) and KCd_ASCT (HR 0.57, p=0.01), with a 4-year PFS of 62%, 45% and 45%, respectively. The advantage with KRd_ASCT vs KRd12 (HR 0.53, p=0.07) and KCd_ASCT (HR 0.49; p=0.03) was also observed in DH pts (4-year PFS 55%, 31% and 33%, respectively). Analyses by single CA were limited by the small number of pts in each subgroup, but a PFS benefit from KRd_ASCT vs KRd12 was observed in pts with del17p (HR 0.61, p=0.3), t(4;14) (HR 0.59, p=0.2) and 1q gain (HR 0.45, p=0.02), consistently with the overall population. In pts with del1p, KRd_ASCT (HR 0.24, p=0.06) and KRd12 (HR 0.33, p=0.09) showed superiority over KCd_ASCT, while amp1q pts had the worst outcome regardless of treatment (KRd_ASCT vs KCd_ASCT, HR 1.16, p=0.73; KRd12 vs KCd_ASCT, HR 1.34, p=0.45).
KRd_ASCT induced similar 1y-MRD neg rates in SR (50%), HiR (50%) and DH (47%) pts. Lower 1y-MRD neg rates were observed with KRd12 vs KRd_ASCT. With KRd12, 1y-MRD neg rates were similar in SR (36%) and HiR (39%) but lower in DH (25%) pts; with KCd_ASCT, HiR (48% vs 29%, p=0.04) and DH (48% vs 17%, p=0.03) pts had significantly lower 1y-MRD neg rates than SR pts. Importantly, 1y-MRD neg pts showed a similar 4-year PFS regardless of risk status (SR, 87%, HiR 87%, DH 83%) and treatment arm.
KR improved PFS vs R in SR (3-year PFS 90% vs 73%, HR 0.42, p=0.06), HiR (3-year PFS 69% vs 56%, HR 0.6, p=0.04) and DH pts (3-year PFS 67% vs 42%, HR 0.53, p=0.1). Despite the small subgroups, a benefit from KR vs R was observed in pts with del17p (HR 0.59, p=0.37), t(4;14) (HR 0.59, p=0.3), 1q gain (HR 0.54, p=0.07) and del1p (HR 0.23, p=0.08), while amp1q pts showed the worst outcome and no benefit from KR vs R (HR 0.83, p=0.7).
Summary/Conclusion: KRd_ASCT and KR maintenance are highly effective in SR, HiR and DH pts, with impressive 1y-MRD neg rates (KRd_ASCT: HiR 50%, DH 47%), 4-year PFS from diagnosis (KRd_ASCT: HiR 62%, DH 55%) and 3-year PFS from maintenance (KR: HiR 69%, DH 67%), thus supporting their use in HiR pts, who represent an unmet medical need. Achieving 1y-MRD neg mitigated the higher risk of progression/death in HiR and DH pts, as compared to SR pts.

S183 UPDATED INTERIM ANALYSIS OF THE GMMG-CONCEPT TRIAL INVESTIGATING ISATUXIMAB, CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (ISA-KRD) IN FRONTLINE TREATMENT OF HIGH-RISK MULTIPLE MYELOMA

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Background: As high-risk (HR) multiple myeloma (MM) patients (pts) still have a significantly impaired prognostic outcome, there is an unmet clinical need for potent therapeutic strategies already in front-line therapy for newly diagnosed (ND) MM, leading to improvement of long-term survival. Ultra-high-risk patients with ≥ 3 HR cytogenetic aberrations (CA) have a median overall survival (OS) of less than 2 years. Recent data indicate that achievement of deep remissions, including negativity for minimal residual disease (MRD) may translate into prolonged progression-free (PFS) and OS.
Aims: The GMMG-CONCEPT trial (NCT03104842) investigates the quadruplet regimen isatuximab plus carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in HR NDMM pts including primary high-dose melphalan for patients being transplant-eligible. First results showed an overall response rate (ORR) of 100% for induction treatment in the prespecified interim analysis (IA) of the first 50 patients included. Here, we report an update for PFS of the IA population.
Methods: 153 pts with HR NDMM were included into the trial, an extension cohort of another 93 patients is planned to start recruitment in 2021. HR MM is defined by the presence of del17p or t(4;14) or t(14;16) or > 3 copies 1q21 in combination with ISS II or III stage disease. Transplant-eligible (TE) patients undergo high-dose therapy after induction (Arm A) while transplant-ineligible (TI) patients receive 2 additional Isa-KRd cycles (Arm B). Afterwards, both arms receive another 4 Isa-KRd cycles as consolidation, followed by Isa-KR maintenance. Primary endpoint is MRD negativity measured by next-generation flow after consolidation. This IA reports on PFS data of the IA population with PFS defined as combined endpoint of progressive disease (PD) or death, whichever occurs first.
Results: 50 pts (46 arm A, 4 arm B) were included in the IA population. CA defining high-risk were del17p in 52%, t(4;14) in 38%, t(14;16) in 12% and > 3 copies 1q21 in 42%. 20% of pts showed increased LDH, 26% had 2 CA, 4% showed ≥ 3 CA. Overall (ORR) and best response rates were presented previously. ORR defined as best response achieved during induction was 100% with 90% of pts achieving a very good partial response or better. Early data on MRD negativity showed MRD negative remissions in 20/33 evaluated pts during induction. The updated IA analysis was performed with a median follow-up of 24.9 months. For the overall population analysed, 12- and 24-month PFS (95%>confidence level) was 79.6% (68.3%; 90.9%) and 75.5% (63.5%; 87.6%). In Arm A, PFS-rates were 80.0% (68.3%; 91.7%) and 75.6% (63.0%; 88.1%) for 12 and 24 months, respectively. For the 4 TI pts in Arm B, a 12-months-PFS of 75.0% (32.6%; 100%) was reported. With longer follow-up, no new safety signals occurred. End of treatment (EoT) occurred in 20 pts in Arm A and was due to PD in 8 pts, death in 4 pts or other reasons (8 pts). Reason for EoT (1 pt) in Arm B was death.
Summary/Conclusion: With a best ORR of 100% during quadruplet induction treatment, we here report an update of the IA for PFS of the first 50 pts in the CONCEPT trial. In these solely HR NDMM pts an encouraging PFS rate of 79.6% and 75.5% after 12- and 24-months is reported. Our data underline the high potency of quadruplet treatment with Isa-KRd especially in patients with HR disease. The study completed recruitment, further results will be reported.

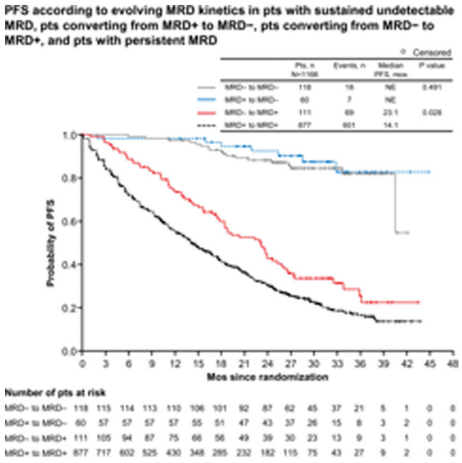
S184 MEASURABLE RESIDUAL DISEASE (MRD) EVALUATION DURING IXAZOMIB (IXA) MAINTENANCE IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM): A LARGE ANALYSIS OF 1280 PATIENTS (PTS) ENROLLED IN TOURMALINE-MM3 AND -MM4

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Background: MRD status is the most powerful prognostic factor in NDMM and sustained MRD negativity is a surrogate for prolonged survival. Interest is growing for using MRD to guide treatment intensity and duration, particularly during maintenance. Paradoxically, MRD data in this setting is scarce and knowledge of the volatility of MRD status throughout treatment is limited.
Aims: To present a pooled analysis of the Phase 3 TOURMALINE-MM3 and -MM4 trials, the largest maintenance dataset ever reported, to evaluate the impact of evolving MRD kinetics on progression-free survival (PFS) in NDMM pts receiving ixa or placebo (pbo) maintenance.
Methods: Pts with ≥partial response (PR) following proteasome inhibitor and/or immunomodulatory drug induction plus a single transplant (MM3) or 6–12 months (mos) of standard-of-care induction therapy (MM4) were randomized (3:2) to oral ixa 3 mg (increased to 4 mg if tolerated after 4 cycles) or pbo in 28-day cycles for up to 2 years (or 26 cycles). PFS from randomization was the primary endpoint; correlation of MRD status with outcomes was a prespecified secondary endpoint in both trials. 2077 bone marrow aspirates were collected from all pts in complete response (CR; MM3 & MM4) or very good PR (MM3 only) at screening, cycle 13, and cycle 26/end of treatment, and at time of new suspected CR (MM3 & MM4). MRD status was determined using a validated 8-color flow cytometry approach standardized across three geographic regions (38 countries); median limit of detection was $7.4x10^{-6}$. Pts with
Results: At screening, MRD status was available for 1280 pts: 262 were MRD– (ixa n=161/767 [21%]; pbo n=101/513 [20%]) and 1018 MRD+ (ixa n=606 [79%]; pbo n=412 [80%]). In pts who were MRD+ at study entry, there was significant PFS benefit for ixa vs pbo (median 18.8 vs 11.6 mos, hazard ratio [HR] 0.65, 95% CI 0.55–0.76, p<.001). 10% of pts showed sustained MRD negativity, 5% converted from MRD+ to MRD–, 10% from MRD– to MRD+ and 75% had persistent MRD. Median PFS (mPFS) was not reached in pts with sustained MRD negativity (Figure; ixa vs pbo HR 0.89, p=.815). mPFS was also not reached in pts converting from MRD+ to MRD– during treatment; there was significant benefit with ixa vs pbo (HR 0.14, p=.007). By comparison, mPFS was inferior in pts converting from MRD– to MRD+ (23.1 mos) and dismal in pts with persistent MRD (14.1 mos); mPFS with ixa vs pbo was 23.2 vs 19.3 mos (HR 0.81, p=.411) and 17.5 vs 11.1 mos (HR 0.68, p<.001) in these groups, respectively. Other disease characteristics had no prognostic value once pts were stratified into these four MRD kinetics subgroups. Overall, failure to achieve/sustain MRD– status post-screening resulted in a >8-fold increased risk of progression and/or death (HR 8.20, 95% CI 5.49–12.2, p<.001).



Summary/Conclusion: This large dataset demonstrated that the prognostic value of MRD status at the start of maintenance can be enhanced by measuring MRD kinetics during treatment. Our results support the achievement and sustainability of MRD negativity as a treatment endpoint in the maintenance setting and showed poor outcomes in MRD– pts converting to MRD+, underscoring the value of serial MRD assessments to anticipate relapse and guide treatment decisions. Accordingly, ixa showed significant PFS benefit vs pbo in pts who were MRD+ at study entry and pts with persistent MRD.

New diagnostic and therapeutic approaches in multiple myeloma and AL amyloidosis

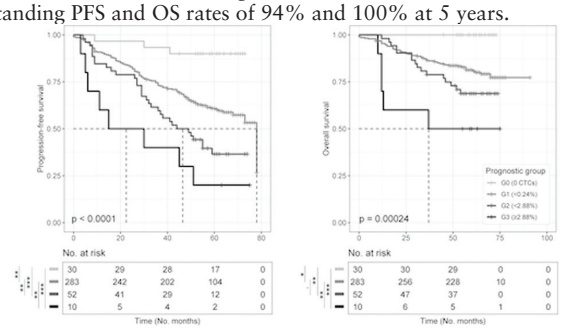
S185 CIRCULATING TUMOR CELLS (CTC) ARE THE MOST RELEVANT DIAGNOSTIC BIOMARKER IN TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA (MM)

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Background: There is great expectation in liquid biopsies to stratify patients with cancer. These could be particularly valuable in MM where despite patchy infiltration and likelihood of extramedullary disease, quantification of tumor burden continues being performed in bone marrow (BM). However, there are no large studies analyzing if liquid biopsies using next-generation methods yield superior prognostic information than conventional cytology in BM.
Aims: To establish the clinical significance of CTC burden in peripheral blood (PB) and to define cutoffs for risk stratification of newly-diagnosed MM patients.
Methods: This study included 375 transplant-eligible patients enrolled in the GEM2012MENOS65 clinical trial and treated with six induction cycles of VRD followed by autologous transplant and consolidation with two VRD courses. Afterwards, patients received Rd (with or without ixazomib) for two years and either stopped maintenance if MRD negative or continued three more years if MRD positive (GEM2014MAIN). EuroFlow next-generation flow was used to evaluate CTCs in PB at diagnosis and MRD in BM throughout treatment. Cutoffs were defined using maximally selected rank statistics considering PFS. Median follow-up is of 5 years.
Results: CTC were detected in 345/375 (92%) of patients. There was a modest correlation between the percentage of CTCs in PB and tumor burden in BM by morphology (R^2=0.35, p<0.0001) and flow cytometry (R^2=0.41, p<0.0001). These data suggests that CTC egression is not directly related with tumor burden in BM.
Patients stratification into 4 subgroups according to the percentage of CTC (Group 0: 0%, Group 1: >0% to <0.24%, Group 2: ≥0.24% to <2.88%, and Group 3: ≥2.88%) resulted in significant differences in PFS (median not reached [NR] vs 78, 47 and 23 months, and hazard ratios of 4.9, 8.8 and 15.8, respectively; p<0.0001) and overall survival ([OS] 100%, 81%, 69% and 50% at 5 years, p=0.0002). In a multivariable analysis including quantification of tumor burden in PB using NGF and in BM by morphology and flow cytometry, the percentage of CTC was selected as the only independent prognostic factor for PFS (p=0.001). In a subsequent multivariable analysis including the percentage of CTC in PB, ISS, LDH and FISH cytogenetics, quantification of CTC was selected as the most relevant prognostic factor for PFS. Indeed, risk stratification according to the CTC cutoffs previously defined was prognostic in all risk groups including patients with standard-risk FISH (median PFS NR in Groups 0 & 1 vs 44 and 30 months in Groups 2 & 3, respectively: p=0.005).

We further investigated if deep responses to treatment were able to abrogate the poor prognosis of elevated CTC at diagnosis. Patients in Groups 2 & 3 showed significantly inferior PFS (median of 59 and 48 months) than cases in Groups 0 & 1 (median NR; p=0.004) despite achieving CR. By contrast, there were no significant differences in PFS of MRD negative patients stratified according to the percentage of CTC (p=0.017). Patients with 0% CTC and negative MRD before maintenance showed outstanding PFS and OS rates of 94% and 100% at 5 years.



Summary/Conclusion: Evaluation of CTC in PB outperformed quantification of tumor burden in BM and was the most relevant prognostic factor at baseline. Attaining undetectable MRD as opposed to CR should be considered as the treatment endpoint in patients with elevated percentages of CTC in PB. Patients with undetectable CTC at diagnosis and undetectable MRD after treatment intensification showed long-term survival with fixed duration maintenance therapy.

S186 UPDATES FROM ICARIA-MM, A PHASE 3 STUDY OF ISATUXIMAB (ISA) PLUS POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE (PD) VERSUS PD IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM)

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Background: Isa is an approved monoclonal antibody that binds to a specific epitope on the CD38 receptor. The Phase 3 ICARIA-MM study (NCT02990338) demonstrated significantly improved progression-free survival (PFS) with Isa-Pd vs Pd (*P*=0.001) and a manageable safety profile (Attal M, et al. *Lancet* 2019;394:2096-2107).
Aims: Here we report updated ICARIA results.
Methods: Pts with RRMM (N=307) who have received ≥2 prior therapies, including lenalidomide (Len) and a proteasome inhibitor (PI), were randomized to Isa-Pd (n=154) or Pd (n=153). Isa was administered intravenously at 10 mg/kg weekly for 4 weeks, and every other week thereafter. This preplanned second interim analysis assessed longer term outcomes, including time to next treatment (TTNT), overall survival (OS), time from randomization to disease progression on first subsequent therapy or death (PFS2), and safety.
Results: Pts had a median of 3 prior lines of therapy (IQR 2–4; table). As of Oct 1, 2020 (median follow-up, 35.3 months [mo]), 27 Isa-Pd pts (18%) vs 12 Pd pts (8%) were still on treatment; 60% vs 72% had proceeded to subsequent therapy. Median TTNT was 15.5 mo with Isa-Pd vs 8.9 mo with Pd (hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.42–0.74; *P*<0.0001); 24% vs 58% of pts with subsequent therapy received daratumumab (dara). Overall response rate (ORR) in subsequent treatment with dara monotherapy was higher after Pd (38%) than Isa-Pd (14%), but was similar (32% vs 31%) with dara combination therapy (table). Median PFS2 in the intent-to-treat population was 17.5 mo with Isa-Pd vs 12.9 mo with Pd (HR 0.76; 95% CI 0.58–0.99; *P*=0.0202). Median OS was 24.6 mo with Isa-Pd vs 17.7 mo with Pd (HR 0.76; 95% CI 0.58–1.01; one-sided *P*=0.0280). Median treatment duration was 47.6 weeks (range 1.3–171.6) with Isa-Pd vs 24.0 weeks (range 1.0–168.6) with Pd. Serious treatment-emergent adverse event (TEAEs) were seen in 73% of Isa-Pd pts vs 60% of Pd pts. Most frequent non-hematologic TEAEs (any grade) with Isa-Pd were infusion reaction (38%), upper respiratory tract infection (34%), and diarrhea (30%). Grade 3–4 neutropenia (85% vs 71%) and thrombocytopenia (34% vs 25%) were more frequent with Isa-Pd than with Pd.

Prior treatments, n (%)	Isa-Pd (n=154)	Pd (n=153)
Len	154 (100)	153 (100)
PI	154 (100)	153 (100)
Len-refractory	144 (94)	140 (92)
PI-refractory	118 (77)	115 (75)
ORR on subsequent dara combination treatments, n/N* (%)		
ALL	4/13 (31)	7/22 (32)
+Immunomodulator	2/5 (40)	2/7 (29)
+Alkylator	0/4 (0)	1/5 (20)
+PI	2/5 (40)	4/12 (33)

*N=number of patients with best overall response assessment

Summary/Conclusion: Isa-Pd demonstrates a significant improvement in TTNT and PFS2 compared with Pd. A strong trend in OS benefit was also seen in the Isa-Pd arm, with approximately 7 mo improvement in median OS. The overall safety profile remains unchanged from prior analyses.

S187 IBERDOMIDE (IBER) IN COMBINATION WITH DEXAMETHASONE (DEX) AND DARATUMUMAB (DARA), BORTEZOMIB (BORT), OR CARFILZOMIB (CFZ) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

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Background: IBER is an oral, novel cereblon E3 ligase modulator (CELMoD) compound with marked synergistic tumoricidal and immune-stimulatory effects in combination with proteasome inhibitors (PIs) or anti-CD38 monoclonal antibodies, preclinically and clinically. CC-220-MM-001 (NCT02773030) is an ongoing phase 1/2 study evaluating the maximum tolerated dose, recommended phase 2 dose (RP2D), safety, and preliminary efficacy of IBER with different treatment combinations in independent cohorts, in pts with RRMM.
Aims: To report results from the IBER+DARA+DEX (IberDd), IBER+BORT+DEX (IberVd), and IBER+CFZ+DEX (IberKd) cohorts of the CC-220-MM-001 study.
Methods: Eligible pts received ≥2 prior regimens in the IberDd and IberKd cohorts, and ≥1 prior regimen in the IberVd cohort, containing lenalidomide or pomalidomide, and a PI. All pts had progressed ≤60 days of their last MM therapy. Escalating oral doses of IBER were given on Day (D)1–21 of each 28-D cycle in the IberDd cohort and in the IberKd cohort with weekly CFZ, and on D1–14 of each 21-D cycle in the IberVd cohort. DEX was given weekly in all 3 cohorts.
Results: As of Dec 14, 2020, 34 pts had received IberDd, 24 pts IberVd, and 7 pts IberKd. Exposure to prior regimens was heterogeneous (Table), all pts were refractory to their last prior regimen, and median number of

prior therapies was 4.0 (2–12), 5.5 (1–14), and 6.0 (2–8), with IberDd, IberVd, and IberKd, respectively. IBER doses ranged from 1.0mg to 1.6mg. Median follow-up was 3.9 (0.1–20.7), 5.5 (1.2–18.0), and 5.1 (3.5–15.7) months, 15 (44%), 9 (38%), and 3 (43%) pts continue on treatment, and median cycles received was 4.0 (1–21), 7.5 (1–24), and 5.0 (3–16) with IberDd, IberVd, and IberKd, respectively.
Most frequent hematologic grade (G) 3–4 treatment-emergent adverse events (TEAEs) were neutropenia (63%), anemia (28%), leukopenia (28%), and lymphopenia (25%) with IberDd, neutropenia (29%) and thrombocytopenia (25%) with IberVd, and lymphopenia (57%) and neutropenia (43%) with IberKd. In all cohorts, neutropenia was managed with G-CSF. One pt (IberDd; 1.2mg) had G4 neutropenic sepsis. Occurrence of G3–4 non-hematologic TEAEs was low in all 3 cohorts. There were 12 (38%), 8 (33%), and 3 (43%) pts with ≥1 IBER dose reduction, with IberDd, IberVd, and IberKd, respectively.
In the IberDd cohort, the overall response rate (ORR) was 41% (12/29 pts: 1 stringent complete response [sCR], 2 CRs, 2 very good partial responses [VGPRs], 7 partial responses [PRs]), the clinical benefit rate (CBR) was 52%, and disease control rate (DCR) was 86%. In the IberVd cohort, ORR was 58% (14/24 pts: 2 CRs, 5 VGPRs, 7 PRs), CBR was 67%, and DCR was 92%. Responses with IberDd and IberVd were observed in DARA- and BORT-refractory pts, respectively. In the IberKd cohort, ORR was 57% (4/7 pts: 1 sCR, 2 VGPRs, 1 PR), CBR was 57%, and DCR was 86%. Median time to response was 4.1 (4.0–12.0), 3.6 (3.0–13.1), and 4.1 (4.1–8.1) weeks, in the IberDd, IberVd, and IberKd cohorts, respectively. Median duration of response is 63.3 weeks in the IberVd cohort, and not reached in the IberDd and IberKd cohorts.
RP2D was determined at 1.6mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts.
Updated data will be presented at the meeting.

Table. Baseline characteristics and prior therapies

Characteristics	IberDd (n = 34)	IberVd (n = 24)	IberKd (n = 7)
Age, median (range), years	66 (40–77)	64 (47–81)	61 (36–69)
Time since initial diagnosis, median (range), years	8.0 (1.1–19.1)	7.1 (3.0–16.0)	7.7 (2.4–13.5)
ISS at study entry, n (%)			
Stage I	20 (58.8)	13 (54.2)	6 (85.7)
Stage II	9 (26.5)	9 (37.5)	0
Stage III	4 (11.8)	2 (8.3)	1 (14.3)
Presence of EMP, n (%)	7 (20.6)	4 (16.7)	1 (14.3)
Prior therapies, median (range)	4.0 (2–12)	5.5 (1–14)	6.0 (2–8)
ASCT, n (%)	29 (85.3)	21 (87.5)[a]	7 (100)
BORT, n (%)	33 (97.1)	23 (95.8)	7 (100)
CFZ, n (%)	24 (70.6)	11 (45.8)	4 (57.1)
LEN, n (%)	34 (100)	24 (100)	7 (100)
POM, n (%)	24 (70.6)	18 (75.0)	7 (100)
DARA, n (%)	18 (52.9)	19 (79.2)	7 (100)
Anti-BCMA, n (%)	2 (5.9)	2 (8.3)	1 (14.3)
IMiD agent-refractory,[b] n (%)	33 (97.1)	19 (79.2)	6 (85.7)
PI-refractory, n (%)	28 (82.4)	16 (66.7)	5 (71.4)
BORT, n (%)	14 (41.2)	10 (41.7)	4 (57.1)
CFZ, n (%)	21 (61.8)	8 (33.3)	4 (57.1)
Anti-CD38 mAb-refractory, n (%)	16 (47.1)	19 (79.2)	5 (71.4)
DARA, n (%)	16 (47.1)	18 (75.0)	5 (71.4)
Triple-class refractory,[c] n (%)	14 (41.2)	11 (45.8)	4 (57.1)

[a]4 patients received both autologous and allogenic stem cell transplant; [b]Defined as refractory to LEN or POM; [c]Defined as refractory to ≥1 IMiD agent, ≥1 PI, and ≥1 anti-CD38 mAb.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; DEX, dexamethasone; EMP, extramedullary plasmacytoma; IBER, iberdomide; IberDd, IBER+DARA+DEX; IberKd, IBER+CFZ+DEX; IberVd, IBER+BORT+DEX; ISS, International Staging System; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; POM, pomalidomide.

Summary/Conclusion: In heavily pretreated pts with RRMM, IberDd, IberVd, and IberKd showed a manageable safety profile and promising efficacy including CRs, even among DARA- and BORT-refractory pts. The study is ongoing. These results support further development of IBER-based regimens in MM, including the initiation of phase 3 combination studies.

S188 ONCE WEEKLY SELINEXOR, CARFILZOMIB, AND DEXAMETHASONE (XKD) IN CARFILZOMIB NONREFRACTORY MULTIPLE MYELOMA (MM) PATIENTS

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL in combination with low dose dexamethasone (dex) ± bortezomib (BOR) is FDA approved for previously treated MM. The synergy of SEL with the PI BOR has been confirmed in the phase 3 BOSTON study in MM patients (pts) with 1-3 prior therapies; once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS), time to next therapy, and overall response rate (ORR) as compared to standard twice weekly BOR/dex (Vd), despite XVd using 40% less BOR and 25% less dex than standard Vd.
Aims: To determine if the addition of QW SEL to the PI carfilzomib (CAR)-dex (XKd) would be an active and tolerable regimen in pts with heavily pretreated MM.
Methods: In the XKd arm of the multi-arm Phase 1b/2 STOMP study, SEL at 80 or 100 mg QW was evaluated in combination with CAR at 56 or 70 mg/m^2 QW plus dex at 40 mg QW in pts with heavily pretreated MM not refractory to CAR. Study objectives were to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) and assess the safety and activity of the XKd regimen.
Results: As of 4 Jan 2021, 27 pts were enrolled: 18 (67%) were male, median age 71 years (range 50-76), and median of 4 (range 1-8) prior lines of therapy. All 27 pts were previously treated with BOR, 26 (96%) lenalidomide (LEN), 19 (70%) pomalidomide (POM), 18 (67%) daratumumab (dara). The majority of pts (67%) were triple-class treated (PI, IMiD, and anti-CD38 mAb), and 44% had documented triple-class refractory MM. Nine pts (33%) had MM quad-refractory to BOR, LEN, POM, and dara. Common hematologic treatment-related adverse events (TRAEs) (total, grade ≥3) included thrombocytopenia (74%, 56%), anemia (59%, 19%), and neutropenia (30%, 7%), typically without concurrent symptoms. Non-hematologic TRAEs included nausea (67%, 4%), fatigue (52%, 7%), and anorexia (52%, 4%). RP2D was identified as SEL 80 mg QW, CAR 56 mg/m^2 QW, and dex 40 mg QW.
As of 3 Feb 2021, ORR was 78% (21/27) with 5 pts reaching CR (19%), 8 VGPR (30%), and 8 PR (30%). Median PFS was 23.7 months. Among 18 pts previously treated with dara, ORR was 67% and median PFS was 23.7 months. In 9 pts with MM refractory to BOR, LEN, POM, and dara, ORR was 67% and 4 pts had VGPR (44%).
Summary/Conclusion: In pts with heavily pretreated MM, weekly XKd is highly active with an ORR of 78% and deep responses (≥VGPR 48%) with an overall PFS of 23 months. All AEs, including grade 3/4 thrombocytopenia, can be managed with appropriate supportive care and dose modifications. These data support further investigation of XKd in pts with previously treated MM including those with prior dara treatment.

S189 UPDATED RESULTS FROM PHASE 3 ANDROMEDA STUDY OF PATIENTS WITH NEWLY DIAGNOSED LIGHT CHAIN AMYLOIDOSIS TREATED WITH BORTEZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE PLUS SUBCUTANEOUS DARATUMUMAB

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Background: Light chain amyloidosis (AL) is a systemic plasma cell disease where organ impairment and death can occur due to insoluble amyloid fibrils deposition. Adding subcutaneous daratumumab to the standard of care (bortezomib, cyclophosphamide, and dexamethasone [VCd]) in ANDROMEDA (NCT03201965) led to superior outcomes versus VCd alone (primary results), including greater hematologic complete response (CR) rates and an acceptable safety profile. In January 2021, Daratumumab+VCd was approved for patients with newly diagnosed AL amyloidosis.
Aims: To report updated primary results with longer follow up from the ANDROMEDA study.
Methods: ANDROMEDA is an ongoing open-label, randomized, active-controlled, phase 3 trial. Adult patients with newly diagnosed AL amyloidosis were randomly assigned 1:1 to receive daratumumab+VCd or VCd for six 28-day cycles. Written informed consent was obtained from all patients. Bortezomib dosed at 1.3 mg/m^2, cyclophosphamide at 300 mg/m^2 (up to 500 mg weekly), and dexamethasone at 40 mg were administered every week. Subcutaneous daratumumab was administered once weekly in cycles 1 and 2 and every 2 weeks in cycles 3 to 6. Patients in the daratumumab+VCd arm received only subcutaneous daratumumab after cycle 6, every 4 weeks (up to a total of 24 cycles from first dose). Disease status was assessed every 4 weeks in cycles 1 to 6 and every 8 weeks thereafter. Overall hematologic CR rate (intent-to-treat population) was the primary endpoint. Time to hematologic response, major organ deterioration progression-free survival, survival, organ response rate, and safety were the secondary endpoints.
Results: Among 388 randomized patients, 195 received daratumumab+VCd and 193 received VCd alone. At the November 2020 cutoff, the median duration of treatment for daratumumab+VCd and VCd arms was 18.5 and 5.3 months, respectively, and 78 patients (40%) in the daratumumab+VCd arm were still receiving treatment. The overall hematologic CR rate in the daratumumab+VCd arm (59%) was significantly higher versus the VCd arm (19%; odds ratio [95% CI], 5.9 [3.7–9.4]; P<0.0001). More patients achieved a very good partial response or better (≥VGPR) with daratumumab+VCd (79%) compared with VCd alone (50%; odds ratio [95% CI], 3.7 [2.4–5.9]; P<0.0001). Among patients who responded, the median time from randomization to ≥VGPR was shorter in the daratumumab+VCd arm (0.56 months) versus the VCd arm (0.82 months). Greater cardiac response rates were achieved at 6 months with daratumumab+VCd (42%) versus VCd alone (22%) and at 12 months (57% versus 28%); similarly, renal response rates were greater with daratumumab+VCd (54%) versus VCd alone (27%) at 6 months and at 12 months (57% versus 27%). Overall, 71 patients died (daratumumab+VCd, 31; VCd, 40). Starting cycle 7, no grade 3/4 treatment-emergent adverse events occurred in ≥5% of patients in the daratumumab+VCd arm. After cycle 6, no systemic administration-related reactions were reported with in the daratumumab+VCd. Major organ deterioration progression-free survival is scheduled to be updated after approximately 200 events.
Summary/Conclusion: Updated results from the ANDROMEDA study further support that in patients with newly diagnosed AL amyloidosis, the daratumumab+VCd combination is clinically superior compared with VCd alone. Following its recent approval, the daratumumab+VCd combination represents a new standard of care for patients with AL amyloidosis.

T cell re-directing therapies in relapsed/refractory multiple myeloma

S190 EFFICACY AND SAFETY OF THE BCMA-DIRECTED CAR-T CELL THERAPY, CILTACABTAGENE AUTOLEUCEL, IN PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA AFTER 1–3 PRIOR LINES OF THERAPY: INITIAL RESULTS FROM CARTITUDE-2

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Background: Ciltacabtagene autoleucel (Cilta-cel) is a chimeric antigen receptor T (CAR-T) cell therapy expressing two B-cell maturation antigen (BCMA)-targeting, single-domain antibodies designed to confer avidity. CARTITUDE-2 (NCT04133636) is a multicohort, phase 2 study evaluating cilta-cel safety and efficacy in various clinical settings for patients with multiple myeloma (MM) and exploring suitability of outpatient administration.
Aims: We report initial results from Cohort A of CARTITUDE-2.
Methods: All patients provided informed consent. Patients from Cohort A had progressive MM after 1–3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), were lenalidomide refractory, and had no prior exposure to BCMA-targeting agents. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) was given 5–7 days after initiating lymphodepletion (cyclophosphamide [300 mg/m^2] and fludarabine [30 mg/m^2] daily for 3 days). The primary objective was minimal residual disease (MRD) 10^{-5} negativity. Secondary outcomes were response rates per International Myeloma Working Group criteria and safety (adverse events [AEs] were graded per Common Terminology Criteria for Adverse Events; cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS] were graded per American Society for Transplantation and Cellular Therapy).
Results: At the data cutoff of Feb 2021 (median follow-up of 5.8 months; range: 2.5–9.8), 20 patients (65% male; median age 60 years [range: 38–75]) had received cilta-cel; one patient was treated in an outpatient setting. Patients received a median of 2 prior LOT (range: 1–3); 12 patients received <3 prior LOT and 8 received 3 prior LOT. All patients were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab. The majority (95%) were refractory to their last LOT, and 40% were triple refractory. The overall response rate was 95% (95% CI: 75–100) with 75% (95% CI: 51–91) achieving ≥complete response, and 85% (95% CI: 62–97) achieving ≥very good partial response. Median time to first response was 1.0 month (range: 0.7–3.3), and median time to best response was 1.9 months (range: 0.9–5.1). The median duration of response was not reached. All patients (n=4) with MRD-evaluable samples at 10^{-5} at the time of data cutoff were MRD-negative. Hematologic AEs (in ≥20% of patients) were neutropenia (95%; grade 3/4: 90%), thrombocytopenia (80%; grade 3/4: 35%), anemia (65%; grade 3/4: 40%), lymphopenia (60%; grade 3/4: 55%), and leukopenia (55%; all grade 3/4). CRS occurred in 85% of patients; 10% were grade 3/4. The median time to CRS onset was 7 days (range: 5–9), with a median duration of 3.5 days (range: 2–11). CAR-T cell neurotoxicity occurred in 20% of patients (all grade 1/2). Three patients had ICANS (1 was grade 1; 2 were grade 2) with median time to onset of 8 days (range: 7–11) and median duration of 2 days (range: 1–2). One patient had grade 2 facial paralysis with time to onset of 29 days and duration of 51 days. One death occurred due to COVID-19, which was assessed as treatment-related by investigator. The safety profile was manageable in the patient treated in an outpatient setting.
Summary/Conclusion: A single cilta-cel infusion at the recommended phase 2 dose led to early and deep responses with manageable safety in patients with MM who had received 1–3 prior LOT. Updated efficacy and safety findings will inform suitability of outpatient treatment in this and other cohorts of CARTITUDE-2 as well as the CARTITUDE-4 study.

S191 TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D (GPRC5D) × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS OF A PHASE 1, FIRST-IN-HUMAN STUDY

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Background: As patients with multiple myeloma (MM) continue to relapse on current therapies, new immunotherapy targets are needed. G protein-coupled receptor family C group 5 member D (GPRC5D) is an orphan receptor that is expressed on malignant plasma cells in MM. Talquetamab (JNJ-64407564) is a bispecific immunoglobulin G4 antibody that binds to CD3 and the novel target GPRC5D to redirect T cells to kill MM cells.
Aims: To report updated phase 1 results of patients with relapsed/refractory MM treated with talquetamab at the recommended phase 2 dose (RP2D).
Methods: Eligible pts with MM who had relapsed or refractory disease or were intolerant to standard therapies, were administered talquetamab either intravenously (IV; range 0.5–180 µg/kg) or subcutaneously (SC; range 5.0–800 µg/kg) in a weekly or biweekly dosing schedule. The primary objectives of the study were to identify the RP2D (part 1) and to characterize the safety and tolerability of talquetamab at the RP2D (part 2). Adverse events (AEs) were graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and cytokine release syndrome (CRS) was graded per Lee 2014 criteria. Response was assessed per International Myeloma Working Group criteria. All patients provided informed consent.
Results: As of Feb 8, 2021, 174 patients received talquetamab IV (n=102) or SC (n=72). Across parts 1 and 2 of the study, 28 patients were treated at the RP2D, identified as weekly SC 405 µg/kg, with 10.0 and 60.0 µg/kg step-up doses. Patients treated at the RP2D had a median age of 61.5 years (range 46–80 years) and had received a median of 5.5 prior lines of therapy (range 2–14; 100%/79% triple-class/penta-drug exposed; 71%/18% triple-class/penta-drug refractory; 86% refractory to last line of therapy; 21% with prior B-cell maturation antigen–directed therapy). No dose-limiting toxicities occurred at the RP2D in part 1 of the study. The most common AEs at the RP2D were CRS (79%; 4% were grade 3; median time to onset was day after SC dose), neutropenia (64%; 54% were grade 3/4), anemia (57%; 29% were grade 3/4) and dysgeusia (57%; all were grade 1/2). Infections were reported in 32% of patients (4% were grade 3/4) and neurotoxicity reported in 7% (no grade 3/4 events). In all, 75% of patients who received the RP2D had skin-related AEs, none of which were grade 3/4, including 18% with nail disorders. In response-evaluable patients (n=24), the overall response rate at the RP2D was 63%, with 50% reaching very good partial response or better; 9/17 (53%) evaluable triple-class refractory patients and 3/3 (100%) penta-drug refractory patients had a response. The median time to first confirmed response at the RP2D was 1.0 month (range 0.2–3.8). Responses were durable and deepened over time; the median follow-up was 6.2 month [range 2.7–9.7+] for responders at the RP2D. Talquetamab exposure at the RP2D was maintained over the maximum EC target level from an ex vivo cytotoxicity assay. Consistent T cell activation was also observed at the RP2D.
Summary/Conclusion: Talquetamab, at the RP2D of weekly 405 µg/kg SC, demonstrated a high clinical response rate and was well-tolerated in patients with relapsed/refractory MM. Based on the pharmacokinetic data, other SC dosing strategies are also being explored. The promising efficacy and safety profile, and the convenience of SC dosing support monotherapy development and combination approaches with this novel agent.

S192 MAGNETISMM-1: PHASE 1 STUDY OF ELRANATAMAB (PF-06863135), A B-CELL MATURATION ANTIGEN (BCMA) TARGETED CD3-ENGAGING BISPECIFIC ANTIBODY, FOR PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (MM)

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Background: Elranatamab (PF-06863135) is a humanized bispecific monoclonal antibody (IgG2a) that targets BCMA, a member of the tumor necrosis factor receptor superfamily expressed in MM, and CD3 on T cells. MagnetisMM-1 (ClinicalTrials.gov ID: NCT03269136) is a Phase 1 study of elranatamab designed to evaluate selective therapeutic targeting and activation of T cells re-directed against BCMA-expressing malignant plasma cells.
Aims: The aim of MagnetisMM-1 is to characterize the efficacy, safety, pharmacokinetics, and pharmacodynamics of elranatamab as a single agent and in combination with immunomodulatory agents for patients with relapsed or refractory MM.
Methods: Patients (pts) received single agent elranatamab at 80, 130, 215, 360, 600, and 1000µg/kg/week subcutaneously (SC). A modified toxicity probability interval method was used for escalation, with monitoring for dose-limiting toxicity (DLT) to end of the first cycle. Treatment-emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events (v4.03), and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria (Lee et al. Biol Blood Marrow Transplant. 2019;25:625). Response was assessed by International Myeloma Working Group criteria. Pharmacokinetics, cytokine profiling, and T cell immunophenotyping were performed.
Results: 30 pts had received elranatamab as of 4-Aug-2020 at 80 (n=6), 130 (n=4), 215 (n=4), 360 (n=4), 600 (n=6), or 1000 (n=6) µg/kg SC weekly. Pts had a median of 8 prior treatments; 87% had triple refractory disease, 97% had prior anti-CD38 therapy, and 23% had prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T cell therapy. The most common all causality TEAEs included lymphopenia (n=24, 80%; 20% G3, 60% G4), CRS (n=22, 73%; none >G2), anemia (n=17, 57%; 43% G3, 3% G4), injection site reaction (n=16, 53%; none >G2), thrombocytopenia (n=16, 53%; 23% G3, 17% G4), and neutropenia (n=12, 40%; 17% G3, 17% G4). Both CRS and immune effector cell-associated neurotoxicity syndrome (n=6, 20%) were limited to ≤G2 with median durations of 2 and 1.5 days, respectively. No DLT was observed. Exposure increased with dose, and T_{max} ranged from 3–7 days. Cytokine increases occurred with the first dose, and increased T-cell proliferation was observed in peripheral blood. The overall response rate (ORR) for doses ≥215µg/kg was 75% (n=15/20) including partial response (PR; n=6), very good PR (VGPR; n=3), complete response (CR; n=1), and stringent CR (sCR; n=5). Median time to response was 22 days, and 3 of 4 pts (75%) with prior BCMA-directed therapy achieved response (VGPR, n=2 and sCR, n=1). The recommended Phase 2 dose for single agent elranatamab is 1000 µg/kg SC weekly. Updated data, including duration of response, will be presented.
Summary/Conclusion: Elranatamab demonstrated a manageable safety profile and wide therapeutic index. Doses ≥215µg/kg SC achieved ORR of 75% with CR/sCR rate of 30%. These results demonstrate the safety and efficacy of elranatamab in this relapsed/refractory population, confirm the feasibility and potential of BCMA-directed immunotherapy for malignant plasma cell disorders, and support ongoing development of elranatamab for pts with MM.

S193 TECLISTAMAB, A B-CELL MATURATION ANTIGEN (BCMA) × CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED PHASE 1 RESULTS

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Background: B-cell maturation antigen (BCMA)-targeted immunotherapies are promising treatment options for patients with relapsed/refractory multiple myeloma (MM). Teclistamab (JNJ-64007957) is a bispecific immunoglobulin G4 antibody that binds to both BCMA and CD3 to redirect CD3+ T cells to BCMA-expressing MM cells.
Aims: To report updated results from the first-in-human phase 1 study of teclistamab in patients with relapsed/refractory MM who were treated at the recommended phase 2 dose (RP2D).
To report updated results from the first-in-human phase 1 study of teclistamab in patients with relapsed/refractory MM who were treated at the recommended phase 2 dose (RP2D).
Methods: Eligible patients had relapsed/refractory MM or were intolerant to established therapies. The primary objectives of the study were to identify the RP2D (part 1) and to characterize the safety and tolerability of teclistamab at the RP2D (part 2). Teclistamab was given either intravenously (IV; range 0.3–19.2 µg/kg biweekly; range 19.2–720 µg/kg weekly) or subcutaneously (SC; range 80.0–3000 µg/kg weekly) in different cohorts, with step-up dosing for doses ≥38.4 µg/kg. Adverse events (AEs) were graded by Common Terminology Criteria for Adverse Events v4.03, and cytokine release syndrome (CRS) was graded by Lee et al 2014 criteria. Response was assessed per International Myeloma Working Group criteria. All patients provided informed consent.
Results: As of Feb 4, 2021, 156 patients had received teclistamab IV (n=84) or SC (n=72). The identified RP2D of weekly SC 1500 µg/kg teclistamab with 60.0 and 300 µg/kg step-up doses, was given to 40 patients; the median follow-up was 4.3 months (range 1.1–10.4+). Of the patients treated at the RP2D, the median age was 62.5 years (range, 39–84), 65% were men and a median of 5 prior lines of therapy was received (range 2–11; 100% triple-class exposed; 65% penta-drug exposed; 83% triple-class refractory; 35% penta-drug refractory; 85% refractory to their last line of therapy). No dose-limiting toxicities occurred at the RP2D in part 1 of the study. The most common AEs at the RP2D were CRS (70%; no grade 3/4 events) and neutropenia (60%; 40% were grade 3/4); grade 1 neurotoxicity was reported in 1 (3%) patient. The median time to CRS onset occurred later with SC dosing compared with IV dosing (day after SC injection vs. day of IV infusion). The overall response rate in response-evaluable patients treated at the RP2D (n = 40) was 65%; 58% of patients achieved a very good partial response or better, and 30% of patients achieved a complete response (CR) or better. The median time to first confirmed response was 1.0 month (range 0.2–3.1). At the RP2D, the median duration of response was not reached with 23/26 responders (88%) alive and continuing treatment at a median follow-up of 5.3 months (range 1.2–10.4+). Responses continued to deepen over time. Of 14 evaluable patients across all cohorts, 9 with CR were minimal residual disease–negative at 10^{-6}. At the RP2D, teclistamab exposure was sustained across the dosing interval and exceeded target levels. Consistent T cell activation was also observed at the RP2D.
Summary/Conclusion: At the RP2D of weekly 1500 µg/kg SC, teclistamab was well-tolerated and demonstrated encouraging efficacy with durable, deepening responses, warranting further investigation as monotherapy and in combination with other agents. With the extended exposure profile at the RP2D and delayed and low-grade CRS observed with SC administration, alternative SC dosing strategies are being explored.

S194 AN UPDATED PHASE 1 STUDY OF A NOVEL FULLY HUMAN BCMA-TARGETING CAR-T CELLS (CT103A) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background: About 33 to 88% of patients with relapsed/refractory multiple myeloma (RRMM) had objective anti-myeloma responses after treatment with anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cells. However, it remains a great challenge to achieve durable responses, and relapse or disease progression is observed in approximately 28 to 88% of patients. Previous studies suggest that CARs with humanized or fully human single-chain variable fragments (scFvs) may bypass the potential host anti-CAR immunogenicity and retain anti-tumor activity.
Aims: We developed a novel BCMA-targeting CAR construct (CT103A) with a fully human scFv, and conducted an open-label, single-arm phase I clinical trial to evaluate the safety and efficacy, including overall response rate (ORR), minimal residual disease (MRD), and also pharmacokinetics, and pharmacodynamics. The initial results in RRMM have been previously reported. Here, we report updated data of its safety and efficacy in the phase I trial.
Methods: Written informed consent was obtained from each participant, in compliance with the Declaration of Helsinki. Enrolled patients had at least three lines of prior therapies that must include a proteasome inhibitor and an immunomodulatory agent. Clinical response and disease progression were evaluated according to the IMWG consensus criteria at serial time points after CT103A infusion. The definition of extramedullary myeloma (EMM) is the presence of soft tissue masses in extraosseous locations resulting from hematogenous spread, which are not contiguous to the involved bone. MRD was assessed by multiparametric flow cytometry, and CAR transgene copies in the patient peripheral blood mononuclear cell were monitored by digital droplet polymerase chain reaction.
Results: A total of 35 patients were enrolled, among which 29 had high-risk cytogenetics. All patients received 1.0, 3.0, or 6.0 × 10^6/kg CAR-T cells after leukapheresis in the dose-escalation phase and 1.0 dose in the dose-expansion cohort. In escalation, 1.0 dose was determined as RP2D. The cut-off date was December 31, 2020. The median follow-up after CT103A infusion was 520 days (121 to 832 days). Hematologic toxicities were the most common adverse events. 74.3% of the patients experienced grade 1 or 2 cytokine release syndromes (CRS). All CRS could be efficiently controlled. Neurotoxicity (grade 2 ICANS) was observed only in one patient with the symptom of drowsiness, who was later spontaneously relieved without any treatment. For efficacy, 3m ORR rate was 94.2%, ≥VGPR was 74.3%, CR/sCR was 45.7%. 5/8 patients with EMM achieved ≥VGPR, among whom one with both EMM and plasma cell leukemia achieved VGPR. Moreover, 6/9 patients who have received prior CAR-T treatment achieved ≥VGPR. Besides, all 34 patients who performed MRD detection were MRD-negative at one month, and 31 patients kept negative until the last follow-up. The median time to reach the peak of CT103A expansion in 35 patients was 12 (7, 17) days. CAR-T cells were persistent in 100% of the patients, among whom maximum duration had exceeded two years. What's more, only 1 of 35 patients were detected positive for anti-drug antibody, which was reported to be a high-risk factor for disease relapse/progression after CAR-T therapy.
Summary/Conclusion: CT103A is safe, highly productive, and long persistent in RRMM patients and can be developed as a promising therapy for RRMM. Patients who relapsed from prior non-human BCMA CAR T-cell therapy could still benefit from CT103A. This approach is being explored in the phase II study.

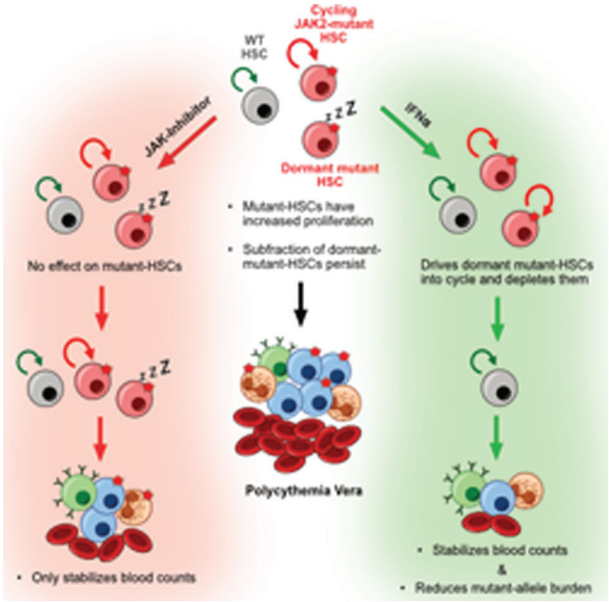
New pathways and molecular mechanisms in MPN

S195 INTERFERON-ALPHA TREATMENT RESULTS IN THE DEPLETION OF DORMANT JAK2-MUTANT HSC IN A MURINE MODEL OF POLYCYTHEMIA VERA

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Background: The majority of patients with *Bcr-Abl* negative myeloproliferative neoplasms (MPN) have a JAK2-V617F mutation. Targeted therapy with JAK-inhibitors have been shown to normalize blood parameters but do not lead to a significant reduction in the mutant allelic burden. Interferon-alpha (IFNα) therapy is the only treatment option available that can achieve molecular remission. However, long-term treatment with IFNα is required and patients frequently exhibit adverse side-effects. Thus it is important to elucidate the mechanism of action of IFNα in achieving molecular remission, which is still not completely understood. Previous studies in JAK2-mutant MPN mouse model have shown that IFNα treatment leads to the depletion of the mutant hematopoietic stem cells (HSCs). Our previous findings have shown that IFNα can drive wildtype dormant HSCs into cell cycle, leading to attrition of functional HSCs. We hypothesize that IFNα treatment eliminates the functional disease-propagating JAK2-mutant HSCs by breaking their dormant status.
Aims: To assess the inherent proliferative index of JAK2-mutant HSCs and the effect of IFNα treatment on mutant-HSC dormancy in comparison to JAK-inhibitor treatment.
Methods: A BrdU pulse-chase experiment was performed on a JAK2-V617F mouse model of MPN, to assess the inherent proliferation of JAK2-mutant HSCs. The dilution of BrdU-label in the mutant HSCs was assessed at different time-points post BrdU-pulse. To further compare the effects of IFN-α and Fedratinib (JAK-inhibitor) on dormant mutant HSCs, mice exhibiting MPN symptoms were pulse-labelled with BrdU as before. The mice were then treated with pegylated-IFNα (600ng or 300ng) or Fedratinib (120mg/kg) for 4 weeks. The proportion of BrdU-label-retaining HSCs in the bone marrow and the changes in blood parameters were assessed 48 hours after final treatment.
Results: The dilution of BrdU-label was observed to be faster in the JAK2-mutant HSCs compared to wildtype-HSCs during disease progression, indicating that JAK2-mutant HSCs have increased cycling and proliferation. However, a sub-fraction of dormant BrdU-label-retaining mutant HSCs were still observed after 20 weeks of chase. While both Fedratinib and peg-IFNα treatment was observed to stabilize blood parameters in the JAK2-mutant mice, only peg-IFNα was observed to significantly reduce the mutant allelic burden in the peripheral blood and eliminate the BrdU-positive dormant mutant HSCs.



Summary/Conclusion: JAK2-mutant HSCs have an inherently higher cycling compared to wildtype-HSCs. However, we identify for the first time a dormant sub-fraction of mutant HSCs within the bone marrow. These dormant HSCs may be responsible for disease propagation and relapse after therapy. In support of this, dormant HSCs were unaffected by Fedratinib treatment in mice where hematologic parameters had been normalized, while peg-IFNα was found to eliminate the dormant mutant HSCs. These data provide a new model to explore novel strategies to eliminate therapy resistant HSCs in the setting of JAK2 mutated MPNs.

S196 CALR FRAMESHIFT MUTATIONS ACCELERATE MATURATION OF MEGAKARYOCYTES IN MPN PATIENT-DERIVED IPS CELLS

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Background: In myeloproliferative neoplasms (MPN), somatic driver mutations of *calreticulin (CALR)*, present in up to 30% of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF), include 52bp deletions (del52) and 5bp insertions (ins5) in exon 9. Mutant CALR acts by firmly binding to the thrombopoietin receptor (MPL), leading to constitutive activation of Janus kinases (e.g. JAK2) and associated downstream signaling. This results in cellular transformation, including enhanced megakaryopoiesis. The mechanism of increased megakaryopoiesis and the role of mutant *CALR* zygosity has not fully been elucidated to date.
Aims: Establishment of an MPN patient-derived induced pluripotent stem (iPS) cell model focusing on CALR mutations in megakaryocytic development.
Methods: iPS cells were reprogrammed from PBMCs of MPN patients with *CALR*del52 or *CALR*ins5 mutations, or from healthy donors. Since reprogramming of CALR-mutant cells only resulted in homozygous (hom) and heterozygous (het) clones but not *CALR*wt clones, *CALR* mutations were repaired using CRISPR/Cas9n gene editing. iPS cells were differentiated into myeloid cells, with a particular focus on megakaryocytes (MKs). Bulk populations were analyzed by flow cytometry, and CD61+ MKs were purified and further analyzed for RNA expression and ultrastructural morphology.
Results: We established an iPS cell model including *CALR*ins5 and del52 hom and het clones and CRISPR-repaired isogenic (WT_{cr}) clones. Homozygous *CALR*del52 and *CALR*ins5 iPS clones were found to lack myeloperoxidase (MPO) activity, as has been described for patients with hom *CALR* mutations, and MPO activity as an indicator of CALR wt protein function was restored in WT_{cr} clones. We established a protocol allowing efficient generation of iPS cell-derived MKs with characteristics of primary MKs, such as formation of a demarcation membrane system, cytoplasmic pro-platelet protrusions, and MK-typical granules. We demonstrate that hom and het *CALR*ins5- and del52-mutated iPS cells generate a significantly higher number of MKs than related WT_{cr} clones ($p<0.05$ each). Moreover, MK generation of *CALR*ins5 and del52 cells is TPO-independent in contrast to WT_{cr} and healthy donor clones. Enhanced megakaryopoiesis was due to an accelerated maturation process of *CALR*-mutated MKs, since the number of CD42b+ cells among the population of CD61+CD41+ MKs on day 10 was higher in hom (p=0.001[del52], p=0.18[ins5]) and het (p=0.044[ins5]) *CALR*-mutated cells vs. WT_{cr} MKs. In contrast, on day 14, the number of CD42+ MKs in CD61+CD41+ population was similar for all genotypes, suggesting that the WT_{cr} MKs had taken longer to mature. Nonetheless, differences in the expression of megakaryocytic genes were observed between genotypes, with an increased *MPL* expression in *CALR*ins5 MKs compared to WT_{cr} MKs (p=0.0062[het], p=0.052[hom]). Accelerated megakaryopoiesis in *CALR*ins5-mutated clones was corroborated by upregulation of the late MK maturation marker *NFE2* (p=0.0061[het], p=0.052[hom]), and an increased granularity of hom *CALR*ins5 mutated vs. unmutated MKs (p=0.0089).

Summary/Conclusion: We demonstrate that het and hom *CALR*ins5- and del52-mutated iPS cells recapitulate features observed in ET and PMF patients, such as an increased number of MKs, and that this can be reversed by repair of the mutation, suggesting that mutant CALR is responsible for these effects. Mechanistically, our data show that mutant CALR induces an accelerated maturation process of MKs, which is in line with accelerated platelet turnover seen in ET and PMF patients.

S197 TYK2 INHIBITION IS A NOVEL SELECTIVE THERAPEUTIC APPROACH FOR CALR- BUT NOT JAK2V617F-MUTANT MYELOPROLIFERATIVE NEOPLASMS

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Background: The classical Philadelphia-chromosome-negative (Ph-) myeloproliferative neoplasms (MPNs) consist of three entities: polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), carrying three mutually exclusive driver mutations in the genes of janus kinase 2 (*JAK2*), calreticulin (*CALR*) and the thrombopoietin (TPO) receptor (*MPL*). JAK2V617F-mutant cells were shown to be more sensitive to interferon alpha (IFNa) treatment compared to CALR-mutant cells and this IFNa "priming" involved increased phosphorylation of JAK1 and signal transducer and activator of transcription (STAT) 1 in JAK2V617F- vs. CALR-mutant cells. IFNa stimulation leads to phosphorylation of tyrosine kinase (TYK) 2 and JAK1, which are constitutively associated with the IFNa receptor-1 or -2 (IFNAR1/2), respectively, and activate downstream signaling pathways. However, the role of TYK2 in the survival and IFNa response of JAK2- vs. CALR-mutant MPN cells is still incompletely understood.
Aims: Analysis of the role of TYK2 in MPN cells to further investigate the differential response of JAK2V617F- and CALR-mutant cells to IFNa treatment and evaluate TYK2 as a potential target in MPN.
Methods: We used CRISPR/Cas9 technology to generate *TYK2*-deficient $32D^{MPL}$ JAK2V617F or CALRdel52 cells and subsequently analyzed the IFNa response on cell viability (MTT assays), downstream JAK-STAT signaling and gene expression. Furthermore, we evaluated the effects of the TYK2-specific inhibitor deucravacitinib in $32D^{MPL}$ mutant cells and in primary MPN patient material using colony formation unit assays.
Results: Basal phosphorylation of TYK2 (pTYK2) was increased in $32D^{MPL}$ CALRdel52-mutant cells compared to JAK2V617F-mutant as well as empty vector cells ($p<0.001$). Generation of a *TYK2* knockout in $32D^{MPL}$ CALRdel52 cells was not successful, while pTYK2-deficient JAK2V617F-mutant cells were readily produced, underlining an important role of TYK2 in CALR-mutant cells. In pTYK2-deficient $32D^{MPL}$ JAK2V617F cells, IFNa effects were significantly reduced, including loss of viability, activation of pSTAT1 and pSTAT3 and IFNa target genes. However, induction of apoptosis after IFNa treatment was not altered. We analyzed the effect of deucravacitinib and found that cell viability of $32D^{MPL}$ CALRdel52- but not JAK2V617F-mutant cells was significantly decreased even at low concentrations [0.5 µM] of the inhibitor. Western Blotting confirmed complete loss of TYK2 phosphorylation after deucravacitinib treatment in both cell lines as well as reduced phosphorylation of downstream signaling molecules. In primary peripheral blood-derived mononuclear cells of patients with MPN, the TYK2 inhibitor decreased CALR- but not JAK2V617F-mutant allele burden in vitro, and clonogenic growth of ET- and PMF- but not PV-derived cells was inhibited.
Summary/Conclusion: Our data demonstrate an essential role for TYK2 in CALR-mutant but not JAK2V617F-mutant MPN cells and suggest pharmacologic TYK2 inhibition as a novel promising treatment approach in CALR-mutant MPNs.

S198 IDENTIFICATION AND PHENOTYPIC CHARACTERIZATION OF DISEASE-INITIATING CD34+/CD38– STEM CELLS IN BCR-ABL1-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

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Background: The classical Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) are characterized by uncontrolled expansion of myeloid progenitor cells, elevated blood counts, phenotype-driver mutations in certain target-genes (*JAK2*, *CALR*, *MPL*) and an increased risk of leukemic transformation. Despite being considered stem-cell disorders, the phenotype of the disease-initiating neoplastic stem cells (NSC) in MPN remains unknown.
Aims: The aim of the study is to identify MPN-initiating NSC and characterize their phenotype in order to facilitate their enrichment and develop novel treatment strategies.
Methods: As assessed by multicolor flow cytometry and a panel of monoclonal antibodies (n=50), we were able to define target expression profiles of putative $CD34^+/CD38^-$ NSC and $CD34^+/CD38^+$ progenitor cells in patients with chronic phase MPN (n=93) and post-MPN secondary acute myeloid leukemia (sAML, n=11). To confirm the disease-initiating ability of primary MPN NSC, xenotransplantation experiments with NSGS mice were performed.
Results: In almost all patients, the MPN NSC expressed several receptors involved in NSC-niche interaction, including CD97, CD99, CD117 and CD184. In contrast, NSC expressed CD26 only in a subset of patients with primary myelofibrosis (PMF). MPN NSC expressed significantly higher levels of CD184 compared to stem cells in healthy controls ($p<0.0001$) or sAML ($p<0.01$). Among the cytokine receptors tested, CD25 was identified on NSC in most patients with PMF and sAML, and in a few with essential thrombocythemia (ET), but not in patients with polycythemia vera (PV). PMF NSC also displayed higher levels of CD25 than the PMF progenitor cells ($p<0.01$). MPN NSC did not exhibit substantial amounts of IL-1RAP and erythropoietin receptor. We next examined the expression of various immunological targets and resistance-mediating immune checkpoints. In all patients tested, NSC were found to express CD33. We also found that $CD34^+/CD38^+$ progenitor cells in ET display higher levels of CD33 than NSC ($p<0.01$). However, neither NSC nor the progenitor cells in MPN expressed higher levels of CD33 compared to normal stem cells or normal progenitor cells. MPN NSC and sAML stem cells consistently expressed the "don't eat me" checkpoint CD47 and the classical checkpoint CD274 (PD-L1). MPN NSC displayed significantly higher levels of CD274 compared to normal stem cells ($p<0.001$) or stem cells in sAML ($p<0.05$). No difference in the expression of surface antigens on MPN NSC were observed between patients harboring mutations in the *JAK2* and *CALR* genes. Engraftment of human $CD45^+CD33^+$ cells in the bone marrow of NSGS mice was found in 15/15 mice injected with bulk mononuclear cells (MNC) containing $CD34^+$ cells and in 0/15 NSGS mice injected with CD34-depleted MNC after 28 weeks. Whereas the $CD38^-$ sub-fraction of MPN MNC produced leukemic engraftment in 10/14 mice (71.4%) only 2/13 mice (15.4%) engrafted when injected with the $CD38^+$ sub-fractions of MPN NSC. Engraftment of clonal MPN cells was confirmed by demonstrating the presence of *JAK2*-V617F mutation in engrafted human cells in mouse BM samples.
Summary/Conclusion: Together, we show that MPN NSC reside in a $CD34^+/CD38^-$ fraction of the malignant clone and display a unique phenotype, including immune checkpoint molecules, cytokine receptors and other target antigens. Our results should support the isolation of MPN NSC and the development of NSC-eradicating therapies in MPN.

S199 BH3-MIMETICS AND AZACITIDINE SHOW SYNERGISTIC EFFECTS ON JUVENILE MYELOMONOCYTIC LEUKEMIA

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Background: Juvenile myelomonocytic leukemia (JMML) represents an aggressive myeloid neoplasia of early childhood, driven by oncogenic RAS signaling and epigenetic deregulation. Most patients require allogeneic stem cell transplantation (HSCT), but relapse risk remains high. Azacitidine effectively reduces leukemia burden in some JMML patients. Nonetheless, not all patients respond to this treatment, and alternative therapeutic strategies are urgently required. BH3-mimetics inhibit anti-apoptotic BCL-2 proteins (i.e. BCL-2, BCL-XL, MCL-1 and/or BCL-W) thereby inducing apoptosis directly at the mitochondrial level. These compounds hold big promise for anti-cancer therapy, either alone or in combination with other drugs. Recently, venetoclax, a specific BCL-2 inhibitor, was FDA-approved in combination with hypomethylating agents for the treatment of acute myeloid leukemia (AML) in adults.
Aims: Based on these promising results obtained in AML, we investigated different BH3-mimetics in JMML, alone or in combination with azacitidine.
Methods: For this purpose, we generated patient-derived xenograft (PDX) mice and treated them with ABT737, an analogue of navitoclax known to inhibit BCL-2, BCL-XL and BCL-W. Treatment was initiated 8 weeks after transplantating JMML cells. ABT737 was regularly given for the next 28 days (75 mg/kg/d), and on day 29, mice were sacrificed and analyzed by flow cytometry and histopathology. Mock-treated mice were used as controls. In addition, a group of mice was treated with azacitidine as described earlier (i.e. 2 cycles á 5 days followed by 9-day breaks, 3 mg/kg/d).
Results: Both ABT737 and azacitidine led to efficient leukemia depletion. We then analyzed whether both drugs could be used at lower concentration when given in combination, with the aim to minimize any potential side effect. Indeed, a 28 days long treatment with 0.75 mg/kg/d azacitidine (5 days on, 9 days off) and 50 mg/kg/d ABT737 (daily) did not only completely reduce leukemia burden but also depleted all leukemia-initiating cells as confirmed by serial transplantation experiments. The combination of drugs worked significantly better than both drugs alone.
To dissect the roles of BCL-2 and BCL-XL, both inhibited by navitoclax, and to additionally analyze the role of MCL-1 in the survival of JMML cells, we performed *in vitro* experiments using the specific inhibitors ABT199, A1155463 and S63845, respectively. When used alone, only ABT737 and the MCL-1 inhibitor S53845 killed JMML cells efficiently. However, synergistic effects were noted between azacitidine and the BCL-XL inhibitor A1155463. Azacitidine treatment resulted in the upregulation of pro-apoptotic BCL-2 proteins (i.e. BIK, PUMA, BAD and BMF) and a slight downregulation of MCL-1 indicating that azacitidine and the BCL-XL inhibitor synergized at the level of the BCL-2 protein family.
Summary/Conclusion: In sum, our study confirms that the effects of azacitidine are significantly increased by adding BH3-mimetics. Such combination strategies will be especially important for those patients that are resistant to azacitidine monotherapy.

Novel therapies and targets in MPN

S200 RUSFERTIDE (PTG-300) ELIMINATES THE NEED FOR THERAPEUTIC PHLEBOTOMY IN BOTH LOW AND HIGH-RISK POLYCYTHEMIA VERA (PV) PATIENTS

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Background: Polycythemia vera (PV) patients are treated with periodic therapeutic phlebotomy (TP) to maintain hematocrit levels <45% in an effort to reduce the incidence of thrombotic events. PV patients likely spend significant time with hematocrit levels >45%, between TP and increase the risk of thrombosis. Hepcidin is the body's main negative regulator of iron metabolism such that elevated hepcidin levels are expected to reduce iron availability and decrease erythropoiesis. Rusfertide (PTG-300) is a hepcidin-mimetic. We hypothesized that rusfertide would decrease erythropoiesis and phlebotomy requirement in PV patients.
Aims: The current study aims to compare the iron status and phlebotomy requirements in high TP-requiring PV patients before and during treatment with rusfertide.
Methods: PTG-300-04 is a Phase 2 trial consisting of 3 parts: (1) a 28-week dose-finding; (2) a 12-week blinded randomized withdrawal (1:1) rusfertide vs placebo; and (3) a 52-week open label extension (**NCT04057040**). Eligibility criteria include PV diagnosis and ≥3 phlebotomies with or without concurrent cytoreductive therapy to maintain hematocrit <45% in the 24 weeks prior to enrollment. Rusfertide doses of 10, 20, 40, 60 and 80 mg administered subcutaneously weekly were added on to each subject's pre-study treatment for PV and the dose of rusfertide was adjusted to maintain hematocrit <45%.
Results: Thirty-five patients were enrolled to date: 16/35 with low-risk PV, age rangd between 31-75yrs. Prior to enrollment all patients received TP range of TP 3-9; median time between TP = 36 days. In addition, out of 35 patients; 8 patients received concurrently hydroxyurea, 3 patients received concurrently interferon, and 1 patient received concurrently ruxolitinib. The rate of TP after starting rusfertide decreased significantly compared to the rate of TP before starting rusfertide (p< 0.0001). Four subjects required one TP early in the dose-finding period (within 12 weeks) and 3 have subsequently been TP-free after increasing the dose of rusfertide. Thirteen patients have completed 28 weeks of dosing in Part 1. Ten patients were TP-free for 28 weeks; 2 patients required 1 TP each and 1 required 2 compared to >3 TP each over 28 weeks pre-study. Hematocrit was <45% at study entry and remained continuously <45% during the study. Prior to treatment, mean ferritin levels were consistent with systemic iron deficiency while serum ferritin increased progressively toward normal range during the study. Furthermore, both MCV and MCH values increased suggesting a redistribution of iron within erythropoiesis. The most frequent adverse events (AE) were injection site reactions (ISR) reported by 9 patients. Most of the ISR were grade 1 and there were no drug related SAE.
Summary/Conclusion: The current results indicate that rusfertide is an effective agent for the treatment of PV, reversing iron deficiency and eliminating the need for TP in PV patients. Elimination of TP requirements for 7 months in TP-dependent PV patients is significant and unexpected. The effect of rusfertide on PV-related symptoms is also being evaluated. Continued patient enrollment will enable more definitive conclusions regarding the efficacy and safety of rusfertide in PV patients. Rusfertide looks very promising in maintaining hematocrit <45% and in eliminating the therapeutic phlebotomies in both low and high-risk PV patients.

S201 EFFICACY AND SAFETY OF AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: INTERIM RESULTS FROM THE OPEN-LABEL, SINGLE-ARM, PHASE 2 PATHFINDER STUDY

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Background: Systemic mastocytosis (SM) is a rare, clonal, hematologic neoplasm which is driven by the *KIT* D816V mutation in ~95% of cases. Treatment outcomes remain poor for patients (pts) with advanced systemic mastocytosis (AdvSM), which includes aggressive SM (ASM),

SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). In the Phase 1 EXPLORER study (NCT02561988), avapritinib, a potent KIT D816V inhibitor, induced rapid, durable responses which deepened over time in pts with AdvSM regardless of prior therapy or subtype.
Aims: PATHFINDER (NCT03580655) is a pivotal open-label, single-arm Phase 2 study evaluating avapritinib in pts with AdvSM.
Methods: Pts aged ≥18 years with centrally confirmed diagnosis of an AdvSM subtype. Primary endpoint was overall response rate (ORR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria. This pre-specified interim analysis (null hypothesis ORR 28% based on midostaurin) included 32 ORR-evaluable pts. Mean baseline change in AdvSM-Symptom Assessment Form Total Symptom Score (TSS) and safety were secondary endpoints. All pts gave informed consent.
Results: As of June 23, 2020, 62 pts with AdvSM received avapritinib primarily at 200 mg orally once daily (QD); 52/62 (84%) pts remained on treatment. Median age was 69 years (range 31–88), 45% were female, 31% had ECOG PS 2–3, and 68% had prior systemic therapy (55% with midostaurin). The primary endpoint was met with an ORR of 75% (95% CI 57–89) in 32 ORR-evaluable pts as per the pre-specified interim analysis (P=1.6x10-9; median follow-up 10.4 months) (**Table**). Complete remission with full or partial hematologic recovery occurred in 6 (19%) pts. Median time to response was 2 (range 0.3–12) months; responses deepened over time. Median overall survival (OS) in the ORR-evaluable population was not reached; estimated 12-month OS was 87%. In the safety population (N=62), there were ≥50% reductions from baseline for serum tryptase (87%; n=54), marrow mast cells (71%; n=44), and *KIT* D816V variant allele fraction (53%; n=33). Mean TSS at baseline (n=56) was 18.3; fatigue, spots, itching, flushing, and abdominal pain were the most severe symptoms; TSS improved rapidly and was sustained through cycle 11 with mean 36% improvement (P<0.001), corresponding to a mean decrease of 9.8 points from baseline (n=22). Common (≥25%) adverse events (AEs; any grade, Grade ≥3) were peripheral (50%, 3%) and periorbital (35%, 3%) edema, thrombocytopenia (32%, 8%), and anemia (29%, 16%). Overall, 3 (5%) pts discontinued due to a treatment-related AE and 3 (5%) pts discontinued due to disease progression, including 1 pt with transformation to acute myeloid leukemia. There were 3 (5%) deaths, all considered unrelated to treatment. Seven (11%) pts had cognitive AEs (all Grade 1–2). Grade 4 subdural hematoma occurred in 1 (2%) pt with severe thrombocytopenia (platelets <50×10^9/L) at baseline and prior to the event. Subsequent pts with pre-treatment severe thrombocytopenia were excluded, platelet monitoring increased, and dose interruption for severe thrombocytopenia recommended.

Table. Confirmed ORR and best response by mIWG-MRT-ECNM criteria in pts with AdvSM[a]

Outcome, n (%)	All (n=32)	ASM (n=2)	SM-AHN (n=26)	MCL (n=4)	All (n=32)			
					Prior therapy (n=23)	No prior therapy (n=9)	Prior Midostaurin (n=17)	No Prior Midostaurin (n=15)
ORR[b]	24 (75)	2 (100)	21 (81)	1 (25)	17 (74)	7 (78)	14 (82)	10 (67)
95%CI	57–89	16–100	61–93	1–81	52–90	40–97	57–96	38–88
CR	0	0	0	0	0	0	0	0
CRh	6 (19)[c]	1 (50)	5 (19)	0	3 (13)	3 (33)	3 (18)	3 (20)
PR	10 (31)	1 (50)	8 (31)	1 (25)	7 (30)	3 (33)	5 (29)	5 (33)
CI	8 (25)	0	8 (31)	0	7 (30)	1 (11)	6 (35)	2 (13)
SD	4 (13)	0	2 (8)	2 (50)	2 (9)	2 (22)	0	4 (27)
PD	1 (3)	0	0	1 (25)	1 (4)	0	0	1 (7)
NE	3 (9)	0	3 (12)	0	3 (13)	0	3 (18)	0

[a]The PATHFINDER pre-specified interim occurred in 32 ORR-evaluable pts with a diagnosis of AdvSM, who received at least 1 dose of avapritinib and were evaluable per mIWG-MRT-ECNM criteria at baseline and had ≥2 complete post-baseline response assessments and ≥6 cycles of therapy (or came off study).
[b]ORR = CRh + PR + CI, all lasting ≥12 weeks.
[c]Median time to CRh: 5.6 months (range 1.8–6.1).
Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; 95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable for response; ORR, overall response rate; PD, progressive disease; PR, partial remission; pts, patients; SD, stable disease; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

Summary/Conclusion: The PATHFINDER registrational study interim analysis showed avapritinib 200 mg QD starting dose induced rapid, durable responses which deepened over treatment regardless of AdvSM subtype or prior therapy and improved symptoms in pts with AdvSM. Avapritinib was generally well tolerated with few pts discontinuing treatment due to AEs.

S202 TRANSFUSION INDEPENDENCE IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN MYELOFIBROSIS PATIENTS RECEIVING MOMELOTINIB

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Background: Momelotinib (MMB) is a potent JAK1, JAK2 and ACVR1 inhibitor with clinical activity against the hallmark features of myelofibrosis (MF), namely anemia, constitutional symptoms and splenomegaly, across the continuum of JAKi naïve or previously JAKi treated intermediate/high risk MF patients as demonstrated in the previously conducted Phase 3 SIMPLIFY-1 & -2 clinical trials (S1, S2). S1 enrolled JAKi-naïve patients with MF (n=432) double-blind randomized 1:1 to MMB or ruxolitinib (RUX). S2 enrolled patients with MF with hematological toxicity during prior RUX therapy (n=156) randomized 2:1 to open-label MMB or best available therapy (BAT; consisting of RUX in 88% of patients). In both trials, following the 24-week randomized treatment (RT) period, patients could continue MMB (MMB→MMB) and those randomized to RUX/BAT could cross-over to MMB (RUX/BAT→MMB) for extended treatment (ET).
Previously published data from the SIMPLIFY studies demonstrate robust overall survival (OS) for MMB-treated patients in S1 and S2 (median not reached and 34.3 months, respectively) with a maximum follow up of approximately 5 years and median of 2.9 years in S1 and 2.3 years in S2.
Aims: OS data for patients receiving MMB in S1 and S2 are reported here for subgroups defined by Week 24 (W24) transfusion independence (TI) responders vs non-responders, and also other efficacy endpoints.
Methods: Survival was estimated using KM analysis with descriptive log-rank tests for comparison applied (all p-values are descriptive).
Results: As previously reported, W24 TI rates were higher in the MMB arms of S1 (67% vs 49%) and S2 (43% vs 21%). In S1, W24 TI responders in the MMB group show an OS advantage, with median OS not reached and 3-year survival of 80% (HR=0.30; p<0.0001) compared to MMB TI non-responders. Similarly in S2, W24 TI responders in the MMB group show a trend toward better OS compared to TI non-responders (HR=0.57; p=0.0652). The HRs in S1 for MMB responders vs non-responders for W24 SRR and TSS were 0.59 (p=0.0904) and 0.65 (p=0.1657), respectively. Alternative analyses using OS defined from W24 demonstrated consistent results.
Summary/Conclusion: These new analyses suggest JAKi naïve patients receiving MMB who maintain or achieve TI at W24 have favorable OS compared to MMB TI non-responders, with a similar trend observed in S2. These findings are consistent with anemia and transfusion dependency being key predictors of shortened OS in MF and suggest that TI response at W24 may become a surrogate for clinical benefit, supporting the clinical relevance of MMB's differentiated pro-erythropoietic ACVR1 inhibition.

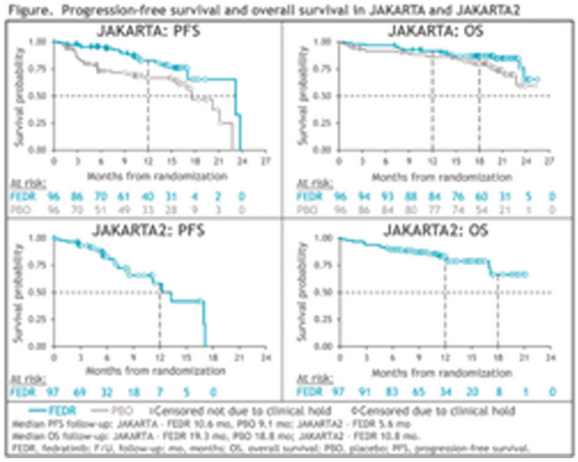
S203 OVERALL AND PROGRESSION-FREE SURVIVAL IN PATIENTS TREATED WITH FEDRATINIB AS FIRST-LINE MYELOFIBROSIS (MF) THERAPY AND AFTER PRIOR RUXOLITINIB (RUX): RESULTS FROM THE JAKARTA AND JAKARTA2 TRIALS

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Background: FEDR is an oral JAK2 inhibitor (JAKi) that improves splenomegaly and symptoms in patients (pts) with intermediate (INT) or high-risk MF, whether used as first-line (1L) treatment (Tx), or in pts previously treated with RUX. In the phase 3, double-blind JAKARTA trial, 1L Tx with FEDR 400 mg/day (d) significantly improved spleen volume and MF symptoms *vs* placebo (PBO) at 24 weeks. Similarly, in the phase 2, single-arm JAKARTA2 trial, FEDR 400 mg/d improved spleen volume and symptom burden from baseline in pts with MF previously treated with RUX. Survival outcomes from these studies have not been reported previously.
Aims: Determine progression-free survival (PFS) and overall survival (OS) with FEDR 400 mg/d in JAKARTA and JAKARTA2.
Methods: Both trials enrolled pts aged ≥18 years with INT- or high-risk MF, platelet counts ≥50 $\times 10^9$/L, and ECOG PS ≤2. In JAKARTA, pts were randomized 1:1:1 to receive 1L FEDR 400 mg/d, FEDR 500 mg/d, or PBO for ≥6 4-week cycles (randomized Tx period). At the end of 6 Tx cycles (or earlier in cases of disease progression [PD]), pts randomized to PBO could cross-over to FEDR. In JAKARTA2, all pts with MF resistant or intolerant to prior RUX (per investigator assessment) received FEDR 400 mg/d (starting dose). Pts in both trials could continue to receive FEDR until PD or unacceptable toxicity. These analyses include pts who received FEDR 400 mg/d in each study and pts in JAKARTA randomized to PBO.
PFS was the time from randomization to PD (IWG-MRT criteria) or death (in the absence of PD/death, PFS was censored at the date of the last valid assessment), and OS was the time from randomization to death. PFS/OS were estimated using Kaplan-Meier methods. Importantly, PFS/OS results for pts in the JAKARTA PBO arm include time after crossover to FEDR. Due to a clinical hold in Nov 2013 (later lifted), both trials were terminated early and survival follow-up stopped; ongoing pts were censored at the time of the clinical hold.
Results: In JAKARTA, 96 pts were randomized to FEDR 400 mg/d and 96 to PBO; 71 pts (74%) in the PBO arm crossed-over to FEDR on-study. At study termination, survival follow-up was halted for 74 (77%) and 65 (68%) pts randomized to FEDR 400 mg/d and PBO, respectively. PFS was significantly prolonged with FEDR *vs* PBO: median 23.2 *vs* 17.5 mo, respectively (HR 0.42 [95%CI 0.23, 0.76]; *P*=0.004), and 1-year PFS rates were 83% *vs* 67% (**Figure**). Median OS was not reached (NR) in either Tx arm (HR 0.57 [0.30, 1.10]; *P*=0.094); 1-year and 18-mo survival rates in the FEDR arm were 92% and 87%, respectively, and in the PBO arm were 86% and 80%.
JAKARTA2 enrolled 97 pts, and 79 (81%) were censored for survival at study termination. Median PFS was 13.3 mo (95%CI 8.4, 17.1) and 1-year PFS was 59%. Median OS was NR (95%CI 17.1, NR) (**Figure**), and 1-year and 18-mo survival rates were 84% and 67%, respectively.

Figure. Progression-free survival and overall survival in JAKARTA and JAKARTA2



Summary/Conclusion: FEDR significantly improved PFS *vs* PBO as 1L MF Tx. Separation of PFS/OS curves between FEDR and PBO in JAKARTA, despite FEDR Tx in the PBO arm after Tx crossover, suggests pts may derive greater benefit from early FEDR use. For pts in JAKARTA2 treated with FEDR after prior RUX, median PFS, median OS, and 1-year survival rate compare favorably with outcomes after RUX discontinuation from a recent analysis of similar pts with MF included in large healthcare databases (6.0 mo, 11.1 mo, and 47%, respectively) (Mascarenhas, 2020). These survival outcomes were greatly impacted by the FEDR clinical hold. The ongoing FREEDOM and FREEDOM2 trials will further assess survival with FEDR in pts with MF.

S204 JAKTINIB, A NOVAL JAK INHIBITOR IN TREATMENT OF PATIENTS WITH ADVANCED MYELOFIBROSIS: PRELIMINARY RESULTS FROM A PHASE 2 STUDY

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Background: Myelofibrosis (MF) is associated with splenomegaly, cytopenias, constitutional symptoms, and bone marrow fibrosis, with limited therapeutic options. Jaktinib, a novel, small-molecule inhibitor of JAK, is currently being studied in MF patients (pts). We present preliminary data from ZGJAK002, a Phase 2 open-label and multi-center study, evaluating two different regimens of Jaktinib in patients with MF.
Aims: To investigate the efficacy and safety of Jaktinib in MF pts.
Methods: Eligibility: MF pts included primary per WHO criteria (2016) or post-essential thrombocythemia / polycythemia vera MF according to IWG-MRT criteria; DIPSS-PLUS ≥int-2 (int-1 with symptomatic splenomegaly or hepatomegaly, require a treatment). By 1:1 ratio, 104 pts from 21 centers were randomized to Jaktinib 100mg BID or 200mg QD, administrated orally. The primary endpoint: the proportion of pts with spleen volume reduction from baseline ≥35% (SVR35) at week 24 (W24), assessed by Independent Review Committee based on MRI/CT images. Secondary endpoints: at W24 compared to baseline, the proportion of pts with ≥50% reduction on MPN-SAF TSS, improvements in RBC transfusion and hemoglobin (Hgb), etc.
Results: As of 30, Nov, 2020, 104 pts completed treatments of 24 weeks and planned visits. Baseline characteristics were generally balanced and shown in Table 1.
At W24, the SVR35 were 51.9% (27/52) in the 100mg BID and 30.8% (16/52) in the 200mg QD (*P*=0.0459), the median duration of response has not reached yet for the 100mg BID and 47.9 weeks for the 200mg QD. The proportion of pts achieved ≥50% improvement in TSS at W24 from baseline for BID and QD arms were 57.7% (30/52) and 53.8% (28/52), respectively. The mean percent of TSS change from baseline was -53.03 and -35.87, respectively. Approximately 1/3 (16/49) of combined pts had Hgb elevated ≥20g/L from baseline's ≤100g/L.
The most common Grade ≥3 hematological TEAEs were anemia (100mg BID 21.2%, 200mg QD 26.9%), thrombocytopenia (13.5%, 11.5%), and neutropenia (3.8%, 11.5%). Most common non-hematological TEAEs were upper respiratory tract infection (26.9%, 28.8%), elevated creatinine (21.3%, 30.8%) and elevated bilirubin (20.5%, 13.5%) predominantly grade 1 or 2. A total of 51 (49.0%) pts had ≥1 dose reduction/interruption, mostly due to thrombocytopenia (30.8%), anemia (22.1%), and neutropenia (8.7%).

Table 1. Demographics and baseline Characteristics.

Variable	100mg Bid (N=52)	200mg Qd (N=52)
Age (year) [median (Min-Max)]	60.0 (25-77)	62.0 (31-75)
Gender [Male/Female n (%)]	29(55.8)/23 (44.2)	31 (59.6)/21 (40.4)
Myelofibrosis subtype [n (%)]		
PMF	38 (73.1)	41 (78.8)
Post-PV MF	10 (19.2)	4 (7.7)
Post-ET MF	4 (7.7)	7 (13.5)
DIPSS-PLUS risk status [n (%)]		
High	1 (1.9)	0
Int-2	31 (59.6)	35 (67.3)
Int-1	20 (38.5)	17 (32.7)
Spleen volume [median (Min-Max)] cm^3	1588.37 (459.08 - 4349.87)	1457.9525 (589.16 - 5207.66)
JAK2 V617F-positive [n (%)]	39 (75.0)	32 (61.5)
Drug exposure duration (Months) [median (Min-Max)]	12.7 (0.5 - 22.8)	11.7 (1.3 - 20.4)

Summary/Conclusion: Jaktinib is generally well-tolerated and safe in MF pts. Reductions in spleen volume and constitutional symptom burden, and improvements in RBC transfusion dependency and Hgb levels were observed. The rate of spleen volume reduction was higher in the 100mg BID arm than the 200mg QD arm.

Hodgkin lymphoma - Clinical

S205 BRENTUXIMAB VEDOTIN WITH CHEMOTHERAPY FOR PATIENTS WITH PREVIOUSLY UNTREATED, STAGE III OR IV CLASSICAL HODGKIN LYMPHOMA: A 5-YEAR UPDATE OF THE PHASE 3 ECHELON-1 STUDY (NCT01712490)

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Background: Historically, nearly all relapses in classical Hodgkin lymphoma (cHL) occur within 5 years of treatment (Radford, BMJ 1997). In the phase 3 ECHELON-1 study (NCT01712490) in patients (pts) with newly-diagnosed Stage III/IV cHL, treatment with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) significantly improved modified progression-free survival (PFS) per independent review facility vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (Connors et al, NEJM 2018). After 3 and 4 years' follow-up, sustained PFS per investigator (INV) benefits were seen with A+AVD vs ABVD in the intent-to-treat (ITT) population as well as across most key pt subgroups (Bartlett, Blood 2019; Straus, Blood 2020). These improvements were irrespective of interim positron emission tomography (PET) scan status, disease stage, and baseline disease risk factor score.
Aims: We report updated efficacy and safety results after 5-years' follow-up of the ECHELON-1 study.
Methods: Pts with previously untreated Stage III/IV cHL were randomized to receive ≤6 cycles of intravenous A+AVD (n=664) or ABVD (n=670) on days 1 and 15 of a 28-day cycle. After cycle 2, pts had an interim PET scan (PET2). Analyses were performed after extended follow-up (cutoff date Sept' 18, 2020) to assess PFS per INV, peripheral neuropathy (PN) resolution and improvement (improvement ≥1 grade from worst grade as of the latest assessment) in pts with ongoing symptoms at end of treatment (EoT), rate of secondary malignancies, and incidence and outcomes of pregnancies among pts and their partners.
Results: At a median follow-up of 60.9 months (95% confidence interval [CI] 55.2–56.7), estimated 5-year PFS per INV rates were 82.2% (95% CI 79.0–85.0) for A+AVD and 75.3% (95% CI 71.7–78.5) for ABVD. A+AVD demonstrated favorable PFS per INV vs ABVD (hazard ratio [HR] 0.681; 95% CI 0.534–0.867; p=0.002) (Table). Estimated 5-year PFS with A+AVD vs ABVD in the ITT population was 84.9% vs 78.9% in PET2-negative pts (HR 0.663; 95% CI 0.502–0.876; p=0.004) and 60.6% vs 45.9% in PET2-positive pts (HR 0.702; 95% CI 0.393–1.255; p=0.229). In the A+AVD and ABVD arms, 85% and 86% of pts with treatment-emergent PN had complete resolution or improvement of symptoms, respectively. Median time to complete resolution of ongoing PN events at EoT was 34 weeks (range 0–262) in the A+AVD arm and 16 weeks (range 0–267) in the ABVD arm; median time to improvement was 49 weeks (range 8–270) and 12 weeks (range 2–70), respectively. Maximum severity of ongoing PN was grade 1 (17%), grade 2 (9%), grade 3 (3%), and grade 4 (<1%) in the A+AVD arm (total=29%), and grade 1 (14%), 2 (6%) or 3 (1%) in the ABVD arm (total=21%). Secondary malignancies occurred in 19 and 29 pts in A+AVD and ABVD arms, respectively. In total, 131 pregnancies were reported; both arms showed similar proportions of ongoing pregnancies or live births in female pts (87% and 75% in the A+AVD and ABVD arms, respectively).

Table: PFS per INV at 60.9 months by PET2 status and age in the ITT population

Group, % (95% CI)	A+AVD	ABVD	HR (95% CI) p-value
All pts	n=664	n=670	0.681 (0.543–0.867)
	82.2 (79.0–85.0)	75.3 (71.7–78.5)	0.002
PET2-negative	n=588	n=578	0.663 (0.502–0.876)
	84.9 (81.7–87.6)	78.9 (75.2–82.1)	0.004
PET2-positive	n=47	n=58	0.702 (0.393–1.255)
	60.6 (45.0–73.1)	45.9 (32.7–58.2)	0.229
Pts aged <60 years	n=580	n=568	0.665 (0.505–0.876)
	84.3 (81.0–87.1)	77.8 (74.0–81.1)	0.003
PET2-negative	n=521	n=493	0.675 (0.492–0.927)
	86.6 (83.3–89.3)	81.5 (77.7–84.7)	0.014
PET2-positive	n=42	n=50	0.702 (0.370–1.331)
	63.1 (46.4–75.9)	49.3 (34.7–62.3)	0.274
Pts aged ≥60 years	n=84	n=102	0.820 (0.494–1.362)
	67.1 (55.1–76.5)	61.6 (50.9–70.7)	0.443
PET2-negative	n=67	n=85	0.720 (0.401–1.292)
	71.9 (59.0–81.3)	64.9 (53.5–74.2)	0.268
PET2-positive	n=5	n=8	0.923 (0.229–3.715)
	40.0 (5.2–75.3)	25.0 (3.7–55.8)	0.910

Summary/Conclusion: After 60.9 months' median follow-up, robust and durable treatment benefits improvements that were independent of disease stage, risk factor score, and PET2 status were seen with A+AVD vs ABVD. Treatment adaptation by interim PET2 status was not required for A+AVD and bleomycin exposure was avoided. Treatment with A+AVD provides sustained PFS benefits and a manageable safety profile with symptoms of PN improving or resolving over time and similar pregnancy rates in both treatment arms, suggesting that A+AVD is an attractive treatment option for all pts with previously untreated Stage III or IV cHL.

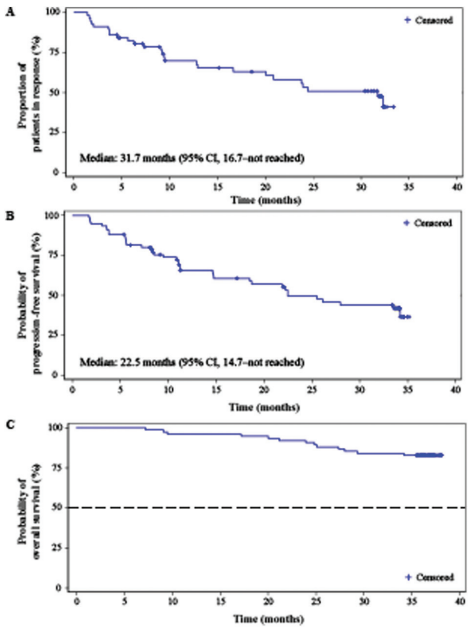
S206 CAMRELIZUMAB FOR RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: THREE-YEAR OUTCOME OF A MULTICENTER, PHASE 2 STUDY

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Background: Camrelizumab (a humanized high-affinity IgG4 mAb against PD-1) showed potent antitumor activity, well tolerance, and controllable safety in Chinese patients with relapsed or refractory classical Hodgkin lymphoma (r/r cHL), based on the primary analysis results of a multicenter, phase 2 study (ClinicalTrials.gov, NCT03155425). The long-term efficacy and safety of camrelizumab are warranted to be assessed.
Aims: To report the extended follow-up data regarding the durability of response, survival benefit, and long-term medication safety of camrelizumab in r/r cHL patients.
Methods: Between Jun 9, 2017 and Sep 18, 2017, 75 patients who had failed to achieve a remission or experienced progression after autologous stem cell transplantation or had received at least two lines of systemic chemotherapies were enrolled in this study. Camrelizumab at a dose of 200 mg were administrated every two weeks. The primary endpoint was objective response rate per independent review committee (IRC).
Results: As of Aug 31, 2020, the median follow-up duration was 36.2 months (range, 7.2–38.1). Per IRC assessment, objective responses were achieved in 57 patients (76.0%; 95% CI, 64.7–85.1), similar to result of the primary analysis. The Kaplan-Meier estimated median duration of response was 31.7 months (95% CI, 16.7–not reached; Figure A). At data cutoff, 50.7% of patients (38/75) had disease progression or died. The median progression-free survival was 22.5 months (95% CI, 14.7–not reached; Figure B). Thirteen (17.3%) deaths occurred, and the median overall survival was not reached (Figure C). The 36-month OS rate was 82.7% (95% CI, 72.0–89.5). The most common treatment-related adverse events (TRAEs) included reactive capillary endothelial proliferation (RCEP; 73/75, 97.3%), pyrexia (33/75, 44.0%), upper respiratory tract infection (27/75, 36.0%), and hypothyroidism (24/75, 32.0%). Despite a high incidence, all RCEP were grade 1 (59/73, 80.8%) or grade 2 (14/73, 19.2%) in severity. In general, RCEP occurred early during treatment; the median time to onset was 0.9 months (range, 0.1–2.5). Re-occurrence of RCEP was very rare (8 out of 42 patients who were still on camrelizumab therapy after 12 months, 19.0%; 2 out of 32 patients who were still on camrelizumab therapy after 24 months, 6.3%). Complete resolution of all RCEP lesions was observed in 49 of the 73 patients (67.1%), and the median time to regression was 8.2 months (range, 1.7–30.8). Grade 3 or 4 TRAEs were reported in 26 (34.7%) patients. No treatment-related deaths occurred. TRAEs led to treatment discontinuation only in 5 (6.7%) patients. No new safety signals were identified.



Summary/Conclusion: With extended follow-up, camrelizumab monotherapy continues to provide a robust and durable response, long progression-free and overall survival, as well as manageable safety in patients with r/r cHL.

S207 TISLELIZUMAB (BGB-A317) FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: LONG-TERM FOLLOW-UP EFFICACY AND SAFETY RESULTS FROM A PHASE 2 STUDY

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Background: Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity/specificity for programmed cell death protein 1 (PD-1). It was engineered to minimize binding to Fc-γ receptors on macrophages, thereby decreasing antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti–PD-1 therapy. Tislelizumab therapy was highly active in autologous stem cell transplantation (ASCT)-failed or ineligible patients with relapsed/refractory classical Hodgkin lymphoma (R/R cHL; *Leukemia*. 2020;34:533). Here, we report results from up to 3 years of follow-up.
Aims: To evaluate efficacy and safety of tislelizumab monotherapy in patients with R/R cHL in a single-arm, multicenter phase 2 study (ClinicalTrials.gov: NCT03209973).
Methods: Patients were eligible for the study if they failed to achieve a response or progressed after ASCT or received ≥2 lines of prior systemic chemotherapy for cHL and were ineligible for ASCT. Patients with R/R cHL enrolled in this study received 200 mg tislelizumab administered intravenously every 3 weeks until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee per Lugano criteria (*J Clin Oncol*. 2014;32:3059). Secondary endpoints were progression-free survival, duration of response, complete response (CR) rate, and time to response per independent review committee, safety, and tolerability.
Results: A total of 70 patients from 11 centers in China were enrolled and treated; patient characteristics have been previously reported. As of the data cutoff date (Nov 2, 2020), median follow-up was 33.8 months (range, 3.4-38.6). Patients still on treatment at the end of study (n=33; 47.1%) entered a long-term extension study. Efficacy data are presented in the Table. The ORR as assessed by IRC was 87.1%, and 67.1% of patients achieved CR. Among the 13 patients who received prior ASCT, 11 (84.6%) achieved CR. The most common treatment-emergent adverse events (AEs; ≥30%) were pyrexia (57.1%), upper respiratory tract infection (38.6%), hypothyroidism (37.1%), and increased weight (34.3%). Treatment-related grade ≥3 AEs (≥2 patients) were pneumonitis, hypertension, neutropenia, lipase increased, weight increased, and increased creatine phosphokinase (2.9% each). Immune-related AEs were reported in 32 patients (45.7%), with grade ≥3 AEs in 8 patients (11.4%): pneumonitis (n=4) and skin adverse reactions, nephritis, lipase increased, and blood creatine phosphokinase increased (n=1 each). AEs led to treatment discontinuation in 6 patients (8.6%).

Table

	N=70	95% CI
ORR, n (%)	61 (87.1)	77.0-93.9*
CR, n (%)	47 (67.1)	54.9-77.9*
mDOR†, mo	31.3	20.73-NE
mPFS†, mo	31.5	16.53-NE
mOS†, mo	Not reached	NE-NE
24-mo event free rate, %	93.9	84.5-97.7

CR, complete response; DOR, duration of response; m, median; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Two-sided Clopper-Pearson 95% CI. †Based on Kaplan-Meier estimation.

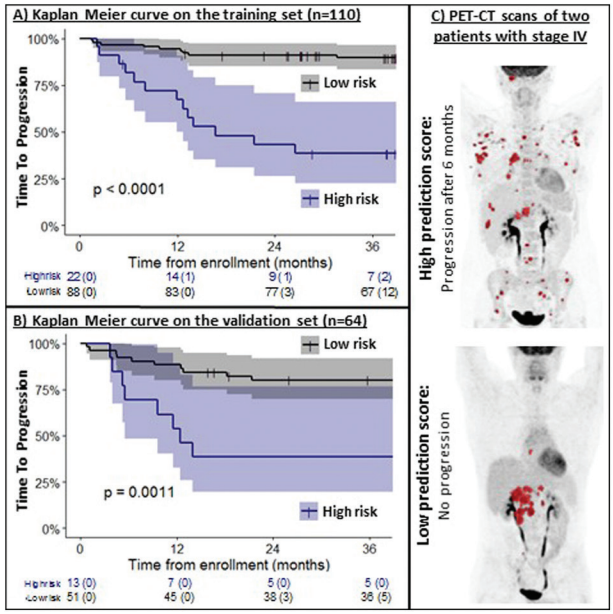
Summary/Conclusion: Long-term follow-up data from patients with R/R cHL treated with tislelizumab further demonstrated the substantial therapeutic activity and continued progression-free survival benefit. There were no new safety concerns identified for long-term treatment with tislelizumab.

S208 PREDICTIVE VALUE OF QUANTITATIVE 18F-FDG-PET RADIOMICS ANALYSIS IN 174 PATIENTS WITH RELAPSED/ REFRACTORY HODGKIN LYMPHOMA

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Background: About 20% of patients with classical Hodgkin lymphoma (cHL) relapse or are primary refractory to first-line treatment and require second-line therapy followed by autologous stem cell transplant. There is no one standard second-line therapy and it is possible that not all patients require such an aggressive approach to achieve cure. An individualized risk-stratified salvage treatment approach could lead to better disease control in high-risk patients and less toxicity in low-risk patients. Quantitative analysis of baseline ^{18}F-FDG-PET-CT scans could provide a comprehensible risk-assessment complementary to clinical risk-factors.
Aims: The aim of this study was to predict the 3-year time to progression (TTP) in relapsed/refractory (r/r) cHL patients using clinical and PET-CT parameters.
Methods: We analysed baseline ^{18}F-FDG-PET-CT scans from r/r cHL patients treated within three clinical trials with ICE, ICE and brentuximab vedotin (BV) or DHAP and BV. For the clinical risk model we used the following parameters: primary refractory *vs* relapse, age, Ann Arbor stage and B-symptoms. Metabolic tumor volume (MTV) was calculated using semi-automatic segmentation method with a fixed threshold of standard uptake value (SUV) ≥4.0. Radiomics features were extracted in compliance with the Image Biomarker Standardization Initiative. We developed a predictive model using logistic regression and backward selection on robust radiomics features, e.g. SUVpeak (highest 1mL region FDG uptake) and several novel dispersity features, representing dissemination and differences in volume and SUV of lesions within a patient. Patients who died without progression were censored at time of death. The model was trained on patients treated with BV + chemotherapy. Model performance was assessed by calculating the area under the curve (AUC) of the receiver operating characteristics curve and cross-validation (CV) of 5 folds with 2000 repeats. Results were validated in an independent cohort of patients treated with chemotherapy only. High-risk groups were defined based on the prevalence of events in the training cohort (22/110; 20%).
Results: We included 174 r/r cHL patients; n=110 in the training set (BV-DHAP and BV-ICE cohort) and n=64 in the validation set (ICE cohort). The clinical model resulted in an AUC of 0.81 on the training set (tAUC), CV-AUC of 0.76 and AUC of 0.74 on the validation set (vAUC). Radiomics analysis resulted in a selection of 6 PET features: MTV and 5 dispersity features. The radiomics model showed a tAUC of 0.73, CV-AUC of 0.63 and vAUC of 0.70. Combining clinical and radiomics parameters yielded a tAUC of 0.90, CV-AUC of 0.79 and vAUC of 0.77. In the training set, patients in the high-risk group (n=22) had a 3-year TTP of 38% *vs* 90% for patients in the low-risk group (n=88)(p<0.0001) (**Figure 1A**). In the validation set, patients in the high-risk group (n=13) had a 3-year TTP of 39% *vs* 80% for patients in the low risk group (n=51)(p=0.0011)(**Figure 1B**). In **Figure 1C** we included an example of PET-CT scans of two patients with stage IV disease and a high and low prediction score.



Summary/Conclusion: This is the first radiomics analysis in a large cohort of r/r cHL patients. Combining radiomics and clinical features results in a strong prediction model for 3-year TTP with a tAUC of 0.90, CV-AUC of 0.79 and a vAUC of 0.77 in an independent validation cohort. The model uses robust PET features that adress inter-lesional heterogeneity in distance, metabolic volume and SUV. Therefore, this model is suitable for application in clinical trials and could guide risk-stratified treatment in r/r cHL.

S209 BRENTUXIMAB VEDOTIN-CONTAINING ESCALATED BEACOPP VARIANTS FOR NEWLY DIAGNOSED ADVANCED CLASSICAL HODGKIN LYMPHOMA: FOLLOW-UP ANALYSIS OF A RANDOMIZED PHASE II STUDY FROM THE GERMAN HODGKIN STUDY GROUP

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Background: Patients with newly diagnosed advanced classical Hodgkin lymphoma (cHL) receiving intensive treatment with escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (eBEACOPP) have excellent outcomes. However, especially late sequelae represent an ongoing concern in connection with the eBEACOPP protocol. Recent eBEACOPP-based approaches therefore aim at reducing treatment toxicity without compromising efficacy. The BrECADD (brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, dexamethasone) and BrECAPP (brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, procarbazine, prednisone) protocols combining an eBEACOPP backbone with the CD30-directed antibody-drug conjugate brentuximab vedotin (BV) were evaluated in a randomized phase II study conducted by the German Hodgkin Study Group (GHSG). Results at a median observation time of 17 months were published previously. High response rates and reduced acute toxicity in comparison with standard eBEACOPP have been reported.
Aims: To investigate efficacy and safety of the BrECADD and BrECAPP protocols after extended follow-up.
Methods: Between October 2012 and May 2014, a total 104 patients (aged 18 to 60) who had the initial diagnosis of advanced cHL were included in the study. Study participants were randomly assigned to receive either BrECADD or BrECAPP. PFS and OS were estimated using the Kaplan-Meier method.
Results: After a median observation time of 34 months (IQR: 28.7-39.5), the 3-year PFS estimates for patients treated with BrECADD and BrECAPP were 89.7% (95%>CI: 81.0%>98.3%) and 90.2% (95%>CI:

80.9%>99.5%), respectively. Overall, 8 patients had primary disease progression or cHL recurrence (BrECADD: 4 patients; BrECAPP: 4 patients). The median time between the end of first-line treatment and disease progression or relapse was 13 months. Second-line treatment consisted of high-dose chemotherapy and autologous stem cell transplantation in all cases. There were 2 deaths of whom 1 was cHL-related. No second primary malignancies occurred. The 3-year OS estimates were 95.4% (95%>CI: 89.2%>100%) for patients who had received BrECADD and 100% for patients who had been treated with BrECAPP.
Summary/Conclusion: The present follow-up analysis of a randomized phase II study evaluating the BrECADD and BrECAPP protocols in newly diagnosed advanced cHL confirmed the high efficacy of these regimens. There were no new safety signals. The BrECADD protocol currently challenges standard eBEACOPP in the randomized GHSG phase III HD21 study.

Indolent & mantle cell lymphoma - Clinical

S210 EFFICACY AND SAFETY OF TISAGENLECLEUCEL IN ADULT PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: PRIMARY ANALYSIS OF THE PHASE 2 ELARA TRIAL

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Background: Most patients with relapsed/refractory follicular lymphoma (r/r FL) experience multiple relapses and progressively worse clinical outcomes with each line of therapy, underlining a need for novel therapies. Tisagenlecleucel has demonstrated durable responses and manageable safety in adult patients with r/r diffuse large B-cell lymphoma.
Aims: To report the primary analysis of ELARA (NCT03568461), an international, single-arm phase 2 trial of tisagenlecleucel in adult patients with r/r FL.
Methods: Eligible patients (≥18 years) had r/r FL (grades 1-3A) after ≥2 lines of therapy or had failed autologous stem cell transplant. Bridging therapy was permitted followed by disease assessment prior to tisagenlecleucel infusion. Patients received tisagenlecleucel (0.6-6×108 CAR+ viable T cells) after lymphodepleting chemotherapy. The primary endpoint was complete response rate (CRR) by central review per Lugano 2014 criteria. Secondary endpoints included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival, safety, and cellular kinetics. Predefined primary analysis occurred when ≥90 treated patients had ≥6 months of follow-up.
Results: As of September 28, 2020, 98 patients were enrolled and 97 received tisagenlecleucel (median follow-up, 10.6 months). At study entry, median age among treated patients was 57 years (range, 29-73), 85% had stage III-IV disease, 60% had a FLIPI score ≥3, 65% had bulky disease, and 42% had LDH greater than the upper limit of normal. The median number of prior therapies was 4 (range, 2-13); 78% of patients were refractory to their last treatment (76% to any ≥2 prior regimens) and 60% progressed within 2 years of initial anti-CD20-containing treatment. Of 94 patients evaluable for efficacy, the CRR was 66% (95% CI, 56-75) and the ORR was 86% (95% CI, 78-92). CRRs/ORRs were comparable among key high-risk subgroups. Estimated DOR (CR) and PFS rates at 6 month were 94% (95% CI, 82-98) and 76% (95% CI, 65-84), respectively. Of 97 patients evaluable for safety, 65% experienced grade ≥3 adverse events within 8 weeks post-infusion, most commonly neutropenia (28%) and anemia (13%). Any-grade cytokine release syndrome (per Lee scale) occurred in 49% of patients (grade ≥3, 0%). Any-grade neurological events (per CTCAE v4.03) occurred in 9% of patients (grade 3, 0%; grade 4, 1 patient and recovered). Three patients died from progressive disease.
Cellular kinetic parameters for tisagenlecleucel were estimated using transgene levels (by qPCR) in peripheral blood. Median maximal expansion (C_{max}) and exposure during the first 28 days following infusion ($AUC_{0\text{-}28d}$) were similar between responders (CR or partial response) and non-responders (stable or progressive disease). Maximum transgene levels were reached by a median of 10 days in responders and 12.9 days in non-responders; transgene persistence was detected up to 370 days and 187 days, respectively.
Summary/Conclusion: These data demonstrate the efficacy and acceptable safety of tisagenlecleucel in patients with r/r FL, including high-risk patients after multiple lines of prior therapy, and suggest that tisagenlecleucel may be a promising therapy for patients with r/r FL.

S211 CHRONOS-3: RANDOMIZED PHASE III STUDY OF COPANLISIB PLUS RITUXIMAB VS RITUXIMAB/PLACEBO IN RELAPSED INDOLENT NON-HODGKIN LYMPHOMA

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Background: Rituximab (R)-based therapies are standard for patients (pts) with relapsed advanced indolent non-Hodgkin lymphoma (iNHL). Copanlisib (C) is a PI3K inhibitor approved as monotherapy for relapsed follicular lymphoma (FL) in pts who have had ≥2 prior systemic therapies.
Aims: We report primary data from the Phase III CHRONOS-3 study of treatment with C+R *vs* placebo (P)+R in relapsed iNHL (NCT02367040).
Methods: Pts with relapsed iNHL who were progression-free and treatment-free for ≥12 months (mo) after last R-based therapy or unwilling/unfit to receive chemotherapy were randomized 2:1 to receive C+R or P+R. C 60 mg/P was given i.v. on days 1, 8, and 15 (28-day cycle); R 375 mg/m^2 was given i.v. on days 1, 8, 15, and 22 during cycle 1 and on day 1 of cycles 3, 5, 7, and 9. Primary endpoint: centrally assessed progression-free survival (PFS). Secondary endpoints: objective response rate (ORR), duration of response, complete response rate (CRR), overall

survival (OS), and treatment-emergent adverse events (TEAEs). The data cut-off date was August 31, 2020. All pts provided informed consent.
Results: 307 pts were randomized to C+R and 151 to P+R. FL was the most common lymphoma histology subtype (60.0%), followed by marginal zone (MZL, 20.7%), small lymphocytic (SLL, 10.9%), and lymphoplasmacytic/Waldenström macroglobulinemia (LPL/WM, 8.3%). Median age was 63 years (range 28-91). With a median follow-up of 19.2 mo, the primary study endpoint was met: C+R significantly reduced the risk of disease progression/death *vs* P+R (hazard ratio [HR] 0.52 [95% CI 0.39, 0.69]; 1-sided p=0.000002); median PFS was 21.5 mo (95% CI 17.8, 33.0) *vs* 13.8 mo (95% CI 10.2, 17.5), respectively. Reductions in risk of progression/death were seen across all histology subtypes (HR [95% CI]): FL 0.580 [0.404, 0.833]; MZL 0.475 [0.245, 0.923]; SLL 0.243 [0.111, 0.530]; LPL/WM 0.443 [0.160, 1.231]. ORRs were 80.8% (CRR 33.9%) for C+R and 47.7% (CRR 14.6%) for P+R. Higher ORRs and CRRs were seen across all iNHL subtypes with C+R treatment. Median OS was not estimable. Most common TEAEs (all grades [G]/G3+) in pts receiving C+R were hyperglycemia (69.4%/56.4%), hypertension (49.2%/39.7% [all G3]), and diarrhea (33.6%/4.9% [all G3]). For pts receiving P+R, hyperglycemia (23.3%/8.2% [all G3]), hypertension (19.2%/8.9% [all G3]), neutropenia (16.4%/12.3%), and upper respiratory tract infection (16.4%/0%) were the most common TEAEs. Serious adverse events were higher with C+R (47.2%) *vs* P+R (18.5%). G5 TEAEs occurred in 6 pts (2.0%) receiving C+R (1 [0.3%] deemed treatment-related; pneumonitis) and 1 (0.7%) receiving P+R.
Summary/Conclusion: C+R demonstrated broad and superior efficacy *vs* P+R in pts with relapsed iNHL. The safety profile of C+R was manageable and consistent with C and R as monotherapy. Copanlisib is the first PI3K inhibitor to be safely combined with R in relapsed iNHL, representing a potential new therapy option for relapsed iNHL across all subtypes.

S212 ATEZOLIZUMAB + OBINUTUZUMAB + VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT NON-HODGKIN'S LYMPHOMA (R/R INHL): PRIMARY ANALYSIS OF A PHASE 2 TRIAL FROM LYSA.

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Background: Relapsed and refractory (R/R) iNHL treatment remains challenging. Atezolizumab (ATE) and obinutuzumab (OBI) are monoclonal antibodies acting respectively to inhibit T-lymphocyte exhaustion or by inducing lymphoma cells cytotoxicity, whereas venetoclax (VEN) is a small molecule inhibiting BCL-2. Combining tumor-targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm. This LYSA sponsored multicenter phase 2 trial (NCT03276468) evaluated ATE, OBI and VEN combination in R/R B-cell lymphomas. Herein, we present primary efficacy and safety data from the iNHL cohort including Follicular Lymphoma (FL) and Marginal Zone Lymphomas (MZL).
Aims: Evaluate the safety and efficacy of atezolizumab, obinutuzumab and venetoclax combination in R/R FL and MZL.
Methods: Patients ≥18 years with biopsy-confirmed R/R FL and MZL who failed at least one line of therapy were eligible. OBI was given IV at 1 g on day (D) 1, 8 and 15 of cycle (C) 1 and on D1 from C2 to C8 every 3 weeks. ATE was given IV, 1.2 g every 3 weeks, started at D2 of C1, then administered at D2 of each cycle for 24 cycles. VEN was given orally at 800 mg/D at full dose, starting on D8C1 for 24 cycles. The primary endpoint was the Overall Response Rate (ORR) evaluated by Lugano criteria at the end of induction (EOI) after 8 cycles of ATE, OBI and VEN (M6) or at premature treatment discontinuation.
Results: At the time of the primary analysis (08 Jan 2021), 78 patients were enrolled. *FL cohort* (n=58): the median follow-up was 14.5 months. Main baseline characteristics were: Ann Arbor Stage III/IV, 85.7%; FLIPI HR, 47.3%; > 2 prior lines of therapy, 32.1%; and exposed to ASCT, 30.4%. The ORR on PET scan at EOI was measured at 53.6% [41.8%>65.1%], including 30.4% of CMR. 37 patients (63%) received the full induction treatment. *MZL cohort* (n=20; 13 nMZL, 5 eMZL, 2 sMZL): the median follow-up was 11.9 months. Main baseline characteristics were: Ann Arbor Stage IV, 100%; bone marrow infiltration, 38.9%; ≥ 2 extra-nodal sites, 50%; and > 2 prior lines of therapy, 22.2%. The ORR on CT scan at EOI was measured at 66.76% [44.6%>84.4%], including 16.7% of CR and 50.0% PR. 11 patients (55%) received the full induction treatment. At time of the present analysis, responses in the 2 cohorts seem durable with only 21,4% of responders who have reported relapse/progression. Out of the 78 pts, a total of 55 (70.5%) pts experienced grade 3–4 adverse event (AE) and 1 patient experienced an AE that led to discontinuation of any drug. Main AE of grade 3 or more were hematologic cytopenias, with only one febrile neutropenia (1.3%). Three pts experienced immune-related AE (1 grade 2 myositis and 2 grade 3 colitis), no tumor lysis syndrome was observed.
Summary/Conclusion: ATE, OBI and VEN triplet appears to be well tolerated, with no unexpected toxicity brought by the combination. The ORR at EOI seems to be comparable to other innovative regiments in this setting, with durable responses to date.

S213 OUTCOMES IN ZUMA-5 WITH AXICABTAGENE CILOLEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA WHO HAD THE HIGH-RISK FEATURE OF EARLY PROGRESSION AFTER FIRST CHEMOIMMUNOTHERAPY

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Background: Progression within 24 months from initiation of the first anti-CD20–containing chemoimmunotherapy (POD24) is an indicator of poor survival in indolent non-Hodgkin lymphoma (iNHL; Casulo & Barr. *Blood*. 2019). In the ZUMA-5 Phase 2 study of axicabtagene ciloleucel (axi-cel) anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed/refractory (R/R) iNHL, overall response rates (ORR) after a median of 17.5 months of follow-up were similarly high in those with and without POD24 (93% and 92%; Jacobson et al. ASH 2020. #700).
Aims: To report updated outcomes with longer follow-up of axi-cel in patients in ZUMA-5 with R/R iNHL who had POD24.
Methods: Adults with R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL) after ≥2 lines of therapy underwent leukapheresis followed by conditioning therapy and axi-cel infusion (2×10^6 CAR T cells/kg). Axi-cel–treated patients with available data on progression after an anti-CD20 monoclonal antibody + alkylating agent were included. The updated efficacy analysis occurred when ≥80 treated patients with FL had at least 18 months of follow-up.
Results: Of 129 patients at baseline, 81 patients (63%; 68 FL, 13 MZL) had POD24, and 48 patients (37%; 40 FL, 8 MZL) did not have POD24. Median prior lines of therapy in patients with and without POD24 were 3 and 3.5, respectively. High-risk characteristics of patients with and without POD24 included stage III/IV disease, 83% and 94%; ≥3 FLIPI, 44% and 43%; high tumor bulk (per GELF criteria), 51% and 44%; and refractory disease, 77% and 63%, respectively.
With a 23.3-month median follow-up, the ORR among efficacy-evaluable patients with POD24 (n=61) and without POD24 (n=37) was 92% each

(complete response rates, 75% and 86%). At data cutoff, 52% of patients with POD24 and 70% without POD24 had ongoing responses. Median duration of response, progression-free survival, and overall survival were not reached in patients with and without POD24; 18-month estimated rates were 60% and 78%, 55% and 84%, and 85% and 94%, respectively. Incidences of Grade ≥3 adverse events were similar in patients with and without POD24 (84% and 88%), including cytopenias (69% and 65%) and infections (15% and 21%). Grade ≥3 cytokine release syndrome (CRS) occurred in 9% and 2% of patients with and without POD24, respectively; Grade ≥3 neurologic events occurred in 17% of patients each. Median times to onset were similar in patients with and without POD24 for CRS (4 days each) and neurologic events (8 days and 7 days); median durations of CRS (7 days and 5 days) and neurologic events (11 days and 13 days) were also similar between groups.
In efficacy-evaluable patients with FL, median peak CAR T-cell levels were similar in patients with and without POD24 (35.8 cells/μL and 34.5 cells/μL). Peak levels of key inflammatory biomarkers and axi-cel product attributes were generally similar in patients with and without POD24.
Summary/Conclusion: Axi-cel showed a high rate of durable responses in patients with POD24 iNHL, a population with high-risk disease. Efficacy results, as well as safety and pharmacological profiles, appeared largely comparable between groups, with the exception of progression-free survival rates.

S214 TOLERABILITY AND EFFICACY OF THE COMBINATION OF PI3KΔ INHIBITOR ZANDELISIB (ME-401) AND BTK INHIBITOR ZANUBRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) B-CELL MALIGNANCIES: INITIAL RESULTS

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Background: Despite significant improvement in the management of B cell malignancies with targeted therapies, new therapies are still needed in patients with relapsed disease. Dual inhibition of PI3Kδ and BTK pathways may overcome existing or acquired monotherapy resistance. Dual inhibition of these pathways displays synergistic activity in cell lines that is evident even at suboptimal concentrations [Blood 2015;125(14):2306-09]. Zandelisib is a potent, selective, and structurally differentiated oral PI3Kδ inhibitor (i), and zanubrutinib is an oral BTKi. Based on their efficacy as monotherapy, we hypothesized that the combination of zandelisib and zanubrutinib can be well tolerated and may improve the depth and durability of responses.
Aims: We evaluated this combination therapy in pts with R/R B-cell malignancies to determine the optimal dose and schedule for further evaluation in disease-specific expansion cohorts (NCT02914938).
Methods: This is a multi-cohort Phase 1b study enrolling patients (pts) with FL, CLL, MZL, MCL, DLBCL, or high-grade B-cell lymphoma (HGBCL), ≥1 prior therapy, adequate bone marrow and organ function, ECOG performance status ≤2, and no prior PI3Ki or BTKi therapy. For this combination therapy, two dose levels were evaluated in 28-day cycles: Cohort A: zandelisib 60 mg once daily for 2 cycles followed by an intermittent schedule (IS) on days 1-7 of subsequent 28-day cycles and zanubrutinib 160 mg twice daily (bid). Cohort B: zandelisib 60 mg on days 1-7 starting in Cycle 1 and zanubrutinib at 80 mg bid. Dose limiting toxicity (DLT) observation period was 28 days for cohort A and extended to 56 days for cohort B to include later occurring toxicities in the DLT definition. Response was assessed per iwCLL or Lugano criteria at month 3, 7, 13 and then every 6 months until progression.
Results: 20 pts who provided consent and met eligibility criteria were treated, 7 in cohort A and 13 in cohort B: 8 FL, 5 CLL, 2 DLBCL, 2 HGBCL, 2 MZL, and 1 MCL. Median age 70 years (range, 44-85) and median prior therapies 2 (1-8). Median follow-up of 2.9 months (0.5-17.4+). There were no DLT in cohort 10A, grade (Gr) ≥3 adverse events (AE) occurred after day 28 in 4 pts, including Gr 4 neutropenia (1 pt), Gr 3 neutropenia, fatigue and CMV colitis (1 pt), Gr 3 AST/ALT and rash (1 pt) and Gr 3 AST/ALT (1 pt). The emergence of Grade 3/4 AE's in 4/7 patients after the DLT window prompted exploration of a lower dose in cohort B. In cohort B, 2 pts had DLT with Gr 3 AST/ALT in Cycle 2, with 1 pt successfully resuming both drugs and 1 discontinued treatment due to recurrence of Gr 3 AST/ALT upon rechallenge. Other Gr 3 AE were all laboratory findings: 1 pt (CLL) had laboratory TLS, neutropenia and thrombocytopenia and 2 pts (FL, DLBCL) had neutropenia. 15% DLT(2/13) was observed in cohort B which is deemed safe to proceed with disease expansion cohort. Response rate was 100% (2 CR 14 PR) in the following 16 pts with indolent NHL and MCL evaluable for response: FL (2 CR, 6 PR), CLL (5 PR), MCL (1 PR) and MZL (2 PR). None of the 3 evaluable pts with aggressive B-cell lymphomas has responded.
Summary/Conclusion: The combination of zandelisib 60 mg on IS from Cycle 1 and zanubrutinib 80 mg bid is well tolerated and achieves a high ORR in R/R indolent B-cell malignancies. This schedule is being evaluated in expansion cohorts in R/R FL and MCL

Aggressive lymphoma - CAR-T & transplant

S215 HIGH INCIDENCE OF PROLONGED COVID-19 AMONG PATIENTS WITH LYMPHOMA TREATED WITH B-CELL DEPLETING IMMUNOTHERAPY

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Background: Treatment of B-lineage lymphoma with B-cell depleting immunotherapy causes B-cell aplasia and impairs immune response. Case studies have reported patients treated with anti-CD20 therapy who suffered from persistent Covid-19.
Aims: We aimed to assess the incidence, risk factors and long-term outcomes of persistent Covid-19 in patients with lymphoma.
Methods: This retrospective multicentric study was conducted in 16 French hospitals. All adult patients with lymphoma who were admitted for Covid-19 in March and April 2020 were included. Persistent Covid-19 was defined as persisting severe Covid-19 symptoms requiring in-hospital stay for >30 days. Patients who re-experienced severe Covid-19 symptoms after initial improvement, requiring repeated hospitalizations for a total in-hospital length of stay >30 days were added to the persistent Covid-19 cases.
Results: One hundred eleven patients were included. Thirty days after admission for Covid-19, 24 patients had died, 55 had been definitively discharged from hospital, 31 were still hospitalized and 1 was later rehospitalized for Covid-19 recurrence. The incidence of persistent Covid-19 was 32/111 (29%). Patients with persistent Covid-19 had a median age of 64 years (range, 43-87) and 63% were male. Twenty-two patients (69%) had at least one significant comorbidity. None of the patients with T-cell (n=8) lymphoma or classical Hodgkin's disease (n=8) experienced persistent Covid-19. In the 32 patients with persistent Covid-19, the median time between first admission and final discharge was 58 days (range, 31-235) and the median duration of Covid-19 symptoms was 83 days (range, 32-237). Eight patients received corticosteroids and 9 convalescent plasma: all patients recovered from their symptoms, except one. Overall, 9 patients with persistent Covid-19 died (27%).
After a median follow-up of 191 days (range, 3-260), the 6-month overall survival was 69% (95% CI 60-78%) for the whole cohort. In multivariate analysis, administration of anti-CD20 monoclonal antibody within 12 months before admission to hospital for Covid-19 was both associated with decreased overall survival (HR 2.13, 95% CI 1.03-4.44, p = 0.043) and prolonged in-hospital stay (HR 1.97, 95% CI 1.24-3.13, p = 0.004). The two other significant factors associated with decreased overall survival and prolonged in-hospital stay: age ≥ 70 years and refractory or relapsed lymphoma.
Summary/Conclusion: Patients with B-cell non-Hodgkin lymphoma hospitalized for Covid-19 have a high incidence of prolonged evolution of SARS-CoV-2 infection. Administration of anti-CD20 therapy within the last 12 months is one of the main risk factors for longer in-hospital stay and death of Covid-19.

The risk of persistent Covid-19 was also higher in patients older than 70 years or with refractory or relapsed disease. These findings may contribute to guide the management of lymphoma patients during the Covid-19 pandemic.

S216 FIRST RESULTS OF DLBCL PATIENTS TREATED WITH CAR-T CELLS AND ENROLLED IN DESCAR-T REGISTRY, A FRENCH REAL-LIFE DATABASE FOR CAR-T CELLS IN HEMATOLOGIC MALIGNANCIES.

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Background: DESCAR-T is the French national registry for patients treated with commercial CAR-T cells (DLBCL and ALL). DESCAR-T has been designed by LYSA/LYSARC and aims to collect real-life data. DESCAR-T was approved by the French authorities in 2019 and is the reference registry for CAR-T cells reimbursement by French health authorities. Data (patients' characteristics, safety, efficacy and long-term outcome…) from time of medical decision to treat with CAR-T cells to up to 15 years after CAR-T cells infusion are registered in DESCAR-T. Several complementary registries are also linked to DESCAR-T database, such as an immune-monitoring database, a blood and tumor biobanking (so-called CeVi-CART) and an imagery platform.
Aims: Herein, we present the first analyses regarding patients' characteristics and outcome of DLBCL patients registered in DESCAR-T.
Methods: All patients with DLBCL registered in DESCAR-T were eligible for the present study. All patients gave informent consent befor DESCAR-T registration.
Results: To date (Jan 2021), 14 out of 24 CAR-T cells accredited French centers have registered patients in DESCAR-T. Seven additional centers will be open for DESCAR-T in the coming months. The first patient was registered in December 2019. At the time of the present analysis, 537 DLBCL patients have been registered. CAR-T cells product has been ordered for 517 patients of whom 463 have been infused with CAR-T cells. At the time of registration in DESCAR-T, median age was 63.0 years (range, 53-70), 40.6% of patients were older than 65 years and 3.5% older than 75 years. Lymphoma subtypes were DLBCL (91%), PMBL (3%), and high-grade B-cell lymphoma (2%). Among patients for whom CAR-T cells have been ordered (n=517), 313 (60.5%) were male, 76 (14.7%) had a PS≥2, 377 (72.9%) had an advanced disease (stage III or IV), and 330 (63.8%) had elevated LDH. Median number of prior lines of treatment was 3 (range, 2 – 3) and 21% of patients have been previously transplanted. Median time from CAR-T cells order to infusion was 50 days [range, 43-60]. Median time from leukapheresis to CAR-T infusion was 41.1 days (range, 36-48). Overall, 65% of patients received Axi-cel and 35% received Tisa-acel. Response was available in 419 infused patients. Best ORR was 70.2% (65.5% - 74.5%). At D30 after CAR-T cell infusion, 157 (38%) patients achieved CR and 112 (27%) achieved PR. Among the 157 patients who achieved a CR at D30, 96 (61%) remained in CR at D90. The median follow-up calculated from CAR-T cells order was 7.4 months (range, 5.8-7.9) and 6m [range, 5.5-6.2] from CAR-T infusion. The median OS calculated from time of CAR-T infusion is 12.7m [range, 10.6-NA].
Summary/Conclusion: This first analysis from DESCAR-T registry seems to confirm CAR-T cells efficacy in real life. And be in line with previously published data. Updated results will be presented at the meeting. Overall, 537 patients with relapsed DLBCL have already been registered in DESCAR-T in 13 months and about 50 new patients are registered each month. This demontrates that CAR-T cells therapy has become a key treatment for R/R DLBCL. In 2021, DESCAR-T will be extended to mantle cell lymphoma and multiple myeloma and treated with CAR-T cells. DESCAR-T is a new CAR-T registry to investigate CAR-T cells products in real life across all hematological malignancies.

S217 GENETIC LANDSCAPES AND CURATIVE EFFECT OF CAR T CELLS IMMUNOTHERAPY IN RELAPSE AND REFRACTORY DLBCLS

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma. Although potentially curable with targeted drug, monoclonal antibody, immunochemotherapy, refractory or relapsed lymphoma occurs in 40% of patients.
Aims: We investigated whether molecular subtypes can be robustly identified using methods potentially applicable in routine clinical practice, providing evidence that curative effect of CAR T cells immunotherapy differs in diverse subtype.
Methods: We have studied 105 relapse and refractory DLBCL (R&R DLBCL) patients using target region sequencing. clustering technique was applied to targeted region sequencing data derived from 105 R&R DLBCL patients cohort with full clinical follow-up(n=94).
Results: A total of 745 potential driver mutations were identified in 199 out of the 339 genes with a similar number in GCB and non-GCB. The most frequently mutated genes were TP53, KMT2D, PIM1, MYD88, CREBBP, CD79B and B2M found in more than 15% of cases. The frequency of TP53 in our R&R DLBCL cohort were higher than initial patients as reported. MYD88 CD79B, TNFAIP3, PRDM1 and SPEN were significantly more frequently mutated in more than 10% of non-GCB-DLBCL patients whereas KMT2D, CREBBP, DDX3X, B2M, TNFRSF14, BCL2, EZH2, CARD11, SOCS1, MYC and KRAS mutations were more common in more than 10% of GCB-DLBCL. PIM1, PCLO, TET2, STK11, TBL1XR1, NUDT15, CCND3 and TP53 in the gene were equally distributed in both DLBCL subtypes. Using clustering techniques applied to targeted region sequencing data derived from 105 R&R DLBCL patients cohort with full clinical follow-up (n=94), we investigated whether molecular subtypes can be robustly identified using methods potentially applicable in routine clinical practice. Six molecular subtypes were resolved, termed A53, MCD, BN2, KCB, N1, and JAK/STAT, along with an unclassified group. The subtypes of BN2 and N1 showed good prognosis, whereas MCD, KCB and JAK/STAT had intermediate outcomes. The subtypes characterized by genetic alterations of TP53 acquired the worst survival, as well demonstrated that TP53 mutations were independent predictors of survival in R&R DLBCL patients. The KCB subtype contained the majority of cases of transformed follicular lymphoma and strongly enriched for cases of double-hit GCB-type DLBCL, with inferior outcomes. Most patients (n=80, 76.2%) in our cohort received chimeric antigen receptor (CAR) T cells immunotherapy. These subtypes differed phenotypically, as judged by differences in gene-expression signatures and responses to immunochemotherapy, with favorable frequency of complete reponse (CR) in the BN2 and N1 subtypes, intermediate in MCD, KCB, and JAK/STAT subtypes, inferior outcomes in the A53 subtypes. We suggested that N1 subtype showed good prognosis due to their sensitive curative effect with CAR T cells immunotherapy.
Summary/Conclusion: Our findings confirm the existence of molecular subtypes of R&R DLBCL, providing evidence that curative effect of CAR T cells immunotherapy differs in diverse subtype. CAR T cells immunotherapy can prolong survival times of in some subtyes thought previously associated with worse outcomes. We provide a potential precision-medicine strategies for R&R DLBCL patients with poor prognosis.
Key words: relapse and refractory DLBCL, gene mutation, molecular subtypes, CAR T cells immunotherapy

S218 FIRST-IN-HUMAN STUDY OF THE EZH1 AND EZH2 DUAL INHIBITOR VALEMETOSTAT TOSYLATE (DS-3201B) IN PATIENTS WITH RELAPSED OR REFRACTORY NON-HODGKIN LYMPHOMAS

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Background: Enhancer of zeste homolog 2 (EZH2) and its close homolog, EZH1, catalyze the attachment of 3 methyl groups to histone H3 at lysine 27 (H3K27me3). H3K27me3 is an epigenetic mark involved in downregulating gene expression associated with tumor suppression and cell differentiation. Altered *EZH2* expression has been implicated in the development and progression of non-Hodgkin lymphomas (NHLs), including peripheral T-cell lymphoma (PTCL), adult T-cell leukemia/lymphoma (ATL), and other cancers. Valemetostat tosylate (DS-3201b; also known as valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 that has demonstrated antitumor activity against hematologic malignancies (Maruyama et al, *Blood*. 2017 [abstract 4070]). We report the interim results from the first-in-human trial of valemetostat in patients with relapsed or refractory (R/R) NHLs, focusing on preliminary efficacy results for R/R PTCL and R/R ATL.
Aims: This ongoing multicenter, phase 1, multiple ascending dose study (NCT02732275) evaluates the safety, pharmacokinetics, and pharmacodynamics of single-agent valemetostat for R/R NHLs. Primary objectives include assessing safety and determining the recommended phase 2 dose; secondary objectives include assessing preliminary efficacy.
Methods: Patients ≥18 (United States) or ≥20 years of age (Japan) with R/R NHL have been enrolled. Valemetostat (150-300 mg/day for the dose-escalation cohort; 200 mg/day for the dose-expansion cohort) is orally administered once daily in continuous 28-day cycles until disease progression or intolerance. The enrollment for the dose-expansion cohort is limited to patients with R/R PTCL or R/R ATL.
Results: At the time of data cutoff (November 2, 2020), 78 patients with R/R NHL were treated with 150-300 mg of valemetostat, including 62 patients who were treated with 200 mg. The median age was 68 (range, 37-88) years. With a median follow-up of 28.1 weeks (range, 3.1-190.9), 22 of 78 patients (28.2%) remained on treatment. Safety results from 78 patients with R/R NHL are reported; 76 patients (97.4%) experienced ≥1 treatment-emergent adverse event (TEAE). Grade ≥3 TEAEs occurred in 51 patients (65.4%), and serious TEAEs (SAEs) grade ≥3 occurred in 16 patients (20.5%); no deaths have been associated with valemetostat. Dose interruption or reduction due to TEAEs occurred in 32 (41%) and 7 (9%) patients, respectively. The most common AEs (≥30% of patients) were platelet count decreased (59.0%), dysgeusia (51.3%), anemia (37.2%), neutrophil count decreased (34.6%), alopecia (32.1%), and white blood cell count decreased (30.8%). Grade ≥3 platelet count decreased and thrombocytopenia occurred in 12 (15.4%) and 4 (5.1%) patients, respectively. Safety outcomes in R/R PTCL and R/R ATL subgroups were similar to those in the overall population. Preliminary efficacy data from 45 patients with R/R PTCL and 14 with R/R ATL are summarized in the Table. Valemetostat resulted in a ≥50% overall response rate (ORR), with potentially durable responses in R/R PTCL and R/R ATL. Efficacy was observed across PTCL subtypes.

Table

Parameter	All PTCL[a] (n=45)	PTCL Subtype				ATL[a,b] (n=14)
		AITL (n=17)	PTCL-NOS (n=21)	ALCL[b] (n=2)	Other TCL (n=5)	
Prior lines of therapy, median (range)	3.0 (1-9)	NA	NA	NA	NA	2.5 (1-8)
Best response, n (%)						
CR	11 (24.4)	7 (41.2)	4 (19.0)	0 (0.0)	0 (0.0)	3 (21.4)
PR	14 (31.1)	5 (29.4)	6 (28.6)	1 (50.0)	2 (40)	4 (28.6)
SD	5 (11.1)	2 (11.8)	3 (14.3)	0 (0.0)	0 (0.0)	2 (14.3)
PD	6 (13.3)	1 (5.9)	4 (19.0)	1 (50.0)	0 (0.0)	3 (21.4)
NE	1 (2.2)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
ORR, n (%) 95% CI	25 (55.6) 40.0-70.4	12 (70.6) 44.0-89.7	10 (47.6) 25.7-70.2	1 (50.0) 1.3-98.7	2 (40.0) 5.3-85.3	7 (50.0) 23.0-77.0
Median DOR, weeks (95% CI)	56.0 (44.43-NE)	44.43 (5.86-NE)	56.0 (8.14-56.0)	NE	NE (8.14-NE)	NE (6.14-NE)
Median TTR, weeks (range)	8.14 (4.1-24.1)	8.14 (4.1-16.3)	7.93 (7.0-24.1)	16.14 (16.1-16.1)	7.64 (7.4-7.9)	8.14 (7.3-84.1)
Median PFS, weeks (95% CI)	52 (16.14-NE)	NA	NA	NA	NA	NE (8.14-NE)

[a] For PTCL, 43 patients were treated with valemetostat 200 mg, and 2 were treated with 150 mg. For ATL, 12 patients were treated with valemetostat 200 mg, and 2 were treated with 150 mg.
[b] Patients with ALCL include those with ALK-positive and ALK-negative ALCL.
[c] Consists of 7 patients with acute and 7 patients with lymphomatous subtypes.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATL, adult T-cell leukemia/lymphoma; CR, complete response; DOR, duration of response; NA, not analyzed; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL not otherwise specified; SD, stable disease; TTR, time to first response.

Summary/Conclusion: These results demonstrate that valemetostat has an acceptable safety profile in patients with R/R NHLs and encouraging efficacy results in patients with R/R PTCL or R/R ATL and warrants further evaluation. Valemetostat is being evaluated in an ongoing phase 2 study in Japan in patients with R/R ATL (NCT04102150) and in a global phase 2 study in patients with R/R PTCL, including R/R ATL (NCT04703192).

S219 MATRIX FOLLOWED BY AUTOLOGOUS TRANSPLANT IS ASSOCIATED WITH EXCELLENT SURVIVAL AND NEUROTOLERABILITY IN PRIMARY CNS LYMPHOMA: RESULTS OF THE IELSG32 TRIAL AT A MEDIAN FOLLOW-UP OF 88 MONTHS

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Background: The IELSG32 trial has shown the significantly better activity and acceptable safety profile of MATRIX regimen and a similar efficacy of consolidation with whole-brain irradiation (WBRT) or autologous transplantation (ASCT) in pts ≤70 yo with primary CNS lymphoma (PCNSL). However, events after a more extended follow-up remain to be addressed.
Aims: To establish the associations among different treatment arms of the IELSG32 trial and OS, late toxicity, incidence of secondary tumors, and cognitive impairment at a median follow-up of 88 (IQR 77-99) months.
Methods: HIV-neg pts 18-70 yo with ECOG PS ≤3 (PS ≤2 if 66-70 yo) with untreated PCNSL were randomly assigned to receive 4 courses of methotrexate-cytarabine (arm A), or arm A plus rituximab (arm B), or arm B plus thiotepa (arm C; MATRIX). Pts with responsive/stable disease were further randomized between WBRT (arm D) and BCNU-thiotepa/ASCT (arm E). Primary endpoints were CRR (1st random) and PFS (2nd random). Effects of treatment on cognitive functions and quality of life (QoL) were addressed comparing results of the IPCG tests panel

and EORTC-QLQ performed immediately after treatment and at the last follow-up visit.
Results: 219 assessable pts (median age 58; range 18-70) were randomized (arm A 75; B 69; C 75). After induction, 167 (76%) pts had responsive or stable disease; 118 (71%) of them were further randomized (arm D 59; E 59), whereas 49 pts were excluded (poor mobilizers, poor conditions, patients' refusal).
15 (7%) pts died of toxicity during treatment. 87 (40%) pts remain relapse-free (A 17; B 28; C 42); 14 of them died of infections (n=4), sudden death (4), cognitive decline (3), second tumor (2), and car accident (1). 117 (53%) pts experienced relapse: 96 died of lymphoma, 14 achieved tumor remission upon salvage therapy and remained relapse-free at 39-121 months, while 7 died of complications during salvage therapy. Second cancers were diagnosed in 8 (4%) pts after 48-96 months from WBRT (5) or ASCT (3); two of them were lethal, the other six remained relapse-free after surgical resection. Deaths in relapse-free pts, deaths occurred during salvage treatment and secondary tumors were not significantly related to induction or consolidation treatments (Table). Neuropsychological tests showed a statistically significant impairment in some attentive and executive functions in pts treated with WBRT, while a significant improvement was noted in these functions as well as in memory and QoL in transplanted pts.
Pts treated with MATRIX (arm C) showed a significantly better PFS, with a 7-yr PFS of 20±5% for arm A, 29±6% for arm B and 52±6% for arm C (A vs C p=0.00002; B vs C p=0.01). PFS was similar in both consolidation arms (7-yr: 55±7% and 50±7%; p=0.35). 87 pts are alive (arm A 18; B 27; C 42), with a 7-yr OS of 26±5%, 37±6% and 56±6%, respectively (A vs C p=0.00007; B vs C p=0.03). OS was similar in both consolidation arms (7-yr: 63±6% and 57±6%, p=0.17). Pts treated with MATRIX and consolidation had a 7-yr OS of 70±6%, without a difference between WBRT and ASCT. In multivariable analysis, IELSG score, number of lesions and induction arm were associated with OS; gender, CSF cytology and consolidation were not.

Table. Second tumors and late complications in pts who completed the planned treatment

	Arm A (42)	Arm B (50)	Arm C (63)	WBRT (70)*	ASCT (60)*
Second tumors (n=8)#	1 (2%)	2 (4%)	5 (8%)	5 (7%)	3 (5%)
Deaths in relapse-free patients (n= 14)	2 (5%)	6 (12%)	6 (9%)	9 (13%)	3 (5%)
Deaths during salvage treatment (n=7)	4 (9%)	0 (0%)	3 (5%)	2 (3%)	2 (3%)

*Actually delivered consolidation within and outside 2nd randomization.
#Acute erythroid leukemia, high-grade glioma, melanoma (2), Paget's disease of the breast, prostate cancer, colon cancer, basal cell carcinoma.

Summary/Conclusion: MATRIX regimen was associated with excellent long-lasting survival in PCNSL pts ≤70 ys. WBRT and ASCT exhibit similar efficacy. In comparison with the other therapeutic arms, MATRIX and ASCT were not associated with higher non-relapse mortality and incidence of second tumors, whereas impairment of specific cognitive functions after WBRT was confirmed.

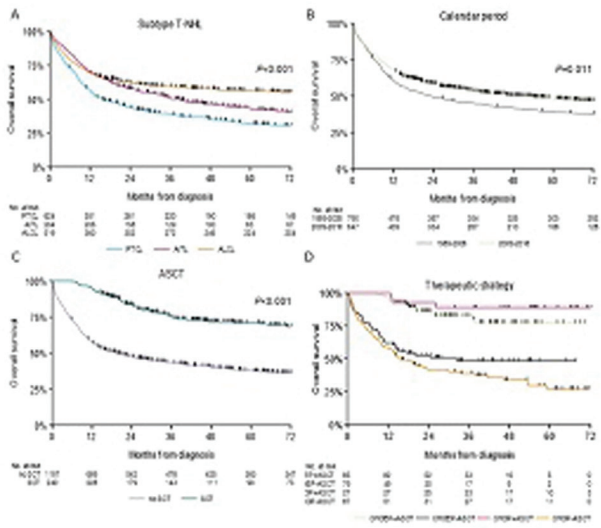
Aggressive lymphoma - Combination therapies

S220 IMPACT OF ETOPOSIDE AND AUTOLOGOUS STEM-CELL TRANSPLANTATION ON SURVIVAL AMONG YOUNG PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA IN THE NETHERLANDS; A NATIONWIDE, POPULATION-BASED COHORT STUDY

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Background: Peripheral T-cell non-Hodgkin lymphoma (T-NHL) is a heterogeneous disease entity with generally a poor survival. Cyclophosphamide-doxorubicin-vincristine-prednisolone (CHOP) has been the standard of care for the majority of T-NHL subtypes for decades. Addition of etoposide to CHOP (CHOEP) and consolidation with autologous stem cell transplantation (ASCT) are offered to young patients with stage II-IV disease, although the efficacy is controversial.
Aims: This nationwide, population-based study aimed to assess the impact of etoposide and ASCT on overall survival (OS) among patients <65 years with stage II-IV disease of the predominant T-NHL subtypes anaplastic large T-cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma not otherwise specified (PTCL NOS).
Methods: All patients with stage II-IV ALCL, AITL and PTCL NOS, 18-64 years old and diagnosed between 1989-2018 were identified from the Netherlands Cancer Registry (NCR), with survival follow-up through 2020. Data on primary therapeutic strategy (*i.e.* chemotherapy or no anti-neoplastic therapy) was available. The exact therapeutic strategy was known for patients diagnosed from 2014. Patients were categorized into two periods (1989-2008, 2009-2018) and the calendar periods were chosen based on the implementation of etoposide and ASCT (from 2009 onwards) for T-NHL in the Netherlands. Multivariable analysis of OS was performed using Cox regression.
Results: A total of 1,439 patients (median age 52 years; 62% males) were selected, including 519 ALCL, 294 AITL and 626 PTCL NOS cases. In 2009-2018, the proportion of AITL was higher as compared to 1989-2009 (27% *vs.* 15%, *P*=0.001). The proportion of patients receiving anti-neoplastic therapy was comparable for both calendar periods (88% and 91%, respectively). With similar trends for the three T-NHL subtypes, 31% of the patients received ASCT in 2009-2018 when compared to 5% of patients before 2009 (*P*<0.001). The median OS for the entire cohort was 22 months. As expected, five-year OS was highest for ALCL, followed by AITL and PTCL (57%, 44%, and 32%; Figure, panel A). Five-year OS increased over time with 11% (Figure, panel B) and was higher for patients who received ASCT as compared to patients without ASCT (70% vs 36%; Figure, panel C).
In 352 patients diagnosed in 2014-2018, the use of CHOEP instead of CHOP increased from 16% in 2014 to 67% in 2018. Of the patients who received CHOP or CHOEP, ASCT was applied in 26% and 51%, respectively. Five-year OS rates were 89% and 77% (*P*=0.248) for patients who received CHOP+ASCT and CHOEP+ASCT, respectively. For patients without ASCT, five-year OS rates were 27% and 48% (*P*=0.160) for patients with CHOP and CHOEP, respectively (Figure, panel D). When simultaneously adjusted for sex, age, and subtype of T-NHL in multivariable analysis, OS risk was similar between patients treated with CHOP+ASCT and patients treated with CHOEP+ASCT. However, OS risk for patients treated with CHOP or CHOEP in the absence of ASCT was lower as compared with patients treated with CHOEP+ASCT. T-NHL subtype was an independent predictor of poor prognosis.



Summary/Conclusion: In this large Dutch population of young patients with advanced ALCL, AITL or PTCL NOS, the use of ASCT consolidation, regardless the addition of etoposide to CHOP, significantly improved OS and could explain the survival benefit in the last decade. This nationwide population-based study corroborates other independent studies suggesting CHO(E)P followed by ASCT as first-line therapeutic regimen for young and fit T-NHL patients.

S221 INTER-B NHL RITUX 2010 TRIAL FOR CHILDREN/ ADOLESCENTS WITH HIGH-RISK MATURE B-CELL NON-HODGKIN'S LYMPHOMA/ACUTE LEUKAEMIA: SAFETY AND EFFICACY IN PATIENTS TREATED WITH RITUXIMAB AND LMB CHEMOTHERAPY.

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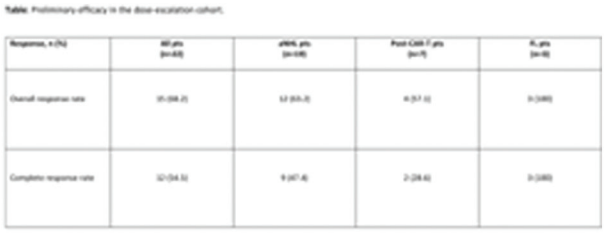
Background: The addition of rituximab to standard Lymphomes Malins B (LMB) chemotherapy improved survival of children and adolescents with high-risk mature B-cell non-Hodgkin's lymphoma and mature acute leukemia (B-NHL/AL) in the international randomized phase III trial Inter-B NHL ritux 2010 (NCT01516580).
Aims: After the first interim analysis, randomization was stopped for efficacy and additional patients were subsequently enrolled and treated with R-LMB for planned secondary aims. Here we report the total cohort of patients treated with R-LMB.
Methods: From December 2011 to June 2017, 298 patients < 18 years with high-risk B-NHL (stage III with LDH level>2N, stage IV) and B-AL were included in the Inter B-NHL Ritux 2010 study and allocated to the R-LMB arm: 164 were reported in the publication (NEJM 2020;382:2207-19) of the randomized part of the study (Main R-cohort) and there are 134 additional patients (Additional R-cohort). Rituximab was given (375 mg/m^2) on days -2 and 1 during the first 2 chemotherapy courses and on day 1 of the 2 following courses (total 6 infusions). Therapeutic groups were as follow: B: Stage III or IV, central nervous system negative; C1: Stage IV/B-AL cerebrospinal fluid (CSF) negative; C3: CSF positive. The endpoint event-free survival (EFS) is defined as the minimum time between inclusion and detection of residual viable tumor cells after the second consolidation course (primary refractory disease), relapse, progressive disease, second cancer, or death from any cause, or the date of the last follow-up for patients who did not have any event.
Results: Median age was 8 years (interquartile range (IQR) 5-12). 88% patients had Burkitt lymphoma (BL). 48% were in group B, 40% in C1 and 12% in C3. 94% patients received at least 6 rituximab administrations. The median follow-up was 45 months (IQR 34-57). There were 20 events (13 treatment failures: primary refractory disease or progression or relapse, 5 toxic deaths, 2 second cancers (histiocytic sarcoma, melanoma)). Seven treatment failures occurred in patients of therapeutic group B, 3 of group C1 and 3 of group C3. All relapses, except one, occurred during the first 10 months. 4-year EFS was 93.0% (95%CI 89.4% to 95.5%) (93.9% in main R-cohort, 91.3% in additional R-cohort). 16 deaths occurred (7 disease-related, 8 toxic deaths at first or further line, 1 from histiocytic sarcoma). 4-year overall survival (OS) was 94.2% (95%CI 90.7% to 96.4%) (95.1% in main R-cohort, 92.0% in additional R-cohort). Among patients with BL, 9 had treatment failures (6 in group B, 2 in group C1, and 1 in group C3) and 7 died. The most frequent grade ≥ 3 acute adverse events after prephase were febrile neutropenia (93%), infection (58%), and stomatitis (78%). One year after inclusion, 102 (59%) of 173 evaluated patients for immunoglobulin level had low IgG level.
Summary/Conclusion: Rituximab in addition to standard LMB therapy achieved outstanding EFS and OS in both randomized and additional parts of the trial in children/adolescents with high-risk B-NHL/AL with significant acute toxicity and hypoglobulinemia. However, some very rare patients still have resistant disease and very poor outcome, notably those with Burkitt lymphoma.

S222 PROMISING TOLERABILITY AND EFFICACY RESULTS FROM DOSE-ESCALATION IN AN ONGOING PHASE IB/II STUDY OF MOSUNETUZUMAB WITH POLATUZUMAB VEDOTIN FOR RELAPSED/REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

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Background: Mosunetuzumab (M), a full-length, humanized, IgG1 bispecific antibody targeting CD20 and CD3, has shown promising efficacy and safety as monotherapy for relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL) (NCT02500407; Assouline, et al. ASH 2020). The combination of M with the anti-CD79b antibody-drug conjugate, polatuzumab vedotin (Pola), showed synergistic anti-lymphoma activity in a mouse xenograft model. These data supported a Phase Ib/II, open-label, multicenter trial of M-Pola for R/R B-NHL (GO40516, NCT03671018).
Aims: To present early clinical data from the Phase Ib cohort of the GO40516 study.
Methods: Patients (pts) with R/R follicular lymphoma (FL; grade [Gr] 1–3a) or aggressive NHL (aNHL), including *de novo* diffuse large B-cell lymphoma (DLBCL), transformed FL (trFL) and FL Gr 3b (FL3b), received Cycle (C) 1 step-up doses of M on Day (D) 1 (1mg) and D8 (2mg), the target dose on C1D15, then continued at the target dose on C2D1 onwards. M was given every 21 days for eight cycles (or 17 cycles if stable disease or a partial response after C8). Pola (1.8mg/kg) was given with M on D1 of each cycle for six cycles.
Results: As of November 17, 2020, 22 pts had received M-Pola (M target doses: 9mg, n=7; 20mg, n=3; 40mg, n=6; 60mg [with D1 dose of 30mg from C3 onwards], n=6). Pts had DLBCL (n=12), FL (n=3), FL3b (n=3) and trFL (n=4). Pt characteristics include: median age of 70 (38–81) years; median of 3 (1–10) prior lines of therapy; 7 (32%) pts had prior chimeric antigen-receptor T-cell (CAR-T) therapy; 17 (77%) and 19 (86%) pts had disease refractory to last prior therapy and prior anti-CD20 therapy, respectively. Median follow-up duration was 9.6 (0.7–23.7) months. The most frequent treatment-related adverse events (AEs) were neutropenia (45.4%), fatigue, nausea and diarrhea (all 36.4%). Cytokine release syndrome (CRS) was observed in 2 pts (9.1%; both Gr 1 by American Society for Transplantation and Cellular Therapy 2019 criteria). One dose-limiting toxicity (Gr 3 new onset atrial fibrillation) was observed in the 40mg cohort. The maximum tolerated dose was not exceeded. The most common Gr ≥3 and serious AEs were both neutropenia, observed in 8 (36.4%) and 3 (13.6%) pts, respectively. Two (9.3%) Gr 5 AEs occurred: sudden cardiac death (n=1) and respiratory failure (n=1); neither was deemed treatment related. No immune effector cell-associated neurotoxicity was observed. The **Table** shows preliminary efficacy data.



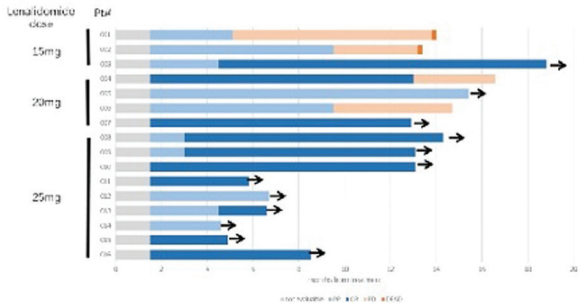
Summary/Conclusion: These data indicate that M-Pola has an acceptable safety profile, with no Gr ≥2 CRS observed, and promising efficacy in pts with R/R NHL with predominantly aggressive disease. The Phase II expansion cohort in R/R DLBCL is ongoing, with no mandatory hospitalization required.
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S223 PHASE IB/II STUDY OF LENALIDOMIDE, RITUXIMAB, HIGH-DOSE METHOREXATE (R2-MTX) REGIMEN, FOLLOWED BY LENALIDOMIDE MAINTAINANCE IN NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA

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Background: Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal NHL with an aggressive clinical course and poor outcomes. High-dose methotrexate (HD-MTX) based regimen significantly improves the outcomes, but 10-35% patients are treatment refractory.
Aims: In this study, we evaluated the safety, efficacy, and feasibility of lenalidomide, rituximab and HD-MTX (R2-MTX) regimen for newly diagnosed PCNSL patients.
Methods: This is a multicenter prospective phase Ib/II study(NCT04120350). Eligible patients had newly diagnosed PCNSL, age≥18 and normal end-organ function. The phase Ib study used the 3+3 dose escalation design. Lenalidomide was dosed at 15mg daily (day 1-14) (level 1), 20mg daily (day 1-14) (level 2) and 25mg daily (day 1-14) (level 3); rituximab was dosed at 375mg/m2 (d0), MTX was dosed at 3.5g/m2 (d1) (all dose levels). Every 21 days were as a course of treatment. R2-MTX regimen was given for 6 cycles, then lenalidomide (25mg daily, day 1-21) at 28-day cycles was given for a maximum of 2 years as maintenance. In phase I study, dose-limiting toxicity (DLT) within first 2 cycles was evaluated to determine the recommended phase II dose.
Results: 17 patients were enrolled from August 2019 to December 2020: 10 patients in phase Ib (3, 4, 3 patients received LEN 15mg, 20mg and 25mg, respectively); and 7 patients in phase II study. No DLTs were observed in phase Ib study, and the recommended phase II dose of lenalidimide was 25mg daily. The last follow-up was January 31th 2021. 11(64.7%) pts were male and the median age was 60 (range 32-74). 13 patients were mediate and high risk group according to IELSG score(2-5 points). Common grade ≥3 adverse events (AEs) of induction therapy were neutropenia (41.2%), infection(5.9%), anemia (5.9%), thrombocytopenia (5.9%) and acute kidney injury (5.9%) (all these AE occurred in one patient who suffered from MTX overdose); other AE (grade 1-2, > 10%) were elevated ALT(47.1%), fatigue(29.1%), nausea/vomiting (23.5%), numbness (23.5%), infection(11.8%), renal injury (11.8%) and rush (11.8%). 16 patients were evaluable for response, and the overall response rate (ORR) was 100%: 10 patients achieved complete remission, and 6 patients achieved partial remission. The median follow-up time was 13.2 (1.3-17.3)months, 4 patients relapsed and 2 patients died for disease progression, the median PFS was 13.3 month (Figure 1).



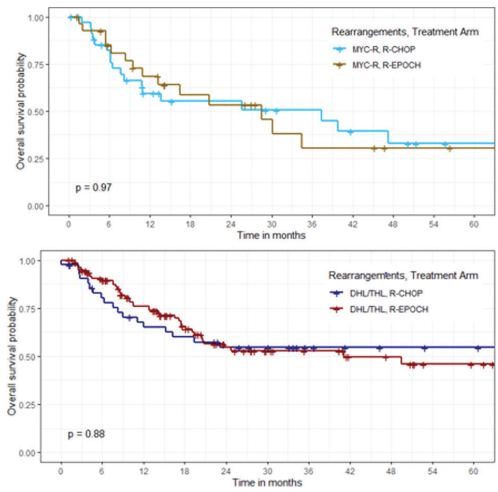
Summary/Conclusion: R2-MTX regimen is a feasible and active combination treatment for newly diagnosed PCNSL patients. It demonstrates excellent response rate, as well as with good tolerability. More clinical data will be updated from this ongoing study (NCT 04120350).

S224 NO DIFFERENCE IN OVERALL SURVIVAL BETWEEN R-CHOP AND R-EPOCH AMONG PATIENTS WITH ADVANCED STAGE MYC-REARRANGED, DOUBLE HIT, OR TRIPLE HIT DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Presence of MYC-rearrangement (MYC-R) in diffuse large B-cell lymphoma (DLBCL) has been associated with poor prognosis, especially if there is presence of concomitant BCL2 and/or BCL6 rearrangements. The latter entities are called double hit lymphoma (DHL) and triple hit lymphoma (THL), respectively. A few retrospective studies and a single arm prospective trial have suggested improved outcomes with the R-EPOCH regimen in DHL and THL patients. Our aim was to evaluate prognostic factors and efficacy of both regimens (R-EPOCH and R-CHOP) in a large cohort of patients with MYC-R DLBCL.
Aims: Our study aimed to compare overall survival of patients with advanced stage MYC-R DLBCL and DHL/THL who were treated with R-CHOP vs. R-EPOCH.
Methods: Data was analyzed from the nationwide Flatiron Health electronic health record–derived de-identified database, for patients diagnosed with DLBCL between 1 January 2011 and 30 June 2020. Only patients with MYC-R/DHL/THL who received R-CHOP or R-EPOCH as a first-line therapy were included in the analysis. Overall survival (OS) from date of diagnosis to date of death or last known alive was calculated using the Kaplan-Meier method and compared between MYC-R and DHL/THL separately using log-rank procedure. Cox proportional hazards regression was used to assess associations between patient characteristics, treatments, and overall mortality. Univariable and multivariable models within MYC-R and DHL/THL cohorts were conducted using these factors to estimate hazard ratios (HRs) and their 95% CIs.
Results: Among 6,809 total DLBCL patients, 443 (6.5%) were found to have MYC-R. Among these, 218 (49%) had advanced stage (III/IV) disease at diagnosis and received R-CHOP or R-EPOCH, and were included in the study. 154 (70%) had high-grade lymphomas (117 DHL, 37 THL). Among those with DHL/THL, 43 received R-CHOP (median age 73y) and 111 received R-EPOCH (median age 67y). Among those with MYC-R DLBCL, 36 received R-CHOP (median age 70y), and 28 received R-EPOCH (median age 61y). There was no difference in 4-year OS rates between R-CHOP and R-EPOCH treatment cohorts among DHL/THL (54.5% [95% CI 40.9-72.6] vs. 49.6% [95%CI 38.8-63.5] Figure). Similarly, there was no difference in 4-year OS rates among MYC-R patients between R-CHOP and R-EPOCH (32.8% [95%CI 17.7-60.9] vs. 30.4% [95% CI 14.4-64.5]). Among DHL/THL patients, 89% deaths occurred within first 2y, and among MYC-R, 78% deaths occurred within 2y of diagnosis. Among entire MYC-R cohort, univariate analysis of treatment type (R-CHOP, R-EPOCH), age ≥60y, sex, race, ECOG ≥2, elevated LDH, and >1 extranodal site, only ECOG ≥2 (p = <0.001) and elevated LDH (p = 0.041) were significant for worse mortality. By multivariate analysis, ECOG ≥2 (HR 2.59 [1.317-5.1]) and elevated LDH (HR 1.61 [1.016-2.6]) were again the only significant variables associated with risk of mortality.



Summary/Conclusion: In our large multi-institutional database study, the 4-year OS was similar between R-CHOP and R-EPOCH among MYC-R DLBCL and DHL/THL. In multivariable analysis, ECOG ≥2 and elevated LDH were the only variables independently associated with poor prognosis in this subgroup. Most deaths occurred within 2y of diagnosis, with similar OS in both arms at 4y. Further studies are needed for better risk stratification of patients with DLBCL for optimizing outcomes.

Lymphoma - Translational research

S225 CIRCULATING TUMOR DNA SEQUENCING REVEALS THE GENOMIC LANDSCAPE OF HODGKIN LYMPHOMA AND FACILITATES HIGHLY SENSITIVE DETECTION OF MINIMAL RESIDUAL DISEASE

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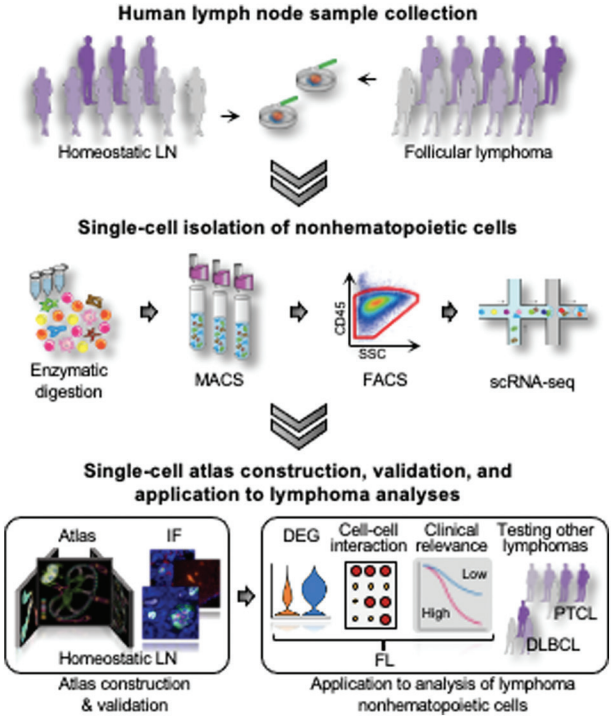
Background: In Hodgkin lymphoma, treatment individualization is hindered by a lack of genomic characterization and technology for sensitive, molecular response assessment due to the scarcity of Hodgkin-Reed Sternberg (HRS) cells in the tumor tissue. Sequencing of cell-free (cf) DNA is a powerful strategy for genomic characterization and development of assays for sensitive disease monitoring.
Aims: The aim of this study is to introduce a targeted cfDNA sequencing platform that is then used to decipher the genomic landscape of HL and to facilitate minimal residual disease assessment (MRD).
Methods: We comprehensively genotyped and assessed minimal residual disease in 324 samples from 121 patients targeting approximately 3 Mb of the genome. All samples underwent pre-analytical processing, extraction of ctDNA and matching germline control DNA and sequencing at > 3000x average coverage post deduplication. An in-house, customised bioinformatics pipeline was developed for two-fold error reduction.
Results: First, we performed technical and clinical validation. We show that our approach can identify mutations with an allele frequency of 0.5% in cfDNA at 92.8% sensitivity and 100% specificity. 91.3% of mutations could be confirmed in tissue samples. For MRD detection, we identified a limit of detection of 0.00945%.
We identified 23 tumor suppressor genes (TSG) and 20 oncogenes (OG) in our HL cohort. Recurrent mutations were identified in several known oncogenic pathways in HL such as JAK-STAT signaling (SOCS1, STAT6, CSF2RB, IL4R), Class I MHC mediated antigen processing and presentation (B2M) and NF-kappa B signaling (TNFAIP3, IKBKB, NFKBIE). Novel findings with potential relevance to HL pathogenesis included recurrent mutations in EZH2, IRF4 and IRF8.
Six distinct COSMIC single base substitution (SBS) signatures were identified, the most common being SBS1 (aging), followed by SBS3 (defective homologous recombination (HR)-based DNA damage repair), SBS6 and SBS15 (defective DNA mismatch repair) SBS9 (somatic hypermutation in lymphoid cells) and finally SBS25 (so far only identified in HL cell lines). Interestingly, SBS3 - the defective HR signature - contributed majorly to mutations in genes crucial for HL oncogenesis, highlighting a potential novel role for defective HR in HL pathogenesis.
When linking HL genotypes to phenotypes, mutations in some genes, such as TP53 or NOTCH1, were associated with a high-risk phenotype and inferior treatment response, while other alterations, such as BRCA1 or MGMT loss were associated with a low-risk phenotype possibly mediated by increased sensitivity to commonly used cytotoxic drugs.
Furthermore, we identified a distinct genotype of large mediastinal mass HL, characterized by a higher frequency of B2M and IKBKB mutations, as well as a higher number of mutations in genes involved in Interferon signaling and JAK-STAT signaling. These alterations suggest remarkable biological similarity of large mediastinal mass HL to PMBCL.
Finally, we examined the relationship between MRD measured by following each patient's unique mutational fingerprint at different timepoints, and interim PET-imaging after 2 cycles of treatment. MRD trajectories separated very early on, with clear differences already observable after 1 week. MRD after 1 week differentiated with 100% accuracy between Deauville 1-3 and Deauville 4-5 patients.
Summary/Conclusion: Here, we present the largest genomic landscape of HL to date and introduce our targeted ctDNA sequencing platform allowing for accurate genotyping using pre-treatment samples and highly sensitive minimal residual disease (MRD) detection.

S226 A COMPREHENSIVE SINGLE-CELL ATLAS OF NONHEMATOPOIETIC CELLS IN HUMAN LYMPH NODE AND LYMPHOMA REVEALS LANDSCAPE OF STROMAL REMODELING

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Background: Activities of nonhematopoietic cells (NHCs) in lymphoma, including mesenchymal stromal cells and endothelial cells, reportedly underlie lymphomagenesis. However, understanding of lymphoma NHC activities have been hampered by unexplained NHC heterogeneity even in normal human lymph node (LN). Particularly, human LN blood endothelial cells (BECs) and non-endothelial stromal cells (NESCs) have not been analyzed at single-cell resolution.
Aims: We aimed to complete a transcriptome atlas of human NHCs in homeostatic LN (HLN) and lymphoma to reveal previously unrecognized heterogeneity. We also sought to reveal the single-cell landscape of stromal remodeling in lymphomas, particularly in follicular lymphoma (FL), to advance understanding of stromal contributions in lymphomagenesis.
Methods: We performed single-cell RNA sequencing of NHCs (>100,000 cells) extracted from human HLN (n=9), nodal FL (n=10), peripheral T-cell lymphoma (PTCL; n=5), and diffuse large B-cell lymphoma (DLBCL; n=3) samples. Data from HLN samples was mainly used for the construction of NHC atlas. Immunofluorescence (IF) staining was performed to validate the results of single-cell analysis and to explore the topological localizations of each NHC subcluster in the LN. Using the NHC atlas, we performed comprehensive comparative analysis with FL NHCs by differentially-expressed gene (DEG) and intercellular ligand-receptor analyses. We also investigated the prognostic impact of putative stroma-derived biomarkers using deposited microarray data of FL patients.
Results: Graph-based clustering analysis revealed that the transcriptional features of NHC subpopulations in HLN are highly conserved in FL NHCs. Unsupervised sub-clustering analysis of BECs, lymphatic endothelial cells (LECs), and NESCs revealed 10, 8, and 12 subclusters, respectively, including some lacking mouse counterpart. IF staining successfully identified each NHC subcluster and its localization in the LN. In FL NHCs, the proportion of arterial BEC subclusters markedly increased relative to HLN, while the proportion of LECs decreased. In FL NESCs, the proportion of marginal reticular cells (MRCs) as well as follicular dendritic cells (FDCs) greatly increased. DEG analysis revealed that the greatest changes in gene expression occurs in NESC subclusters, particularly in MRCs, T-zone reticular cells (TRCs), perivascular stromal cells, and FDCs. Notably, in some NESC subclusters, we observed marked upregulation of genes relevant to solid cancers but previously not associated with lymphomagenesis (e.g. *POSTN*, *EGFL6*, and *FAP*). Combined interactome and DEG analysis revealed that interactions mediated through CXCL12 was unexpectedly upregulated only at stromal cells at adventitia. Additionally, the CCR7-CCL19 interaction was extended to non-TRC stromal cell subclusters. Also, the CXCL13-CXCR5 axis was highly activated in MRCs, indicating that MRCs as well as FDCs participate in FL expansion. Based, on these data, we identified putative stroma-derived biomarker LY6H, LOX, TDO2, and REM1 as promising prognostic predictors in FL. We finally confirmed that our NHC atlas is also useful to assess NHCs in more aggressive lymphomas including PTCL and DLBCL.



Summary/Conclusion: We constructed a comprehensive single-cell atlas of NHCs in human LN highly applicable to lymphoma NHC researches. Our study largely updates NHC taxonomy in LNs and provides a rich resource and deeper insights into lymphoma biology, a contribution that should advance lymphoma management and therapy.

S227 TRACKING CLONAL HEMATOPOIESIS IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA

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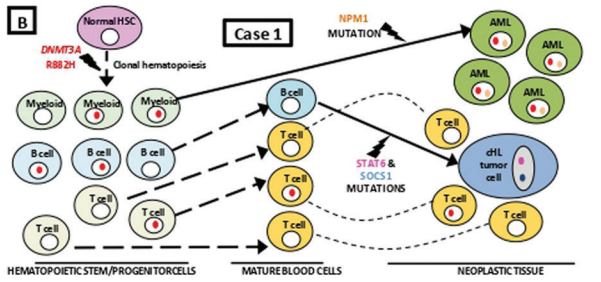
Background: Clonal hematopoiesis (CH) is frequent in the elderly and predisposes to blood tumors, mostly of myeloid and T-cell origin. CH incidence and trajectories are not well characterized in classical Hodgkin lymphoma (cHL), a B-cell neoplasm frequent in the young and uniquely featuring rare cancer cells embedded in a supportive microenvironment largely of hematopoietic origin.
Aims: To assess whether cHL belongs to the spectrum of hematologic malignancies associated with CH, here we report CH frequency and tissue distribution in 40 cHL patients, including the surprising findings on a young case with massive CH who developed acute myeloid leukemia (AML) following therapy for cHL.
Methods: We subjected 40 cHL cases to whole-exome and/or targeted sequencing (mean unique coverage ~150X and ~1000X, respectively) of tumor cells microdissected from the tissue biopsy in parallel with matched non-neoplastic blood cells (n=26 cases) or microdissected lymphoid cells (n=14 cases).
Results: 5/40 cases (12.5%) had blood and/or tissue CH, including 3/5 with >70 years and 2/35 <70 years (Fig. 1A). In 3/5 cases with CH (aged 30, 45 and 73 years), CH extensively spread through the non-neoplastic tissue microenvironment (92%, 32% and 60% of cells), being respectively driven by mutant *KRAS*^{G60D}, *DNMT3A*^{R882H}, and *DNMT3A*^{R882H}+*TET2*^{Q1274*} (Fig. 1A). Notably, in the latter case (Case 5) CH originated also the tumor cell clone, which was infected by the Epstein-Barr virus and had almost no other somatic mutations exome-wide; this is the first description, in a human B-cell lymphoma clone, of mutant *DNMT3A*^{R882}, a hotspot in myeloid and T-cell neoplasms.
In the other case with *DNMT3A*-mutant CH (Case 1; Fig.1B), the same variant R882H caused a massive CH (94% of blood leukocytes; 96% of blood B cells) that was surprisingly absent from the tumor cell clone (instead carrying *STAT6* and *SOCS1* mutations, typical of cHL) and led, 6 years after therapy for cHL, to a likely therapy-unrelated *NPM1*-mutated acute myeloid leukemia (with normal karyotype, wild-type *TP53* and *PPM1D*). Thus, CH trajectories must be fully disentangled to correctly interpret the histogenesis and pathogenesis of multiple myeloid and lymphoid neoplasms arising in patients with CH, as the latter (even when massive) does not necessarily represent the shared genetic background of all neoplastic clones.
Finally, in the 3 cases with extensive CH propagation in the cHL tissue microenvironment (mostly represented by T cells), we observed a polyclonal status of T-cell receptor gene rearrangements, confirming that the mutations underlying CH had occurred in a bone marrow stem or progenitor cell before T-cell lineage commitment. Interestingly, all these 3 cases progressed after first-line chemotherapy, versus 11/35 (31%; p-value 0.043) evaluable cases with absent or non-extensive tissue CH, who otherwise had similar clinical features and received the same first-line therapy (not shown).

FIGURE 1

A

cHL case cohort (n=40)		Pt. #	Time of sampling	Progressed after first-line chemotherapy	CHIP mutation	VAF in whole blood	VAF in microdissected		VAF in whole tissue section
CH PRESENT	AGE (years)						Reactive lymphoid cells	Tumor cells	
YES (n=5)	45	Case 1	Onset	YES	*DNMT3A R882H*	47%	16.4%	ND	NA
	30	Case 2	2nd relapse	YES	*KRAS G60D*	NA	45.9%	ND	22.9%
	83	Case 3	Onset	Not evaluable	*CBL G375S*	NA	2.5%	ND	NA
	81	Case 4	Onset	NO	*TET2 N1487fs84*	3.2%	ND	ND	NA
	73	Case 5	1st relapse	YES	*DNMT3A R882H*	NA	30%	43%	NA
NO (n=35)	Median: 35 Range: 15-75				*TET2 Q1274**		8.4%	31.1%	

VAF, variant allele frequency; NA, Not available; ND, Not detected



Summary/Conclusion: CH can be observed in the cHL tissue, can originate the tumor clone and can propagate to large part of its microenvironment. Considering that both tumor cells and the microenvironment supporting its growth play key roles in cHL pathogenesis, CH might contribute to the development of this lymphoma and influence its prognosis.

S228 BLOCKADE OF NCAPD3 AS A NOVEL THERAPEUTIC APPROACH IN DIFFUSE LARGE B-CELL LYMPHOMA

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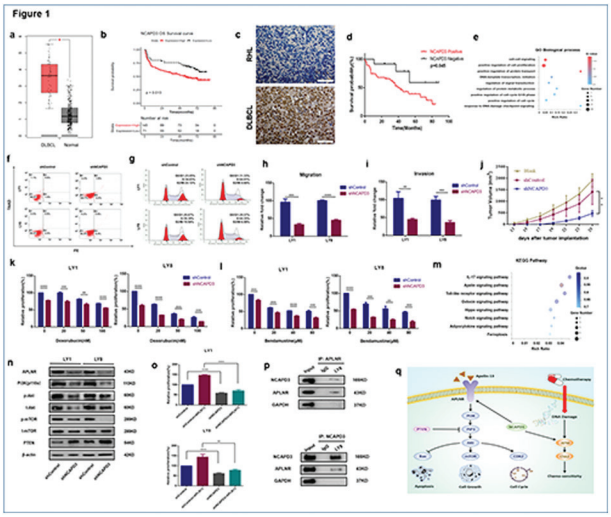
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Background: The Non-SMC Condensin II Complex Subunit D3 (NCAPD3) is a key component of condensin. Existing evidence confirms that somatic mutations in NCAPD3 are linked to deregulated pathways and a large number of diseases, including cancers. However, little is known regarding its biological and clinical significance in diffuse large B-cell lymphoma (DLBCL).
Aims: This series of experiments are aimed to explore the pattern of expression, functional mechanisms and potential clinical relevance of NCAPD3 in DLBCL.
Methods: Archived, paraffin-embedded samples extracted from 70 *de novo* DLBCL patients and 30 reactive hyperplasia cases were collected with informed consents. The GEO and TCGA database were obtained to aid in subsequent survival analysis. Empty lentiviral vectors (shControl) or those coding for shNCAPD3 were stably transfected into DLBCL cell lines which were then assessed using RNA-sequencing (RNA-seq) analysis. DLBCL xenograft models were established by injecting mice subcutaneously with DLBCL cells. ARRIE guidelines were strictly adhered to for all experiments.

Results: TCGA database demonstrated that the expression level of NCAPD3 in DLBCL was raised in comparison to those of normal tissues (Fig. 1a). Kaplan-Meier survival curve revealed that higher NCAPD3 expression levels in DLBCL cases were linked to shorter overall survival times according to GEO database (Fig. 1b). IHC staining showed higher expression levels of NCAPD3 in DLBCL tissues than those in control tissues and significantly related to poorer prognosis (Table 1, Fig 1c, d). High expression levels of NCAPD3 mRNA and protein were confirmed in DLBCL cell lines as well.

Functional enrichment analyses of NCAPD3 according to RNA-seq revealed that NCAPD3 was correlated strongly to cell proliferation, cell cycle and DNA damage signaling (Fig 1e). Knockdown of NCAPD3 significantly suppressed cell proliferation, promoted cell apoptosis, induced cell cycle arrest and impaired cell migration and invasion (Fig 1f-i). Tumors with NCAPD3-repression displayed suppressed tumor growth (Fig 1j) and diminished levels of Ki-67 *in vivo*. Also, NCAPD3 depletion in DLBCL were proved to enhance the chemo-sensitivity of DLBCL through the DNA damage signaling (Fig 1k, l).

With KEGG results derived from the RNA-seq data, NCAPD3 was found to be functionally enriched in the Apelin signaling pathway (Fig. 1m). NCAPD3 and APLNR revealed a significant association in DLBCL according to TCGA database. Western blot demonstrated a decrease in the levels of APLNR and its downstream PI3K/Akt/mTOR components in shNCAPD3 cells in contrast to shControl cells (Fig 1n). The APLNR activator APLN-13 were exposed to DLBCL cells transfected with either shNCAPD3 or shControl, cells containing shNCAPD3 demonstrated decreased proliferation induction (Fig. 1o). The co-IP experiment suggested that NCAPD3 regulates the Apelin/PI3K pathway by directly binding to APLNR (Fig. 1p). In summary, NCAPD3 may modulate DLBCL progression through regulation of the Apelin/PI3K and DNA damage response signaling pathway (Fig. 1q).



Summary/Conclusion: Our clinical and fundamental results highlight the pivotal oncogenic role of NCAPD3 in DLBCL for the first time, suggesting blockade of NCAPD3 as a novel therapeutic approach in DLBCL mediating through the Apelin/PI3K signaling pathway.

S229 A SYSTEMS BIOLOGY APPROACH TO DLBCL PREDICTS EMERGENT PHENOTYPES FROM MOLECULAR DYSREGULATION AND IDENTIFIES DISTINCT ROLES FOR NF-KB SUBUNITS CREL AND RELA.

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Background: Heterogeneity in therapeutic response challenges the successful treatment of Diffuse Large B-Cell Lymphoma (DLBCL). Despite the recognition that DLBCL cases have diverse genetic and transcriptional characteristics, standard first-line therapy has remained unchanged for more than a decade. Further, cell-of-origin stratification into Germinal Centre (GC) and Activated B-cell (ABC) DLBCL fails to define much of the heterogeneity.

Canonical Nuclear Factor KappaB (NF-kB) is a dimeric transcription factor usually consisting of either cRel or RelA bound to p50. While aberrant NF-kB activation is frequently observed in DLBCL, subunit composition in individual DLBCL cases is not routinely characterized but has the potential to improve stratification and identify novel molecular targets for treatment. Computational simulations of NF-kB control over B-cell proliferation and apoptosis accurately predict experimental results with accuracy at both single-cell and cell-population scale. However, the key regulatory networks controlling B-cell differentiation were not factored into these predictive models.

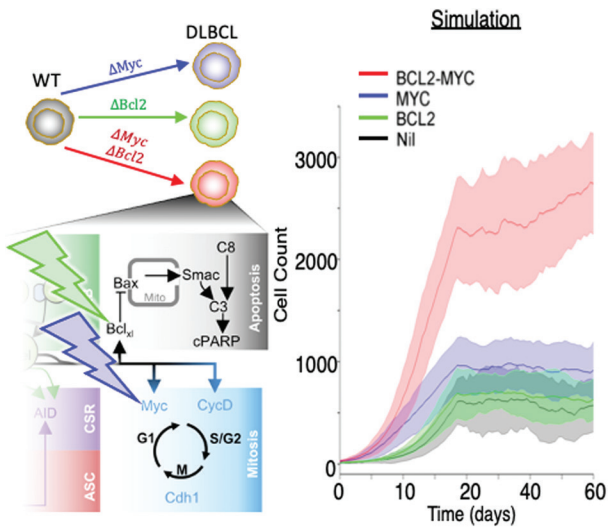
Aims: 1. Elucidate, with single-cell resolution, dynamic NF-kB control over B-cell fate decisions.

2. Develop a novel tool to enable rational therapeutic targeting of in B-cell lymphoma despite substantial heterogeneity.

Methods: Mechanistic systems biology approaches were combined with publically available data and targetted experiments designed to test computational predictions.

Results: Simulation of known regulatory interactions between NF-kB and the molecular networks controlling B-cell fate decisions revealed this molecular signalling network was insufficient to explain healthy B-cell differentiation. A computationally-driven prediction, that cRel must be downregulated during differentiation, lead to the discovery that although cRel drives B-cell proliferation it also blocks terminal differentiation to antibody-secreting plasma cells. We find that dynamic downregulation of cRel, through direct inhibition by Blimp1, is a pre-requisite for B-cell differentiation. The refined simulation, incorporating this novel interaction, accurately recapitulates B-cell population dynamics in wild-type (WT) and cRel knockout cells.

To establish whether a computational systems biology approach could enable accurate simulation of DLBCL we incorporated the aberrantly increased NF-kB activity seen in the disease. Interestingly, NF-kB subunit specific phenotypes emerge. Chronic cRel activity resulted in a differentiation block at the germinal centre stage, as seen in GC-DLBCL. RelA hyperactivity resulted in accumulation of a more differentiated cell type as see in ABC-DLBCL. To explore the potential of this approach to understand dysregulation beyond NF-kB, commonly-occurring mutations affecting MYC and BCL2 were simulated. While individual mutations only marginally perturbed cell counts the combination of MYC and BCL2 dysregulation commonly found in "double-hit" lymphoma had a striking synergistic effect in the model as seen in both experimental systems and clinical outcomes.



Summary/Conclusion: The ability of these computational systems biology models to accurately recapitulate clinically-observed emergent phenotypes from mutational changes enables the creation of mutation-specific "*in silico*" DLBCL laboratories. By incorporating the recently characterise vast mutational heterogeneity seen through whole exome sequencing DLBCL, we can use these models as tools to predict efficacious therapeutic approaches and biomarkers to stratify and treat lymphoma beyond current subtype classification.

Stem cell transplantation - Preclinical/experimental

S230 RESTORING M1/M2 MACROPHAGE POLARIZATION VIA UP-REGULATING PI3K-AKT PATHWAY ALLEVIATES PROLONGED ISOLATED THROMBOCYTOPENIA POST-ALLOTRANSPLANT

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Background: Prolonged isolated thrombocytopenia(PT) is a serious complication following allogeneic hematopoietic stem cell transplantation(allo-HSCT). Our previous studies found dysfunctional megakaryopoiesis are responsible for the occurrence of PT. As an important component of the BM microenvironment, macrophages(MΦs) are heterogeneous and polarized into classically activated MΦs(M1) and alternatively activated MΦs(M2) with distinct function. In this regard, our previous study found that the aberrant M1/M2 polarization plays a critical role in regulating hematopoiesis of poor graft function patients, a clinical manifestation of pancytopenia after allo-HSCT. However, the effect of MΦ polarization on regulating megakaryopoiesis and novel approach targeting aberrant MΦ polarization in PT patients remain to be elucidated.
Aims: To address the polarization state and the function of BM MΦs in PT patients. Moreover, to investigate the effect of M1 and M2 on megakaryopoiesis and potential therapeutic target regulating aberrant MΦ polarization for PT patients.
Methods: This prospective case-control study enrolled 12 PT patients, 24 matched good graft function(GGF) patients and 12 healthy donors(HD). BM MΦs subsets were analyzed by flow cytometry and in situ histological analyses. The functions of BM MΦs were evaluated by cytokine secretion assays and coculture experiment with megakaryocytes(MKs). To determine the the effect of MΦ on megakaryopoiesis, both primary human BM MΦs and THP1 were polarized into M1 and M2 and cocultured with MKs. To further investigate the underlying mechanism of MΦ in regulating MKs, RNA-seq analyses were performed in primary MΦs from patients, and polarized M1 and M2 from HD, respectively. To explore potential approach of targeting the aberrant MΦ polarization, the chemical activators or inhibitors and lentivirus for PI3K-AKT pathway were administrated to the primary MΦs from patients and THP1 derived MΦs. BM MΦ specific PI3K-knockdown mice were constructed and megakaryopoiesis were analyzed. Subsequently, subsequent changes in maturation related signaling pathways of MKs were analyzed.
Results: Compared with GGF patients and HD, aberrant BM M1/M2 polarization, characterized by increased M1 and decreased M2 and accompanied by impaired megakaryopoiesis-supporting ability, was found in PT patients. RNA-seq and western blot analysis showed PI3K-AKT pathway was significantly downregulated in BM MΦs of PT patients. Moreover, in vitro treatment with PI3K-AKT activators restored the impaired megakaryopoiesis-supporting ability of MΦs from PT patients. Furthermore, we found M1 suppress, whereas M2 support MK maturation and platelet formation in humans. Chemical inhibition of PI3K-AKT pathway reduced megakaryopoiesis-supporting ability of M2, which could be alleviated by chemical activation of PI3K-AKT pathway. Importantly, genetic knockdown of PI3K-AKT pathway impaired the megakaryopoiesis-supporting ability of MΦs both in vitro and in a MΦ specific PI3K-knockdown murine model. Furthermore, mechanistic study indicated that TGF-β released by M2 may facilitate megakaryopoiesis through upregulation of the JAK2/STAT5 and MAPK/ERK pathways in MKs.
Summary/Conclusion: The current study demonstrated aberrant BM M1/M2 polarization with impaired megakaryopoiesis-supporting ability involved in the pathogenesis of PT. M2, but not M1, support megakaryopoiesis via up-regulating PI3K-AKT pathway. Although further validation is required, restoring M1/M2 MΦ polarization via up-regulating PI3K-AKT pathway might be a potential therapeutic approach for PT patients.

S231 DISULFIRAM ALLEVIATES ACUTE GRAFT-VERSUS-HOST DISEASE BY INHIBITING MACROPHAGE PYROPTOSIS

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Background: Pyroptosis, a novel form of inflammation-related programmed cell death, often occurs in myeloid cells. Many studies have found that macrophage pyroptosis plays an essential role in multiple inflammatory and autoimmune diseases (Journal of Autoimmunity, 2018). Acute GVHD, an immune disease involving various inflammatory factors, is characterized by macrophage dysfunction, as reported in our previous study (Sci China Life Sci, 2020). However, whether macrophages undergo pyroptosis in aGVHD remains unknown. Disulfiram, an inhibitor of pore formation by GSDMD, could block pyroptosis and cytokine release. Recently, disulfiram treatment was found to be safe to attenuate some immune and inflammatory diseases (Journal of Experimental Medicine, 2019; Nature Immunology, 2020). However, the therapeutic effects of disulfiram on aGVHD remain unknown.
Aims: This study aimed to explore macrophage pyroptosis in aGVHD and investigate the therapeutic effects of pyroptosis inhibitors on aGVHD.
Methods: Macrophages and $CD4^+$ T cells were isolated from the bone marrow and spleens of C57 mice. Morphological analysis was performed by scanning electron microscopy. The expression of GSDMD was assessed by RT-PCR and WB. Cell death was measured by flow cytometry, Hoechst 33342/PI staining and lactate dehydrogenase (LDH) release assays. Inflammatory factors were tested by ELISA and immunohistochemistry. The subgroup of $CD4^+$ T cells was analysed by flow cytometry. The pyroptosis inhibitor disulfiram was administered to the GVHD mouse model to observe its therapeutic effect.
Results: Scanning electron microscopy images showed the formation of membrane pores in the peritoneal macrophages of aGVHD mice. Additionally, more PI positivity and more LDH release were observed in peritoneal macrophages in aGVHD mice. The expression of GSDMD was elevated in the macrophages of aGVHD mice. IL-1β and IL-18 were increased in both serum and target tissues in aGVHD mice. Additionally, elevated levels of IL-1β and IL-18 were observed in the serum of aGVHD patients. These results indicated that macrophages in aGVHD underwent pyroptosis.
Because $CD4^+$ T cells play a critical role in the pathogenesis of aGVHD, we investigated the effect of macrophage pyroptosis on $CD4^+$ T cells. In vitro, macrophage pyroptosis increased the proportion of $CD69^+$, Th1 and Th17 cells in $CD4^+$ T cells, suggesting that macrophage pyroptosis might be involved in the development of aGVHD.
Administration of the pyroptosis inhibitor disulfiram into aGVHD model mice markedly improved the survival of the mice and attenuated the clinical and histopathological scores. Peritoneal macrophages that were PI positive and GSDMD in macrophages of target tissues were decreased in aGVHD mice. IL-1β and IL-18 levels were also decreased in both serum and target tissues in aGVHD mice. Furthermore, disulfiram reduced the proportions of $CD69^+$, Th1 and Th17 cells among $CD4^+$ cells in the spleen of aGVHD mice. These results revealed that macrophage pyroptosis could be a potential therapeutic target in aGVHD and that the pyroptosis inhibitor disulfiram could alleviate aGVHD by inhibiting macrophage pyroptosis.
Summary/Conclusion: Our results firstly demonstrated that macrophage pyroptosis plays a crucial role in the pathogenesis of aGVHD by promoting the activation and differentiation of $CD4^+$ T cells. The pyroptosis inhibitor disulfiram markedly improved the survival and reduced the severity of aGVHD in mice. Macrophage pyroptosis may be a novel supplement to the pathological mechanism in aGVHD and provides a potential therapeutic target for aGVHD.

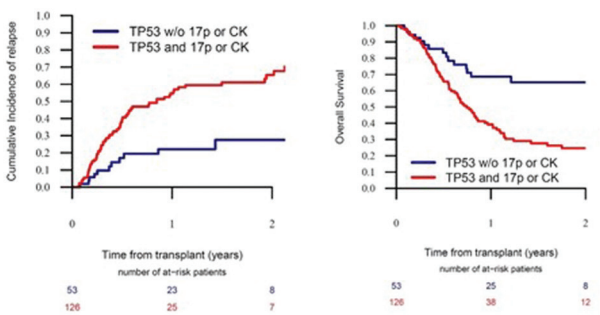
S232 DISEASE RISK IN TP53 MUTANT ACUTE MYELOID LEUKAEMIA FOLLOWING AN ALLOGENEIC STEM CELL TRANSPLANT IS DEPENDENT ON THE PRESENCE OF CO-EXISTING CYTOGENETIC FEATURES: A REPORT FROM THE ALWP OF THE EBMT

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Background: TP53 mutations in patients (pts) with acute myeloid leukaemia (AML) has been associated with an unfavourable outcome including after allogeneic stem cell transplantation (allo-SCT). This has led some to question the benefit of allo-SCT for TP53 mutant AML, although it has not been studied in a large patient cohort.
Aims: To identify factors which influence transplant outcome in pts with mutant TP53 AML.
Methods: We identified pts with AML in first complete remission, and with either intermediate or adverse risk cytogenetics, whose TP53 mutation status was reported to the EBMT registry. All ages, conditioning intensity or donor source were included.
Results: We identified 179 pts with AML with TP53 mutations and compared their characteristics and outcomes to 601 pts with AML without TP53 mutations. Pts were transplanted between 2015-2019. Chromosomal losses in chromosomes 17p (31% vs. 3%), 5q (49% vs. 5%), and 7q (34% vs. 8%) as well as complex (65% vs. 12%) and monosomal karyotypes (41% vs. 8%) were significantly increased in the cohort of pts with mutated TP53, in contrast to those with unmutated TP53.
The overall survival (OS) at 2 years was significantly impaired in pts with mutated TP53 as compared to the cohort without (mutated TP53, 35.1% [95% CI: 26.7-43.7]; without TP53 mutations, 64% [95% CI: 59.1-68.4], p= 0.001). This was a result of an increased cumulative incidence of relapse (CIR) at 2 years in pts with mutated TP53 as compared to the cohort without mutated TP53 (mutated TP53, 55% [95% CI: 45.2-63.8]; without TP53 mutations, 25.2% [95%CI: 21.2-29.3], p= 0.001). The adverse prognostic impact of TP53 mutations on OS (HR=1.5, 95%CI 1.1-2.1) and CIR (HR=1.4, 95%CI: 1.2-1.9) was maintained in a multivariate model that accounted for the adverse prognostic value of other known cytogenetic, and transplant, variables.
In pts with mutated TP53 AML, differences in conditioning intensity, donor source and GVHD prophylaxis strategy did not significantly affect OS or CIR. However, in pts with TP53 mutant AML the presence of either 17p abnormalities (abn17p) or complex karyotype (CK) provided further prognostic value. In pts with mutated TP53 AML without abn17p or CK, the 2-year OS was 65.2% [95%CI: 48.4-77.6]; in comparison, in pts with mutated TP53 AML with either abn17p or CK, the OS was significantly lower (24.6% [95%CI: 16.2-34], p=0.001) (figure). In a multivariate analysis the additive poor prognostic effect of abn17p and CK on the OS of pts with mutated TP53 AML was maintained. In pts with mutant TP53 AML with either abn17p or CK, the leukaemia free survival (LFS) at 2 years was 15.2% ([95% CI: 8-24.6], p=0.001), which was lower than that in pts with mutated TP53 AML, but without abn17p or CK, (LFS: 59.9% [95%CI: 41.7-74.1]). In pts with mutant TP53 AML with either abn17p or CK, the CIR was 65.4% ([95% CI: 53.9-74.8], p=0.001), which was higher than that in pts with mutated TP53 AML, but without abn17p or CK, (CIR: 27.5% [95% CI: 13.4-43.7]) (figure).



Summary/Conclusion: The adverse prognostic effect of TP53 mutations in AML is only evident in pts with co-occurring abn17p or CK. Even in pts with mutated TP53 AML and a co-occurring abn17p or CK, a significant proportion of pts achieved long-term survival. Our data is practice changing and assists in the identification of pts who stand to benefit from an allo-SCT. Finally, the enrichment of abn17p in pts with TP53 mutations, and their additional poor prognostic implication, supports the biological importance of biallelic loss of TP53 activity in AML.

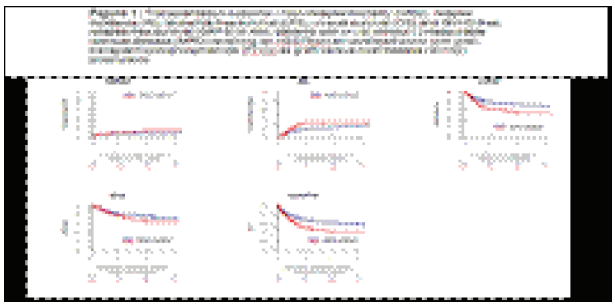
S233 THE ROLE OF PRE -TRANSPLANTATION MEASURABLE RESIDUAL DISEASE (MRD) IN PATIENTS WITH AML IN REMISSION TRANSPLANTED FROM UNRELATED DONORS WITH POST TRANSPLANT CYCLOPHOSPHAMIDE: FROM THE ALWP OF THE EBMT

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Background: GVHD prophylaxis may affect the transplant (HSCT) mediated graft-versus-leukemia (GVL) effect and post- HSCT relapse (RI). Pre-transplant measurable residual disease (MRD) predicts RI and outcome of HSCT with calcineurin based anti GVHD prophylaxis. Post-transplant cyclophosphamide (PTCy) has changed immune reconstitution post-transplant, upregulating T regulatory (Treg) cells while ablating recipient proliferating NK cells. It is therefore conceivable that MRD prediction of RI post-HSCT with PTCy will be different.
Aims: Study aim was *to assess the prognostic* impact of pre-HSCT MRD in adult patients (pts), aged ≥18 y with AML in CR undergoing HSCT from a 9-10/10 unrelated donor (MUD) with PTCy, in 2010-2019.
Methods: Multivariate analysis (MVA) adjusting for potential confounding factors was performed using a Cox's proportional-hazards regression model for main outcomes.
Results: 290 pts were included: MRD^- -189, MRD^+ -101. Median F/U was 17.7 (13.8-23.8) and 21.6 (16.8-26.5) months (p=0.61). Median age was 46.7 (18-74) and 50 (18-72) y, (p=0.018). 55% and 63.4% were male (p=0.77), 44.4% and 50.5% were classified as intermediate cytogenetic risk, while 15.3% and 18.8%, and 11.6% and 15.8% were classified as adverse and favorable risk cytogenetics, respectively (p=0.069). Pre-MUD disease status was CR1 in 76.2% and 80.2%, and CR2 in 23.8% and 19.8% of the pts, respectively (p=0.44). 45% and 43.1% of the pts harbored the FLT3+ mutation (p=0.83), (missing in ~50%). Conditioning was myeloablative in 64% and 59.4% (p=0.44). In vivo T-cell depletion was used in 28.6% and 18.8% of transplants (p=0.068). Graft was peripheral blood in 92.6% and 91.1% of transplants

(p=0.65). Karnofsky performance score was ≥ 90 in 80.6% and 75.5% of pts (p=0.31).
In MRD⁻ and MRD⁺ pts, engraftment was achieved by 97.4% and 97%, respectively. Day 180 incidence of acute (a) GVHD II-IV and III-IV was 28.1% and 25.6% (p=0.67), and 8.2% and 12.3% (p=0.28), respectively, and 2-y total and extensive chronic (c) GVHD was 27.2% and 31.8 % (p=0.6), and 5.9% and 17.6 % (p=0.03). The 2-y NRM was 8.2% and 13.9% (p=0.32). The 2-y RI was significantly lower in MRD- vs MRD+ pts: 20.4% vs 32%, respectively (HR=1.87; 95% CI: 1.12-3.14; p=0.02)") and it was the main cause of death in 35.9% and 50% of pts who died. The 2-y LFS and GRFS was significantly better in MRD⁻ vs MRD⁺ pts being 71.4% vs 51.4%, and 61.3% vs 40.2% (p=0.021 and p=0.01), respectively, while OS did not differ being 76.1% and 65.8%, respectively (p=0.2). These results were confirmed by MVA: RI was significantly lower while LFS and GRFS were significantly higher in MRD⁻ vs MRD⁺ pts: hazard ratio (HR)=1.87 (95% CI 1.12-3.14, p<0.02), HR=1.59 (95% CI 1.02-2.45, p<0.04) and HR=1.69 (95% CI 1.16-2.47, p< 0.01), respectively. NRM and OS were similar between the groups: H=1.07 (95% CI 0.47-2.43, p=0.88) and HR=1.2 (95% CI 0.73-1.95, p=0.48), respectively. Risk of aGVHD II-IV and total cGVHD was also similar, HR=0.89 (95% CI 0.55-1.45, p=0.63), and HR=1.61 (95% CI 0.94-2.77, p=0.08), respectively.



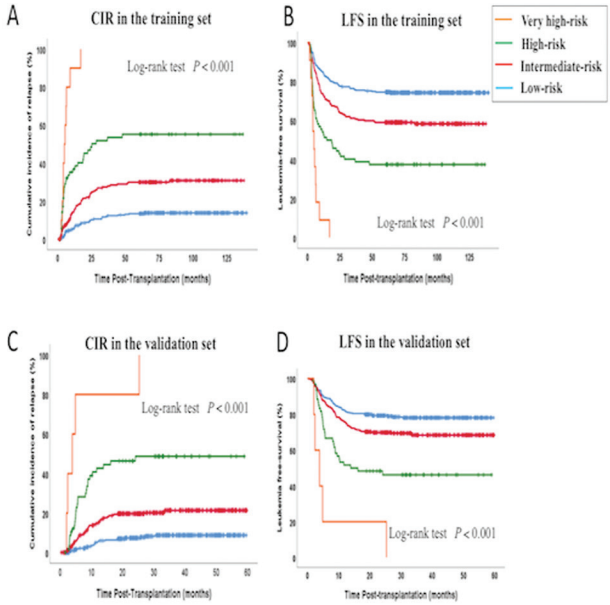
Summary/Conclusion: In AML pts undergoing HSCT from a 9-10/10 MUD in CR with PTCy as GVHD prophylaxis, pre-transplant MRD negativity predicted transplantation outcome correlating with lower relapse rate and better LFS and GRFS, similar to previous reports using conventional GVHD prophylaxis. These findings may indicate that PTCy does not jeopardize the transplant mediated GVL effect and the importance of the pre-HSCT remission depth, despite the PTCy mediated NK inhibitory and Treg cell potentiating activity leading to a lower incidence of cGVHD

S234 AN INTEGRATIVE SCORING SYSTEM MAINLY BASED ON QUANTITATIVE DYNAMICS OF MINIMAL/MEASURABLE RESIDUAL DISEASE FOR RELAPSE PREDICTION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Leukemia relapse remains one of the main causes of mortality in acute lymphoblastic leukemia (ALL) patients after allogeneic hematopoietic stem cell transplantation (HSCT). The cumulative incidence of relapse (CIR) was strongly influenced by minimal/measurable residual disease (MRD) assessed at timepoints after or during induction therapy, after consolidation therapy, pre-HSCT and post-HSCT. Besides, other variables, such as the T cell lineage of ALL blasts and remission status after induction therapy or pre-HSCT, have been reported to be correlated with high CIR in those who received allo-HSCT. Consequently, it could be hypothesized that an integrative scoring system mainly based on the quantitative dynamics of MRD in combination with other variables could be more effective in distinguishing ALL cases into different CIR groups.
Aims: The aim of the study was to establish an integrative scoring system, which could provide better relapse risk determination for ALL patients.
Methods: In total, 1416 patients with ALL who underwent HLA-matched sibling donor transplantation (n=285) or haploidentical transplantation (n=1131) were enrolled in this study. A training (retrospective) group (n=651) and a validation (prospective) group (n=765) were included. Factors that were related to CIR were identified in the training group with a multivariate Cox model. A weighted risk score to each factor based on the hazard ratio (HR) from the regression analysis were assigned, and the prognostic score was then defined as the sum of single-risk parameters.
Results: In the training group, four risk groups -- low- (score = 0), intermediate- (score =1-2), high- (score =2.5-6) and very high-risk (score≥6.5) -- were stratified using the scoring system based on remission status before transplantation, immunophenotype, and quantitative dynamics of pretransplant- and posttransplant- minimal residual disease. The 3-year CIRs for the low-, intermediate-, high-, and very high-risk groups were 10.9%, 24.5%, 47.2%, and 90.0%, respectively (P<0.001). The c-statistic of this final model was 0.69. The risk score was confirmed for the 3-year leukemia-free survival (LFS, P<0.001; c=0.62) and overall survival (OS, P<0.001; c=0.63). In the validation group, the 3-year CIRs for the low-, intermediate-, high-, and very high-risk groups were 7.6%, 19.6%, 45.4%, and 100%, respectively (P<0.001, c=0.69). The risk score was confirmed for the 3-year LFS (P<0.001; c=0.59) and OS (P<0.001; c=0.57).



Summary/Conclusion: Our data indicate that the integrative scoring system can be used for outcome stratification in ALL patients received allografts.

Stem cell transplantation - GvHD

S235 IBRUTINIB VS PLACEBO IN COMBINATION WITH CORTICOSTEROIDS IN PATIENTS WITH NEW-ONSET CHRONIC GRAFT-VERSUS-HOST DISEASE (CGVHD): RESULTS FROM THE RANDOMIZED, DOUBLE-BLIND PHASE 3 INTEGRATE STUDY

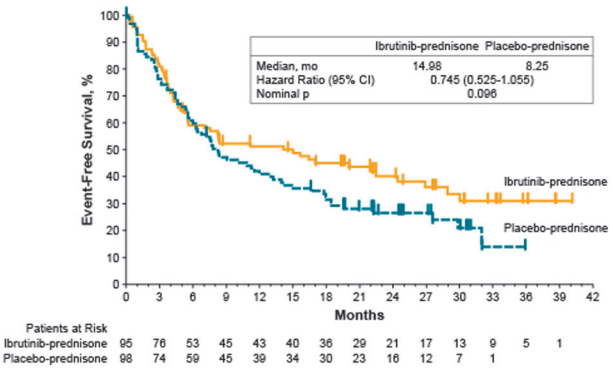
D. Miklos [1,*], M. Abu Zaid [2], J. P. Cooney [3], J. Albring [4], M. Flowers [5], A. P. Skarbnik [6], I. Yakoub-Agha [7], B. -S. Ko [8], B. Bruno [9], E. K. Waller [10], J. Yared [11], S. K. Sohn [12], C. -E. Bulabois [13], T. Teshima [14], D. Jacobsohn [15], H. Greinix [16], A. Mokatrin [17], Y. Lee [17], J. Wahlstrom [17], L. Styles [17], G. Socie [18]

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Background: Approximately 34% of patients (pts) who develop cGVHD after hematopoietic cell transplant require systemic treatment. Many pts experience recurrent cGVHD or become refractory to standard of care first-line corticosteroids. Ibrutinib (ibr) has demonstrated sustained efficacy and safety in cGVHD and is currently the only therapy approved in the United States for adults with cGVHD after failure of ≥1 line of systemic therapy.
Aims: We present the efficacy and safety results from the randomized, double-blind, placebo-controlled phase 3 iNTEGRATE study (PCYC-1140; NCT02959944) of ibr plus corticosteroids in previously untreated pts with cGVHD.
Methods: Eligible pts (aged ≥12 y) had newly diagnosed moderate/severe cGVHD, required systemic corticosteroid therapy, and had no prior systemic treatment for cGVHD. Pts were randomized 1:1 to receive ibr 420 mg/d or placebo (pbo) in combination with prednisone (pred) starting at 1 mg/kg/d. The primary endpoint was response rate (complete or partial response) at 48 wks per the 2014 NIH Consensus Development Project Criteria. Other endpoints included event-free survival (EFS; ie, survival without cGVHD progression, malignancy relapse, or start of subsequent cGVHD therapy), duration of response (DOR), time to withdrawal of corticosteroids and immunosuppressants (except ibr/pbo), improvement of Lee cGVHD Symptom Scale score, overall survival (OS), and safety.
Results: In total, 95 pts received ibr-pred and 98 received pbo-pred. Baseline pt characteristics were well balanced between treatment arms. Median time on treatment was 5.4 mo and 6.4 mo for ibr-pred and pbo-pred arms, respectively; median follow-up was 25 mo for both arms. At the time of the primary analysis, 41% (39/95) of pts treated with ibr-pred had a response at 48 wk vs 37% (36/98) of pts receiving pbo-pred (p=0.54). Though the primary endpoint of the study was not statistically significant, ibr-pred resulted in clinically meaningful improvements in several other key endpoints, prompting evaluation of these endpoints with a longer follow up (reported p-values are nominal). With extended follow up, median DOR was 16 mo with ibr-pred vs 10 mo with pbo-pred (p=0.12). Median EFS was 15 mo with ibr-pred and 8 mo with pbo-pred (hazard ratio 0.75 [95% CI: 0.53-1.1]; p=0.1; **Figure**). 48% vs 39% (p=0.15) of pts receiving ibr-pred vs pbo-pred withdrew corticosteroids, and 38% vs 28% (p=0.08) withdrew immunosuppressants. 40% of pts in the ibr-pred arm experienced an improvement in overall Lee cGVHD Symptom Scale score vs 29% in the pbo-pred arm (p=0.09). Median OS was not reached in either arm; 22% (21/95) of pts in the ibr-pred arm and 19% (19/98) in the pbo-pred arm died from any cause. 49% (46/94) of pts in the ibr-pred arm and 46% (44/96) in the pbo-pred arm experienced a grade ≥3 serious adverse event (AE); 22% (21/94) and 25% (24/96), respectively, experienced an AE leading to discontinuation of study drug.

Figure. EFS with ibr-pred vs pbo-pred in pts with moderate/severe cGVHD.



Summary/Conclusion: In this randomized, pbo-controlled trial of ibr in combination with corticosteroids for NIH-defined moderate/severe cGVHD, the primary endpoint did not meet statistical significance. However, numerical trends of improved clinical outcomes in the ibr-pred arm were noted, including longer DOR and EFS and improved patient-reported outcomes. Safety was consistent with the known profiles of ibr and pred and was similar between treatment arms. The positive trends observed in other important clinical endpoints along with no additional safety trends and concerns suggest that ibr may have value in some previously untreated pts with cGVHD.

S236 EFFICACY AND SAFETY OF RUXOLITINIB IN PATIENTS WITH STEROID-REFRACTORY ACUTE GRAFT-VS-HOST DISEASE AFTER CROSSOVER IN THE PHASE 3 REACH2 STUDY

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Background: Historically, the long-term prognosis has been poor in patients (pts) with acute graft-vs-host disease (aGVHD) who fail initial treatment with steroids. REACH2 (NCT02913261; N=309) is a randomized, phase 3 trial investigating the efficacy and safety of the Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib (RUX) vs best available therapy (BAT) in pts with steroid-refractory (SR) aGVHD. Pts treated with RUX had a significantly higher overall response rate (ORR) at day 28 (primary endpoint) than pts treated with BAT (62.3%; complete response [CR], 34.4%; partial response [PR], 27.9% vs 39.4% [CR, 19.4%; PR, 20.0%]; P<0.001). Durable ORR at day 56 (key secondary endpoint) was also significantly higher with RUX (39.6% vs 21.9%; P<0.001). Pts randomized to BAT could cross over to RUX after day 28. We report safety and efficacy findings from the crossover group in REACH2.
Aims: To evaluate the efficacy and safety of RUX in pts who crossed over from BAT.
Methods: 309 pts aged ≥12 years diagnosed with grade II-IV SR aGVHD were randomized 1:1 to receive RUX 10 mg bid (n=154) or investigator-selected BAT (n=155). All pts provided written informed consent. After day 28, pts in the BAT arm who did not meet the primary endpoint or lost response could cross over to RUX up to week 24.
Results: Overall, 49 pts (31.6%) crossed over to RUX treatment (data cutoff, January 6, 2020). At baseline, the median age in the crossover group was 54 years (range, 13-71 years) and 53.1% of pts were male; 38.8% and 61.2% of pts had grade II and grade III/IV disease, respectively. Overall, ATG (20.4%) and etanercept (20.4%) were the most common BATs; 12 pts (24.5%) were treated with ≥2 BATs. The median time to crossover was 34 days (range, 28-162 days). At data cutoff, 11 pts (22.4%) had completed the crossover treatment period (treatment up to crossover day 56), and 2 were still receiving RUX. 36 crossover pts (73.5%) discontinued RUX treatment, with the most common reasons for discontinuation being adverse events (AEs; 24.5%), death (16.3%), and lack of efficacy (12.2%). A total of 27 crossover pts (55.1%) entered long-term follow-up.
The ORR at day 28 after crossover was 67.3% (CR, 46.9%; PR, 20.4%; 95% CI, 52.5%–80.1%), and the durable ORR at day 56 after crossover was 42.9% (95% CI, 28.8%–57.8%), both consistent with observations in the RUX arm at the primary analysis (Table). The mean EQ-5D-5L health rating improved in pts who crossed over to RUX (crossover baseline, 51.5; crossover week 24, 80.2).
After crossover, the median duration of treatment with RUX was 61.0 days (range, 2.0-383.0 days). Most pts (93.9%) received RUX 20 mg daily. All 49 pts had a dose change, with 63.3% having a dose interruption; 61.2% had a dose change or interruption due to AEs. Dose re-escalation occurred in 38.8% of pts. The safety profile of RUX after crossover from BAT was consistent with that in the RUX arm, with the most common AEs (≥20%) being anemia (30.6%; grade ≥3, 18.4%), thrombocytopenia (30.6%; 26.5%), hypokalemia (22.4%; 8.2%), and neutropenia (20.4%; 20.4%). There were 19 deaths (38.8%), mainly due to aGVHD (n=8).

Table. Overview of Efficacy in the Ruxolitinib Arm, BAT Arm, and Crossover Group in REACH2

Endpoint, n (%)	RUX (n=154)	BAT (n=155)	Crossover group (n=49)
ORR at day 28	96 (**62.3**)	61 (**39.4**)	33 (**67.3**)
Complete response	53 (34.4)	30 (19.4)	23 (46.9%)
Partial response	43 (27.9)	31 (20.0)	10 (20.4%)
Durable ORR at day 56	61 (**39.6**)	34 (**21.9**)	21 (**42.9**)
Complete response	41 (26.6)	25 (16.1)	19 (38.8)
Partial response	20 (13.0)	9 (5.8)	2 (4.1)

Summary/Conclusion: RUX led to high response rates in pts who crossed over from BAT to RUX. ORR and durable ORR were consistent with those seen with RUX during the randomized period. No new safety signals were observed in crossover pts. These findings support the use of RUX in pts with SR aGVHD who failed treatment with other systemic therapies.

S237 A PHASE 1 TRIAL OF THE HEDGEHOG SIGNALLING INHIBITOR GLASDEGIB IN PATIENTS WITH REFRACTORY SCLEROTIC CHRONIC GRAFT-VERSUS-HOST DISEASE

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Background: Sclerotic chronic graft-versus-host disease (scGVHD) represents a distinctive phenotypic variant of GVHD that is characterized by dermal fibrosis, often resulting in severe morbidity. scGVHD is associated with high rates of steroid refractoriness, and therapeutic options in this setting remain limited. Aberrant hedgehog signaling is prominent in scGVHD, leading to the activation of dermal fibroblasts. Targeted inhibition of the pathway ameliorates scGVHD features in experimental models.
Aims: This investigator-led study (NCT03415867) evaluated the safety profile and preliminary efficacy of glasdegib, an oral antagonist of the hedgehog signalling transducer Smoothened (SMO), in adult patients (pts) with active scGVHD after ≥2 lines of prior therapy.
Methods: The trial followed a standard 3 + 3 escalation dose-finding design. Glasdegib was administered once daily (OD) in continuous 28-day cycles. Treatment could be continued beyond Cycle 12 in pts obtaining objective clinical benefit. The primary endpoints of the study were dose-limiting toxicity (DLT) and maximum tolerated dose (MTD). Secondary endpoints included safety, efficacy, PK/PD and immune correlative studies. Responses were assessed per 2014 NIH cGVHD criteria. Additionally, a modified skin/joint partial response category (mPR) was defined as a NIH cGVHD global severity score decrease ≥2 points in the presence of any significant skin/joint scoring improvement (≥1 point for body surface area, skin features or joints/fascia scores; ≥2 points for skin/joint tightening or P-ROM scores). Data cut-off was at the end of Cycle 12.
Results: Twenty pts have been included in the primary analysis. An additional non-DLT-evaluable pt was replaced early after enrolment in Cohort 1 due to a treatment-unrelated cerebrovascular ischemic event. Median age was 47 years (range 27-72). Enrolled pts had failed a median of 4 prior lines of therapy (range 2-10), 50% having received treatment with ruxolitinib. Three pts were included in Cohort 1 (50 mg OD), 3 in Cohort 2 (100 mg OD) and 16 in the expansion cohort (50 mg OD). Two pts in Cohort 2 experienced a DLT (grade [G] 3 muscle cramps), the MTD being thus established at 50 mg OD. Frequent treatment-emergent G≥2 adverse events (AEs) included muscle cramps (85%), alopecia (40%) and dysgeusia (35%). Two pts developed G3 and G4 treatment-related creatine kinase elevations that required interruption of glasdegib but did not result in study discontinuation. Five pts withdrew from the study as a result of treatment-related AEs, and 10 pts required dose adjustments while on treatment. Ten pts remained on the study at the end of Cycle 12. At the data cut-off, 12 (60%) pts had achieved a NIH global severity score PR, 12 (60%) a joints/fascia response (11 PR, 1 CR) and 3 (15%) a skin PR. An improvement ≥2 points in skin/joint tightening and P-ROM scores was observed in 13 (65%) and 11 (55%) pts, respectively. Overall, 12 (60%) pts obtained a skin/joint mPR, with a median time of 3 months to response and a duration ≥6 months in 7 (35%) pts.
In preliminary analyses, treatment with glasdegib was not associated with significant changes in the distribution of T-cell compartments or TCR diversity.

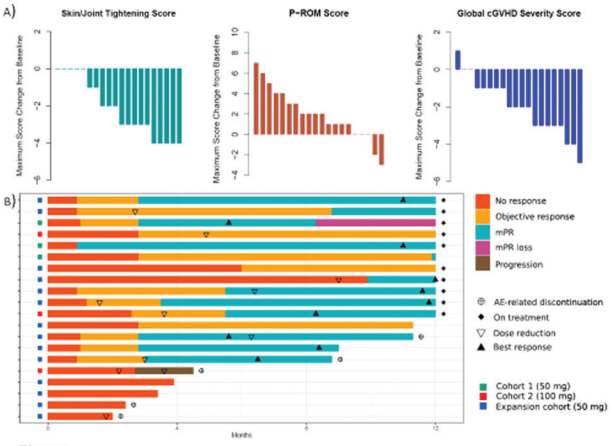


Figure 1.
A) NIH skin/joint tightening, P-ROM and global cGVHD severity scores waterfall plots.
B) Swimmer plot showing treatment courses and clinical outcomes.

Summary/Conclusion: Low doses of glasdegib demonstrate high rates of clinical responses in heavily pretreated pts with scGVHD, resulting in durable responses in one-third of the pts. Treatment schedule adjustments may be required in order to optimise tolerability.

S238 INTERIM RESULTS FROM THE EQUATE STUDY: PRELIMINARY SAFETY AND EFFICACY OF ITOLIZUMAB, A NOVEL TARGETED ANTI-CD6 THERAPY, NEWLY DIAGNOSED ACUTE GRAFT-VERSUS-HOST DISEASE

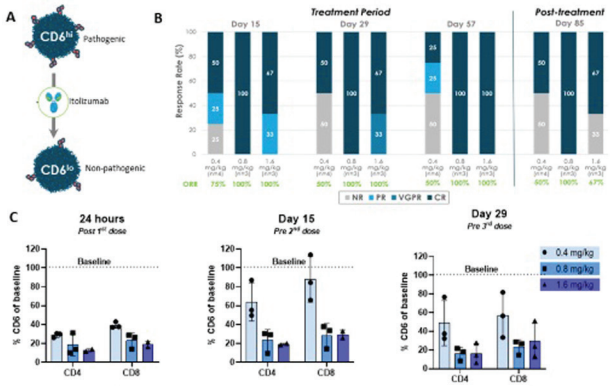
J. Koreth [1,*], A. W. Loren [2], R. Nakamura [3], J. A. Pidala [4], E. K. Waller [5], G. L. Chen [6], S. Anand [7], M. Mielcarek [8], T. Wang [9], J. Pantin [10], G. Meyers [11], M. Schroeder [12], D. Hoda [13], N. Farhadfar [14], J. L. Ferrara [15], K. Polu [16], D. Thomas [16], S. Connelly [16], C. Ng [16], M. Fung [16], L. M. Acevedo [16], J. Rothman [16], C. Cutler [1]

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Background: CD6 is a co-stimulatory receptor predominantly expressed on T cells. $CD6^{high}$ CD4+ T cells were recently shown to drive Th1/Th17 immune responses in inflammatory bowel disease and may have a similar role in acute graft-versus-host disease (aGHVD). The CD6 ligand, activated leukocyte cell adhesion molecule (ALCAM), is expressed on antigen presenting cells, as well as epithelial and endothelial cells of aGVHD target organs (e.g. skin, GI tract). Previous studies in patients receiving allogeneic hematopoietic cell transplants showed that ex vivo depletion of donor CD6+ T cells lowered the incidence of aGVHD, providing a rationale for therapeutically targeting CD6 in aGVHD. Itolizumab is a humanized IgG1 monoclonal antibody that binds CD6 and blocks interaction with ALCAM to inhibit T cell activity and trafficking that is being evaluated as treatment for aGVHD.
Aims: Here we present interim study results from the Primary Cohort of EQUATE, an ongoing US-based Phase 1b/2 study of itolizumab in combination with steroids for newly diagnosed aGVHD.
Methods: Phase 1b is an open-label, dose-escalation study evaluating doses from 0.4 to 2.4 mg/kg (IV Q2 weeks through Day 57). The Primary Cohort enrolled patients with Grade III-IV aGVHD that received itolizumab within 72 hours of first steroid dose. The Expansion Cohort also

includes subjects with Grade II aGVHD and an Ann Arbor [AA] Score of 2 or 3 and who received itolizumab within 7 days of first steroid dose.
Results: A total of 10 subjects in the Primary Cohort have completed treatment through Day 85: 0.4 mg/kg (n=4), 0.8 mg/kg (n=3), and 1.6 mg/kg (n=3). Baseline characteristics were mean age of 48, 90% male, 90% white, 80% with peripheral blood graft source, 80% with HLA matched donor, mean time to GVHD onset of 43 days, and 100% with GI involvement. Mean MAGIC algorithm probability (MAP) was 0.468, and 70% had an AA score of 3. One subject in the 0.4 mg/kg cohort received only one itolizumab dose, whereas all other subjects received 2-5 doses.
Across all doses, the overall response rate (ORR) was 80% at Day 29, with 70% of subjects experiencing a complete response (CR) and 10% experiencing a very good partial response (VGPR). ORR was 70% at Day 85 with 100% of responders experiencing CR (Fig 1B). Response was consistent through Day 169. MAP scores also decreased through Day 85 with a median % decrease from baseline of 18%. At Day 85, median % steroid dose reduction was 89%. Itolizumab dose-dependently decreased CD6 levels on T cells within 24 hours of first dose, which was maintained throughout the treatment period, with a more pronounced effect in the 0.8 and 1.6 mg/kg (Fig 1C).
Safety profile is consistent with that of itolizumab observed to date across other trials and with adverse events (AEs) common in this patient population. All subjects experienced at least 1 AE. Most AEs were mild to moderate in severity. One mild infusion reaction AE was noted. Serious AEs were noted in 5 subjects, including recurrent gut GVHD (n=1), sepsis (n=2; 1 was considered a DLT) and fever (n=1), COVID-19 (n=1) and nocardiosis (n=1), physical deconditioning (n=1), and atrial flutter (n=1). There was one death reported due to an SAE of intestinal infarction deemed not related to study drug. Another death occurred >100 days post dose due to progressive aGVHD and was also not related to study drug.

Figure 1. Itolizumab in aGVHD



A. The expression levels of CD6 are increased on T_{eff} cells (such as Th1, Th2 and Th17 cells) and are associated with autoreactivity and pathogenic phenotype. Itolizumab reduces CD6 expression, and low CD6 expression is associated with a low inflammation, non-pathogenic phenotype. B. Response to itolizumab was observed as early as Day 15 and was sustained at the 2 higher doses through Day 85 CR, complete response; VGPR, very good partial response based on Martin Consensus 2009 Criteria; PR, partial response; NR, no response; PD, progressive disease. C. Cell surface CD6 levels on CD4 and CD8 T cells (based on mean fluorescence intensity) of subjects are presented as % of baseline. Itolizumab dose-dependently reduced the surface levels of CD6 on CD4+ and CD8+ cells by 24 hours following the first dose. CD6 trended toward baseline levels by Day 15 (pre 2nd dose) at the lowest dose of itolizumab (0.4 mg/kg) but not at the 2 higher doses (0.8 and 1.6 mg/kg).

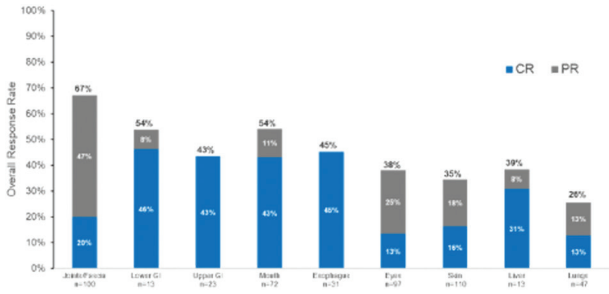
Summary/Conclusion: In summary, the safety and efficacy observed to date and benefit-risk profile support continued study and evaluation in future randomized controlled trials.

S239 BELUMOSUDIL FOR CHRONIC GRAFT-VERSUS HOST DISEASE AFTER 2 OR MORE PRIOR LINES OF THERAPY: THE ROCKSTAR STUDY (KD025-213)

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Background: Belumosudil (KD025) is a novel oral selective rho-associated coiled-coil kinase 2 (ROCK2) inhibitor specifically designed for the treatment of cGVHD, an immune-mediated inflammatory and fibrotic disorder.
Aims: In a previous dose-finding study (KD025-208, N=54), two-thirds of patients achieved a partial or complete response with belumosudil. Herein, we report 12 month updated results from the pivotal randomized phase 2 trial (ROCKstar [KD025-213], N=132).
Methods: We randomly assigned cGVHD patients (pts) after 2-5 prior lines of therapy (LOT) to belumosudil 200mg QD (n=66), or belumosudil 200mg BID (n=66), across 28 sites, stratified according to cGVHD severity and prior ibrutinib use. The primary endpoint was the overall response rate (ORR) per 2014 NIH response criteria, assessed by investigators. Additional endpoints include duration of response, Failure-Free Survival (FFS), improvement in symptoms based on change in Lee symptom score (LSS) and corticosteroid (CS) dose reductions or discontinuations. Treatment was until clinically significant progression or unacceptable toxicity.
Results: Pooled baseline characteristics of the two arms revealed a median age of 56 (21-77); median prior LOT 3; median time from cGVHD diagnosis 29 mos (2-162); 67% with NIH defined severe cGVHD; 34% with prior ibrutinib use; 52% with ≥ 4 organ involvement; and 72% refractory to prior line of therapy
The ORR [95% CI] was 73% [60, 83] with belumosudil QD and 77% [65, 87] with belumosudil BID. Responses were consistent across key subgroups and complete responses were observed in all organ systems as shown in Figure 1. Furthermore, in patients with previous ibrutinib or ruxolitinib use, ORRs were 74% [59, 86] and 68% [51, 83], respectively. The median DOR was 50 weeks. FFS was 76% (68%>83%) at 6 months. Sixty percent pts reported a clinically meaningful improvement (≥7 point reduction) in LSS score. Corticosteroids were discontinued in 21% of patients.
Belumosudil was well tolerated, and AEs were consistent with those expected in this population. AEs (QD, BID) in >20% pts were fatigue (38%), diarrhea (33%), nausea (31%), cough (28%), upper respiratory infections (27%), dyspnea (25%), headache (24%), peripheral edema (23%), vomiting (21%) and muscle spasms (20%). At least 1 serious AE occurred in 38% of patients. Fourteen patients died during the study; 8 due to AEs (2 possibly related to belumosudil) and 6 during long term follow-up (>28 days after last dose). There was a report of 1 case of Epstein-Barr viremia, and 1 report of cytomegalovirus reactivation.



Summary/Conclusion: Treatment with belumosudil was well tolerated at both doses and resulted in high ORRs across key subgroups, meeting the primary end point of this pivotal randomized trial in cGVHD. Responses were durable and clinically meaningful, irrespective of patient and cGVHD characteristics and organ involvement.

Stem cell transplantation - Clinical

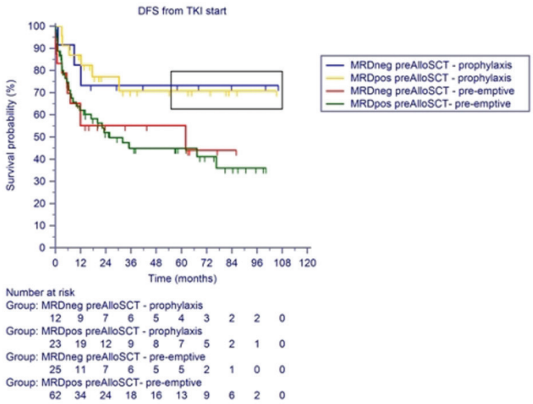
S240 PROPHYLACTIC OR PRE-EMPTIVE USE OF TYROSINE KINASE INHIBITORS POST-ALLOGENEIC STEM CELL TRANSPLANTATION IN BCR-ABL POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA: A SUBANALYSIS OF GITMO PH-POSITIVE ALL STUDY.

A. Candoni [1,*], D. Lazzarotto [1], F. Bonifazi [2], M. V. Dubbini [1], P. Bresciani [3], A. Busca [4], A. Rambaldi [5], W. Arcese [6], A. P. Iori [7], F. Ciceri [8], R. Sorasio [9], G. Irrera [10], R. Fanin [11]

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Regionale Trapianto Cellule Staminali e Terapie Cellulari A. Neri, Grande Ospedale Metropolitano Bianchi-Melacrino-Morelli, Reggio Calabria, [11]University Hospital of Udine- ASUFC, Division of Hematology and SCT-DAME, Udine, Italy

Background: The use of Tyrosine Kinase Inhibitors (TKIs) post-allogeneic hematopoietic stem cell transplant (post-Allo-SCT) is still heterogeneous and their preventive effect on relapse is not clearly established.
Aims: We performed a sub-analysis, focused on this aspect, of the recent published GITMO study (*Candoni et al, BBMT 2019-ClinicalTrials.gov NCT03821727*) that included 441 adult patients with Ph-pos ALL, all treated in the induction phase with TKIs± chemotherapy and undergoing Allo-SCT from 2005 to 2017.
Methods: Only cases in morphological complete remission (CcR) before Allo-SCT and receiving a TKI post-Allo-SCT were included in this analysis, regardless of the pre Allo-SCT Minimal Residual Disease (MRD) status (positive or negative). Patients who started TKIs post-Allo-SCT in a condition of cytological relapse were excluded from this study. MRD (BCR-ABL) was monitored monthly for the first 6 months post Allo-SCT and then every 2 months. TKIs were administered after Allo-SCT prophylactically (starting with MRD neg post-Allo-SCT) or pre-emptively (starting at the first MRD positivity post-SCT and without hematological relapse). The attempt of this analysis was to assess the strategy of use of TKIs post-Allo-SCT (prophylactic or pre-emptive) in patients transplanted while in CcR and to verify the probability of survival and leukemia free survival (OS and DFS) post Allo-SCT, based on TKI strategy adopted (prophylactic or pre-emptive) and according to the MRD status pre-Allo-SCT.
Results: We identified and analyzed 122 cases (85 MRD positive pre-Allo-SCT and 37 MRD negative) that met the inclusion criteria. A pre-emptive TKI strategy was adopted in 87/122-71% cases (25 with MRD neg pre-Allo-SCT) and a prophylactic strategy in 35/122-29% (12 with MRD neg pre-Allo-SCT). The 35 patients treated with TKIs prophylactically started treatment earlier, at a median of 2.97 months (range 0.57-14.17) from Allo-SCT, than the 87 patients treated pre-emptively, which started TKI at a median of 4.37 months (range 0.87-44.27) from Allo-SCT (p=0,01). In the cohort of the MRD pos pre-Allo-SCT, the cases treated pre-emptively had a significant higher percentage of cytological relapse (REL) post-Allo-SCT compared to the cases treated with TKIs prophylactically (cytologic relapse 37% vs 13%, p=0,03). The 5 yrs OS and DFS post Allo-SCT of patients who started TKI in prophylaxis were significantly better (OS 72% and DFS 72%) than those who started TKI in pre-emptive (OS 58% and DFS 47%) regardless of the status of pre-transplant MRD (p=0,008)-**FIGURE 1-DFS.**



Summary/Conclusion: The data obtained from this analysis in a homogeneous population of Ph-pos ALL who underwent Allo-SCT while in CcR, although with the caution of a retrospective study, support the prophylactic use of TKIs post-Allo-SCT as optimal maintenance strategy, resulting in a higher probability of DFS regardless of the MRD status pre-Allo-SCT.

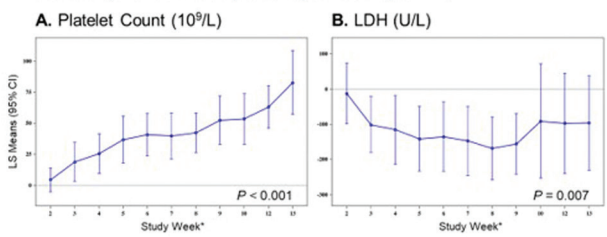
S241 NARSOPLIMAB (OMS721) TREATMENT CONTRIBUTES TO IMPROVEMENTS IN ORGAN FUNCTION IN ADULT PATIENTS WITH HIGH-RISK TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a serious complication of hematopoietic stem cell transplantation that is associated with significant mortality and morbidity and for which there is currently no approved therapy. TA-TMA results from endothelial injury caused by conditioning regimens, immunosuppressants, infection, and GVHD, which in turn activates the lectin pathway of complement.
Aims: Narsoplimab, an inhibitor of mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway and an activator of the coagulation cascade, was studied for treatment of TA-TMA.
Methods: This was a single-arm open-label pivotal trial in adult TA-TMA patients (NCT02222545). All patients provided informed consent. Protocol-specified treatment consisted of IV narsoplimab 4 mg/kg or 370 mg once weekly for 4 or 8 weeks with a 6-week follow-up period. The FDA-agreed primary endpoint required clinical improvements in each of 2 categories: 1) laboratory markers of TMA (platelet count and LDH) *and* 2) organ function (kidney, pulmonary, gastrointestinal, or neurological) or freedom from transfusion (platelets and/or red blood cells). Secondary endpoints included change from baseline in platelet count, LDH, hemoglobin, and haptoglobin. Patients receiving at least 1 dose of narsoplimab (full analysis set [FAS]; N=28) and patients receiving the protocol-specified narsoplimab treatment of at least 4 once-weekly doses (per-protocol [PP]; N=23) were analyzed.
Results: Patients were at high risk for poor outcomes and had multiple comorbidities: kidney and neurological dysfunction were present in 75% (21/28) and 57% (16/28) of patients, respectively, at baseline. Patients received a range of 2–8 scheduled doses of narsoplimab (mean 6.3 doses) and median duration of treatment was 8 weeks. Narsoplimab treatment resulted in clinical response (achievement of the primary endpoint) in 61% (17/28) of the FAS and in 74% (17/23) of the PP population, based on improvements in both laboratory TMA markers and clinical status (organ function and transfusion burden). The time to hematological response (defined as time from first narsoplimab dose to time of achieving both platelet count and LDH primary endpoint criteria) was as early as 7 days (median 36 days) after start of treatment. There was a sustained improvement in platelet count and LDH change from baseline (**Figure 1**). Five patients never achieved platelet engraftment following transplant and were not included in the platelet count analysis. Improvements in kidney function, neurological function, or gastrointestinal function were observed in 67% (18/27), 50% (3/6), and 100% (1/1), respectively, in the FAS and 68% (15/22), 50% (3/6), and 100% (1/1), respectively, in the PP. No patients were evaluable for improvement in pulmonary function. Of patients who received transfusions at baseline, 48% (12/25) in the FAS and 55% (11/20) in the PP achieved freedom from platelet and red blood cell transfusion. Six patients died during the core study period: 1 of septic shock, 2 of progressive AML, 2 of neutropenic sepsis, and 1 of GVHD and TMA. These deaths occurred 3–42 days following the last narsoplimab dose.

Figure 1. Least Squares Means Change from Baseline for Laboratory TMA Markers (Full Analysis Set Population)



* No patient data were censored; all available data were included.
P-values from time-weighted average change from baseline using one-sample *t*-test.

Summary/Conclusion: In this high-risk patient population with TA-TMA, there were no safety concerns observed with narsoplimab, and treatment resulted in clinically meaningful improvements in laboratory markers of TMA and in organ function or freedom from transfusion.

S242 FLUDARABINE AND TBI 8 GY VERSUS FLUDARABINE AND TREOSULFAN CONDITIONING IN PATIENTS WITH AML IN FIRST COMPLETE REMISSION: A STUDY FROM THE ACUTE LEUKEMIA WORKING PARTY OF THE EBMT

G. Bug [1,*], M. Labopin [2], R. Niittyvuopio [3], M. Stelljes [4], H. C. Reinhardt [5], I. Hilgendorf [6], N. Kröger [7], A. Kaare [8], W. Bethge [9], K. Schäfer-Eckart [10], M. Verbeek [11], S. Mielke [12], K. Carlson [13], A. Bazarbachi [14], A. Spyridonidis [15], B. N. Savani [16], A. Nagler [17], M. Mohty [18]

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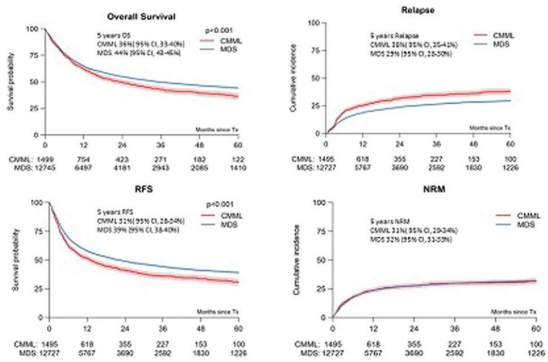
Background: Relapse remains the main cause of treatment failure after allogeneic stem cell transplantation (HSCT) for acute myeloid leukemia (AML) in first complete remission (CR1). The antileukemic activity of myeloablative conditioning is often counterbalanced by an age-dependent increase in non-relapse mortality (NRM). For AML patients >40 years, fludarabine plus a reduced dose of TBI (8Gy) (FluTBI) has yielded favorable long-term outcomes (CIR 30%, NRM 13%; Fasslrinner F et al., Lancet Haematology 2018). Similar data have been obtained with flu plus treosulfan (FT), which is being increasingly used due to its low NRM (Beelen DW et al., Lancet Haematology 2020).
Aims: As no direct comparison of these two conditioning regimens has yet been conducted, we assessed antileukemic activity and safety of FluTBI and FT (30, 36 or 42 mg/m^2) in patients with AML transplanted in CR1.
Methods: This retrospective analysis of data from the EBMT registry included 754 AML (617 FT, 137 FluTBI) patients aged >40 years who underwent a first HSCT in CR1 from 2009-2019. Allografts were from matched siblings (MSD) or 10/10 HLA-matched unrelated donors (MUD). Using propensity score matching, 115 FluTBI patients were pair-matched with 115 FT (exact matching for donor, sAML, adverse cytogenetics and nearest neighbor for age, time diagnosis-HSCT, female to male, Karnofsky performance score (KPS) and in vivo T cell depletion).
Results: Patient characteristics were well balanced in the FluTBI and FT groups with respect to age (median 55.2 [40.1-70.7] vs 54.9 [40.4-74.9] years, KPS <90% (22.6 vs 23.5%), sAML (13% each), adverse cytogenetics (15.7% each), female donor to male recipient (19.1% vs 17.4%) and time from diagnosis to HSCT (median 3.8 (range, 1.8-16.2) vs 4.5 (1.7-16.2) months). An identical proportion of patients in both groups received grafts from MSD (61.7%) and MUD (38.3%). Graft versus host disease (GVHD) prophylaxis was predominantly cyclosporine A (CSA) and methotrexate (85.2 vs 73.9%) or CSA and mycophenolate mofetil (8.7 vs 18.3%), respectively. Additional in vivo T cell depletion with ATG was given in 52.2% and 53.9% of patients, respectively. Median follow-up is 42.4 months (range, 31.5-53.8) in the FluTBI and 23.2 months (20.4-32.7) in the FT group (p=0.14). All but one patient in each group engrafted. FluTBI was associated with a significantly lower relapse incidence (CIR) of 18.3 vs 34.7%, p=0.018, HR 0.51 (95% CI, 0.29-0.89), but higher NRM of 16.8 vs 5.3%, p=0.02, HR 3.0 (1.19-7.59). Infection was the leading cause of death following FluTBI (n=12/38, 31.6%), followed by AML (10/26.3%), GVHD (6/15.7%), interstitial pneumonia (4/10.5%) and secondary malignancy (2/5.3%). In the FT group, 33 patients died, 15 from AML (45.5%), 7 from GVHD (21.2%), and 3 from infection or multiorgan failure (9.1% each), respectively. There was no statistically significant difference between FluTBI and FT in the CI of acute GVHD II-IV (22.8 vs 20.7%; HR 1.05), GVHD III-IV (6.2 vs 9.0%; HR 0.59), chronic GvHD (42.6 vs 47.5%; HR 0.81) or extensive chronic GVHD (16.8 vs 19.6%; HR 0.76). At 2 years, leukemia-free and overall survival were similar in the FluTBI and FT groups (64.9 vs 60.0%, HR 0.84 (0.54-1.31) and 66.9 vs 67.8%, HR 1.08 (0.67-1.75), respectively, with favorable GVHD-free and relapse-free survival in both groups (50.3 vs 45.6%; HR 0.83 [0.58-1.17]).
Summary/Conclusion: Outcomes in LFS, OS and GRFS did not differ between FluTBI and FT. Relapse was lower while NRM higher with FluTBI which may indicate a more intense conditioning.

S243 CMML PATIENTS UNDERGOING ALLOGENEIC HCT HAVE INFERIOR SURVIVAL OUTCOMES IN COMPARISON WITH MDS PATIENTS DUE TO A SIGNIFICANTLY HIGHER RELAPSE RATE. A REGISTRY STUDY OF THE EBMT-CMWP

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Background: The FAB Group originally classified CMML as a form of MDS. In 2001, the World Health Organization reclassified the disease as part of a newly created MDS/MPN overlap entity. Even though characterized by high mortality and relapse rates, allo-HCT remains the only curative treatment for both CMML and MDS.
Aims: In this retrospective registry study, we aimed to identify factors associated with allo-HCT outcomes in CMML, particularly focusing on age, and to compare them with MDS outcomes.
Methods: Patients ≥18 years old who underwent allo-HCT for CMML or MDS between 2010 and 2018 and who were reported to the EBMT registry were included in the analysis. Transformation to AML was an exclusion criterion. CMML outcomes were compared to those of the MDS population transplanted in the same period. Overall Survival (OS) and Relapse Free Survival (RFS) rates were estimated by Kaplan-Meier methods; relapse incidence (REL) and NRM were analyzed as competing risks. Adjusted (cause specific) hazard ratios (HR) were obtained using Cox proportional hazard models. Age was modeled as a continuous linear variable and using restricted cubic splines.
Results: There were 1,499 CMML patients with a median age of 60.4 (18.9-76.3) years and 69.4% were male. 27% had a Karnofsky status ≤80 and 23% of patients had a Sorror HCT-CI ≥3. 28% had HLA-identical sibling donors, 63% unrelated (MUD or MMUD) donors and 8.3% mismatched related donors. A RIC regimen was used in 62%. There were 12,745 MDS patients with a median age of 59.1 (18-79.7) years and 61.1% were male. Regarding Karnofsky scores, Sorror HCT-CI scores, donor types, conditioning regimens and the rates of primary graft failure, there were no clinically meaningful differences between the CMML and MDS groups. OS, RFS and REL rates, were significantly worse in CMML when compared to MDS (all p<0.0001) whereas NRM was not significantly different, p=0.87 (Figure 1). For CMML, the HR for age as a continuous variable at transplantation (adjusted for other confounders), for each 10-year increase of age, was 1.16 (1.06-1.28) for OS and 1.13 (1.04-1.23) for RFS. The HRs for REL and NRM were 1.06 (0.95-1.19) and 1.21 (1.06-1.37) for each 10-year increase in age, respectively. Age≥65 years in the adjusted model conferred a negative impact on OS, RFS and NRM. The same analysis for MDS shows similar results for each 10-year increase of age as those observed for CMML.



Summary/Conclusion: The comparison of OS, RFS and REL shows significantly worse outcomes in CMML compared to MDS, with no difference in NRM. As expected, age was associated with poorer outcomes in both diseases. Despite observing these significant differences in survival rates between CMML and MDS, we were not able to identify specific factors other than the diseases themselves. The poorer survival outcomes in CMML in comparison to MDS appear to be the consequence of the significantly higher rate of post-transplant relapse. Future research should focus on post-transplant strategies to improve disease control.

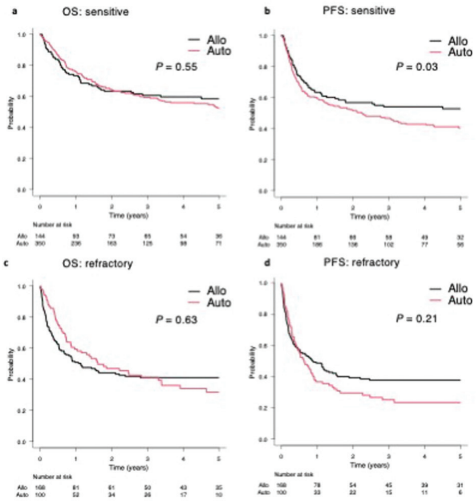
S244 AUTOLOGOUS OR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR PERIPHERAL T-CELL LYMPHOMA-NOT OTHERWISE SPECIFIED AND ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA FAILING FIRST-LINE THERAPY

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Background: Management of the patients with peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL) who failed first-line therapy is a difficult challenge. Salvage chemotherapy followed by autologous hematopoietic cell transplantation (auto-HCT) or allogeneic HCT (allo-HCT) represents the treatment of choice for appropriate candidates. However, there is no consensus on which type of HCT should be applied for such patients.
Aims: To evaluate the impact of auto- or allo-HCT on outcome in PTCL-NOS and AITL failing first-line therapy.
Methods: We performed a retrospective analysis using registry data from the Japan Society for Hematopoietic Cell Transplantation. Adult patients who underwent a first HCT after 2, 3, or 4 lines of therapy —which means first-line therapy failed for some reason— between 2006 and 2018 were included.
Results: A total of 762 patients with PTCL-NOS (n = 449) and AITL (n = 313) undergoing auto-HCT (n = 450) or allo-HCT (n = 312) as their first HCT were analyzed. Among them, 494 were chemo-sensitive (172 were first complete-remission, 112 were first partial-remission, and 210 were relapsed-sensitive) and 268 were chemo-refractory (142 were primary-refractory and 126 were relapsed-refractory). The allo-HCT recipients were more likely younger (median ages, 53 vs 58 years; $P < 0.001$), received more than 2 lines of therapy prior to HCT (63% vs 33%; $P < 0.001$), with higher HCT-comorbidity index ($P < 0.001$) and with worse performance status ($P < 0.001$) compared with the auto-HCT recipients. The time from the diagnosis to auto-HCT and allo-HCT were 11 months (range = 2-214) and 11 months (range = 2-154) ($P = 0.64$), respectively. The median follow-up duration for survivors of auto-HCT and allo-HCT were 36 months (range = 1-150) and 54 months (range = 3-160), respectively. For chemo-sensitive patients, the 4-year overall survival (OS) of auto-HCT and allo-HCT recipients were 56% (95% CI: 49.9-61.7) and 59.8% (95% CI: 50.8-67.8), and the 4-year progression-free survival (PFS) of both groups were 43% (95% CI: 37.2-48.6) and 54.2% (45.2-62.2), respectively (Figure). For chemo-refractory patients, the 4-year OS of auto-HCT and allo-HCT were 34.1% (95% CI: 23.5-44.9) and 41.1% (95% CI: 33.4-48.7), and 4-year PFS of both groups were 23.4% (95% CI: 14.9-33) and 37.8% (95% CI: 30.2-45.2), respectively (Figure). The 2-year non-relapse mortality of auto-HCT and allo-HCT recipients with chemo-sensitive disease were 9.7% (95% CI: 6.7-13.3) and 23.3% (95% CI: 16.6-30.7), while those with chemo-refractory disease were 9.7% (95% CI: 4.7-16.8) and 36.3% (95% CI: 29-43.7), respectively. In the multivariable cox analysis, allo-HCT was a significantly better prognostic factor for PFS in chemo-sensitive patients (hazard ratio [HR], 0.68; 95% CI: 0.5-0.92; $P = 0.01$), and marginally better for PFS in.chemo-refractory patients (HR, 0.73; 95% CI: 0.52-1.01; $P = 0.06$). The subgroup analyses suggested that allo-HCT tended to be associated with better OS for relapsed-sensitive disease (HR 0.61; 95% CI: 0.36-1.04; $P = 0.07$) among chemo-sensitive patients, and primary-refractory disease (HR 0.51; 95% CI: 0.29-0.89; $P = 0.02$) among chemo-refractory patients.

Figure Auto- vs Allo-HCT on outcomes stratified with chemo-sensitivity



Summary/Conclusion: These data showed allo-HCT for PTCL-NOS and AITL failing first-line therapy can result in comparable survival outcomes despite being with more unfavorable factors compared with auto-HCT. Patients with relapsed-sensitive and primary-refractory disease may be a good candidate for allo-HCT if suitable donor is available.

Stem cell biology and microenvironment

S245 INFLAMMATORY-RESPONDING MESENCHYMAL STROMAL CELLS MODULATE THE DYNAMIC BONE MARROW MICROENVIRONMENT RESPONSE TO STRESS

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Background: Inflammation is a key component in a complex biological response of the body to harmful stimuli. In the context of the bone marrow (BM), inflammation is an overarching process central to most if not all forms of stress challenges and disease setting. Current research in the field is focused on understanding inflammation in the context of the Hematopoietic Stem Cell (HSC) and its microenvironment response. While such research provides a descriptive understanding of the microenvironment and its interplay, it falls short in translating into functional applications confounded by a single marker approach of classifying the microenvironment cell diversity.
Aims: To utilize the power of single-cell sequencing coupled with functional proliferation readout to investigate inflammation response over time of an unbiased BM microenvironment.

Methods: We studied the murine BM response to IFNα driven inflammatory stress over time (early- 3 hours, mid- 24 hours and late- 72 hours), using single-cell transcriptomics coupled to FACS based proliferation analysis at each time point (n=3/4 for each time point). We utilized the GFP tagged interferon-stimulated gene (ISG) report mouse model to substantiate our findings. Moreover, we validated our findings in multiple BM populations using genetic mouse models lacking crucial IFNα pathway elements ($IFNAR^{-/-}$ and $STAT1^{-/-}$). Further, to unravel the BM stromal and HSC crosstalk dynamics we performed mouse matched bulk RNA sequencing of the two populations over time (n=3/4 for each time point).
Results: We identify and describe a unique inflammatory-responding Mesenchymal Stromal Cell subset (iMSC) which unlike its BM stromal counterpart responds directly and dynamically to IFNα stimulation. We show that iMSCs specifically produce key inflammation cytokines and secreted factors at the onset of IFNα response (3h). They markedly downregulate Extra Cellular Matrix (ECM) production and thus facilitate microenvironment remodeling at a late time point (24-72h). Using ligand-receptor mapping, we further identified pivotal inflammation-specific interactions between iMSCs and HSCs within the BM.
Summary/Conclusion: We propose a distinctive iMSC signature with direct application in unraveling inflammation dynamics of the BM microenvironment. The proposed iMSC signature has the potential to significantly contribute to our understanding of BM microenvironment perturbations in disease settings, like leukemia and immunodeficiencies.

S246 DORMANCY PROTECTS FUNCTIONAL POTENTIAL OF HEMATOPOIETIC STEM CELLS UNDER HOMEOSTATIC AND STRESS CONDITIONS

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Background: Hematopoietic stem cells (HSCs) are responsible for maintaining blood cell production throughout the lifetime of an organism. In the unperturbed state, they mainly remain quiescent, although they do occasionally enter the cell cycle to meet homeostatic demands of the mature blood cell production. Upon stress, such as inflammation, severe blood loss or chemotherapy, HSCs mount a massive proliferative response to enable elevated production of peripheral blood cells. Previously, our group has linked inflammatory-stress induced exit from dormancy with a decrease in the HSC functional potential (Walter et al, 2015, Nature).
Aims: We wanted to investigate if the HSC attrition was specific to the inflammatory challenge used in our previous research or there was a general link between dormancy and functional potential regardless of the stress-stimuli used. Therefore, we used alternative inflammatory and non-inflammatory stimuli that have been shown to promote HSC cycling.
Methods: We used the ScltTA H2B-GFP mouse model to facilitate tracking of the HSC divisional history. Mice were either repeatedly treated with lipopolysaccharide (LPS); fluorouracil (5-FU); or were serially bled. Mice were then allowed to recover for 4 weeks prior to end point analysis, in which we assessed HSC divisional history as well as its relationship to the self-renewal, differentiation and engraftment potency via in vitro proliferation and differentiation assay as well as via transplantation of the FACS sorted HSCs into lethally irradiated recipient mice.
Results: None of the treatment regimens led to sustained suppression of peripheral blood cell counts, indicating a remarkable capability of the hematopoietic system to sustain mature blood production. The bleeding protocol did not lead to an increase in HSC divisional history despite previous reports on upregulation of Ki67 staining in the HSC pool of the serially bled mice. LPS treatment, on the other hand, led to an increase in HSC exit from dormancy and 5-FU challenge resulted in the activation of the entire HSC pool. In the case of all three treatments, HSCs which have divided extensively exerted decreased functional potency in the in vitro assay as well as in vivo in transplantation studies.
Summary/Conclusion: Our data reveals a remarkable capability of HSCs to sustain mature blood cell production under conditions of severe stress imposed by inflammation, repetitive loss of large blood volumes and recurring exposure to cytotoxic chemotherapeutic agents. The HSCs that have engaged into the cell cycle showed loss of functional potency providing further evidence that dormancy indeed protects HSC's potency and that this is irrespective of the type of stimuli used. We would also suggest that this outcome suggests that HSCs do not undergo self-renewal divisions following exposure to such stimuli. In contrast to LPS and 5-FU treatment, and despite the fact that more than 70% of the total blood volume was removed on three separate occasions, the bleeding protocol did not cause dormant label-retaining HSCs into cycle. This could be explained by blood cell production being sustained under these conditions by either non-label retaining "active HSCs, or more differentiated progenitors. We are currently further investigating the effect that serial bleeding has on hematopoietic progenitor cells as well as HSC dormancy and the relationship between dormancy and functional potential after applying doses of 5-FU that do not activate the entire HSC pool.

S247 MICROENVIRONMENTAL SFRP1 REGULATES REPOPULATING ACTIVITY OF HEMATOPOIETIC STEM CELLS VIA PP2A-MEDIATED REGULATION OF CTNNB1/EP300

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Background: We have previously found that a *Sfrp1* knock-out environment fails to support the regeneration of hematopoetic stem cells (HSC) with the ability to repopulate secondary recipients (Renström et al., 2009).
Aims: We here aim to dissect cell specific requirements of the *Sfrp1* gene in the hematopoietic microenvironment.
Methods: To study the relevance of *Sfrp1* in niche cells for the maintenance of HSCs, we established the Sfrp1flox/flox mouse strain and deleted *Sfrp1* gene specifically in Osterix+ (Sp7) osteolineage cells (Osx-Cre, Sfrp1Δ/Δ, shortened to OS1Δ/Δ mice).
Results: In these OS1Δ/Δ mice, the number of MSCs is reduced, but these show an increased proportion of colony forming units (CFU-F). Furthermore, stromal cells grown ex-vivo show increased senescence-associated β-galactosidase staining. In the hematopoietic compartment of these mice, we found a decrease in myeloid progenitors in the bone marrow (BM), but, the number of HSC-enriched CD34- CD48- CD150+ HSCs (CD34- SLAM cells) in the BM was unchanged, CD34- SLAM cells from OS1Δ/Δ mice show severely reduced frequency of repopulating HSCs. In single cell cultures, we found that CD34- SLAM cells from OS1Δ/Δ mice show poor proliferation with concomitant increased differentiation into mature myeloid cells. As in embryonic stem cells, differentiation is driven by a β-catenin/p300 complex (Miyabayashi et al., 2007), we hypothesized that this complex also drives HSC differentiation. Indeed, both β-catenin and p300 were expressed at higher levels in CD34- SLAM cells from OS1Δ/Δ mice. To disrupt the β-catenin/p300 complex, we inhibited complex formation by targeting p300 phosphorylation using a specific PP2A inhibitor IQ-1. In *in vitro* experiments, IQ-1 treatment rescued the aberrant behavior of OS1Δ/Δ CD34- SLAM cells. More importantly *in vivo* IQ-1 treatment also restored the serial repopulating activity of CD34- SLAM cells OS1Δ/Δ mice *in vivo*. Renstroem, et al., Cell Stem Cell. 2009; 5: 157-67 Miyabayashi et al., Proc Natl Acad Sci U S A. 2007; 104: 5668-73.
Summary/Conclusion: Our results indicate that deletion of stromal Sfrp1 in niche cells diminishes the repopulating activity of HSCs by increasing their differentiation through PP2A-mediated dephosphorylation of the phospho-Ep300-binding site with β-catenin.

S248 LOW-CYTOKINE ENVIRONMENT DETERMINES THE OUTCOME OF EMBRYONIC HEMATOPOIESIS IN MOUSE FETAL LIVER

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Background: Hematopoietic stem cells (HSCs) are at the top of the hierarchy of the blood system. In the adult, they reside in the bone marrow, where they are mostly quiescent, only dividing to maintain the stem cell pool. During embryonic development, HSCs colonize the fetal liver where they expand. The fetal liver microenvironment is assumed to support HSC proliferation and is the only organ that provides the conditions for physiological HSC expansion. HSC transplantation is a widely used cell therapy in numerous disorders, including immunodeficiencies and leukemias. However, this therapy is still associated with high mortality rates, mainly due to infection, graft-versus-host disease (GvHD), and organ dysfunction, urging the need to improve the therapeutics. Robust and

reproducible conditions to expand HSCs *ex vivo* would allow attaining sufficient numbers to reconstitute hematopoiesis in adult patients.
Aims: Understand the complexity of the HSC microenvironment in the fetal liver that promotes HSC expansion and differentiation into distinct lineages, to devise efficient strategies for HSC expansion *ex vivo*.
Methods: We characterized the stromal compartment of the fetal liver by spectral flow cytometry, and identified cytokine-producing cells by single-cell gene expression analysis. To localize the stromal cells in the tissue we used confocal microscopy in thin and thick sections, allowing a 3D reconstruction of the tissue microanatomy. For lineage tracing of yolk-sac erythromyeloid progenitors or HSCs, we used transgenic mice models.
Results: Characterization of fetal liver from E10-newborn revealed that the non-hematopoietic compartment represents only around 5% of total cells. Analysis of hepatoblasts, endothelial, perivascular, and mesothelial cells showed that all subsets express relevant but distinct patterns of hematopoietic cytokines. The chemoattractant *Cxcl12*, produced by perivascular cells, is the most expressed factor across liver development, while other cytokines such as *Epo* and *Il7* are expressed at low-levels by hepatoblasts. *In situ* analysis showed that from the early stages of liver development, c-Kit^{+} hematopoietic cells are abundant close to the mesothelium and distinct hematopoietic lineages accumulate around blood vessels at E16.5. Lineage tracing experiments showed that, opposite to previous views, HSCs do not contribute to erythrocyte production up until birth, indicating that HSC differentiation in the embryo is skewed. We demonstrate that the low-levels of erythropoietin in the fetal liver confer a selective advantage of yolk sac-derived erythroid progenitors over HSC-derived progeny in the production of red blood cells.
Summary/Conclusion: Altogether, our work supports the premise that embryonic hematopoiesis is influenced by distinct niche cells that cooperate to provide the signals required for expansion and/or differentiation of hematopoietic stem and progenitor cells.

S249 REDUCED LEVELS OF THROMBOPOIETIN CONTRIBUTE TO IMPAIRED HEMATOPOIETIC STEM CELL FUNCTION AND DEFECTIVE MEGAKARYOPOIESIS IN BETA-THALASSEMIA

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Background: In the last decade many studies unraveled the regulation of the bone marrow (BM) niche and hematopoietic stem cells (HSC) in steady state conditions and malignancies, but HSC-niche interactions are still underexplored in inherited disorders. We have recently provided the first demonstration of impaired HSC function caused by an altered BM stromal niche in a non-malignant disease, beta-thalassemia (BT) (*Aprile et al., Blood 2020*). BT is a congenital severe anemia and it is corrected by HSC transplantation from normal donors or by gene therapy with autologous HSC. In addition to the BM stroma, we found altered levels of multiple local and systemic factors, including reduction of systemic thrombopoietin (TPO).
Aims: Further investigation of the BM alterations is pivotal to develop supportive therapies to ameliorate the BM niche and preserve long-term HSC. To this aim, we defined the role of defective TPO on HSC and BM microenvironment.
Methods: Gene expression profiling of HSC and megakaryocytes (Mk) from *Hbb*$^{th3/+}$ (*th3*) BT mice was assessed by RNA-seq analysis. Flow cytometry characterization, *in vitro* Mk maturation, histological analysis on the BM of BT mice and patients, *in vivo* biogenesis, half-life and *in vitro* phagocytosis assays were performed. *In vivo* stimulation of TPO was evaluated.
Results: Since TPO is a key regulator of both HSC and Mk, we investigated the dual role of TPO defect in BT. RNA-seq profiling revealed a downregulation of TPO signaling and target stemness genes in *th3* HSC, including *Cdkn1a*, *Hoxa9* and *Hoxb4*, negatively affecting HSC function. The decreased TPO causes a reduced commitment of HSC towards the Mk lineage, with under-expression of Mk-biased genes and lower frequency of CD41^{+}CD9^{high} HSC. *In vivo* stimulation of TPO axis in *th3* mice restored the pool of quiescent HSC, thus demonstrating the contribution of defective TPO signaling in altering BT HSC.
Consistently, histopathological analyses of *th3* mice showed dysmegakaryopoiesis and this defect was confirmed in BM sections from BT patients. Evaluation of Mk nuclear content revealed a decreased maturation of Mk, with loss of the mature polyploid profile. These findings correlate with a reduced *in vivo* Plt biogenesis and impaired *in vitro* differentiation of *th3* Mk. Sorted BT Mk showed the downregulation of niche factors, as *Pf4*, *Cxcl12*, *TnC*, relevant for HSC maintenance. We highlighted a reduced expression of extracellular matrix molecules by BT Mk, whereas overexpression of IFN response genes. Since Mk play a direct role on HSC activity, we are investigating by *in vivo* and imaging studies their contribution to the impaired HSC-niche crosstalk in BT.
We explored the origin of TPO defect: TPO levels fluctuate in response to platelet (Plt) number and its reduction in *th3* mice is associated to the increased count of Plt. A negative correlation between Plt and TPO was confirmed in BT patients. *In vivo* labeling revealed a higher half-life of BT Plt, which accumulate in the circulation because of a reduced clearance by *th3* spleen phagocytes, as assessed by phagocytosis assays. Iron overload and extramedullary erythropoiesis in BT spleen might cause the impaired phagocytic activity.
Summary/Conclusion: Our results uncovered the underexplored contribution of TPO alteration to HSC and BM niche defects in BT by unraveling the dual role of TPO on HSC and Mk in a condition of chronically reduced stimulation. This research elucidates the multifactorial alterations in the BM microenvironment, with a potential relevance in improving HSC transplantation approaches for BT.

Cellular immunotherapy and gene therapy - Experimental

S250 ADCLEC.SYN1, A COMBINATORIAL CAR PLATFORM FOR AML

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Background: Prognosis in relapsed/refractory AML is extremely poor. Despite recent advances with small-molecule therapeutics, the only curative option to date is allogeneic stem cell transplantation, which is often associated with toxicity and therapeutic failure. Therefore, novel therapies with potential for high efficacy yet tolerable safety profile are highly needed. CAR therapy has been clinically validated for CD19-positive B cell malignancies and is currently being evaluated for its application in other malignancies, however suitable CAR targets in AML still need to be identified. Integrating proteomic and transcriptomic target expression data we have previously discovered n=24 CAR candidate targets with a favorable profile in AML and normal tissues and provided a rationale for several combinatorial CAR approaches in AML (Perna et al. Cancer Cell 2017).
Aims: We hypothesized that rational combinatorial CAR design targeting both ADGRE2 and CLEC12A enhances anti-leukemic efficacy without cumulating potential on-target/off-tumor toxicity.
Methods: We validated favorable target pairs among our 24 candidates, based on a multimodal in-depth analysis including multiparameter spectral flow cytometry of primary r/r AML and normal bone marrow samples, along with normal tissue immunohistochemistry studies and mass-spectrometry. To provide a platform for identification of the ideal combinatorial CAR design, we established in-vitro and in-vivo models based on a human AML cell line with up- or down-regulated antigen levels of ADGRE2 and CLEC12A to mimic both AML antigen-low escape and toxicity to normal cells. In addition, we established a humanized mouse model that allowed in-vivo assessment of hematologic toxicities in the context of anti-leukemic CAR efficacy.
Results: We focus here on ADGRE2 and CLEC12A, two cell surface molecules highly co-expressed in AML but with largely non-overlapping expression profiles in normal tissues. Using a bicistronic gamma-retroviral vector, we screened different combinatorial CAR formats targeting ADGRE2 and CLEC12A. Specific to the combined target expression profile in malignant versus normal cells, we fine-tuned both scFv affinities considering total avidity, eventually achieving thresholds for mediating cytolysis in the context of optimized CD3 zeta signaling. In addition, we further optimized the chimeric receptor combination by evaluating different hinge/transmembrane and costimulatory domains. Ultimately, using therapeutically relevant T cell doses we were able to identify a combinatorial CAR format - ADCLEC.syn1 - that allowed complete and durable AML remission across relevant target levels while maintaining a favorable safety profile.
Summary/Conclusion: We developed a novel combinatorial CAR platform – ADCLEC.syn1 – and demonstrated in pre-clinical models its high potential for safe and efficient application in r/r AML.

S251 PRECLINICAL DATA SUPPORTING THE INITIATION OF THE EDIT-301 PHASE I RUBY CLINICAL TRIAL FOR THE POTENTIAL TREATMENT OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited blood disorder affecting ~ 100,000 individuals in the United States. Naturally occurring mutations at the distal CCAAT-box region of the HBG1 and HBG2 promoters are associated with elevated fetal hemoglobin (HbF) expression, which has been shown to be protective against clinical manifestation of SCD.
Aims: EDIT-301 is an investigational autologous cell therapy comprising CD34+ cells genetically modified with CRISPR-Cas at the HBG1 and HBG2 promoters to promote HbF expression for the potential treatment of SCD.
Methods: Editing is achieved using a highly specific CRISPR-Cas12a enzyme, which we have shown to have a superior on-target editing profile at this site compared to *S.pyogenes* Cas9. Preclinical studies were conducted using mobilized peripheral blood (mPB) CD34+ cells from normal and SCD donors transfected at research-scale and/or large-scale. Editing efficiency, HbF induction, functional improvement of SCD red blood cells (RBCs), off-target editing, and engraftment of edited CD34+ cells in NOD scid gamma (NSG) mice were studied.
Results: At research scale, electroporation of mPB CD34+ cells from both normal and SCD donors resulted in on-target editing of ~90%, with more than 50% of HbF expression detected in the erythroid progeny of SCD donor cells in a pancellular fashion (~93% population). This robust HbF induction was associated with significant functional improvement of SCD donor derived RBCs under hypoxia, including reduced sickling and increased deformability. In addition, using a microfluidic assay that mimics blood flow in the microvasculature, we observed a marked improvement in the rheological behavior of SCD RBCs derived from RNP-electroporated CD34+ cells. This rheology improvement was strongly correlated with the high HbF levels achieved in edited RBCs.
We have developed a consistent large-scale process using semi-automated systems. Using this process on normal donor cells, we have achieved CD34+ cell purity >90% and editing levels >80% after RNP electroporation. Evaluation of batches from this representative process demonstrated a highly consistent editing profile and no detectable off-targets. In addition, no HBG transcript or protein variants were detected in the erythroid progeny of the RNP-edited CD34 cells, demonstrating that the editing procedure did not affect the integrity of HbF. Finally, infusion of large scale manufactured edited CD34+ cells into NSG mice led to a polyclonal engraftment, with no difference in hematopoietic reconstitution compared to unedited CD34+ cells. Editing levels of >90% were detected after long term engraftment, demonstrating robust editing of long-term-repopulating hematopoietic stem cells.
Summary/Conclusion: In summary, Cas12a-RNP editing of SCD donor mPB CD34+ cells at the HBG1 and HBG2 promoters resulted in robust HbF induction and reduced sickling as well as markedly improved rheological behavior in erythroid progeny cells. We established a current Good Manufacturing Practices (cGMP) clinical scale process to support EDIT-301 clinical manufacturing. Evaluation of process representative large-scale manufacturing batches demonstrated high and consistent editing of the HBG1 and HBG2 promoters, with no measurable off-targets, and no alteration of the HBG transcript and protein. In vivo, edited CD34+ cells led to polyclonal engraftment and reconstituted all blood cell lineages at levels comparable to unedited cells. These results support the dosing of EDIT301 in the upcoming RUBY trial, a phase 1/2 study of patients with severe SCD.

S252 LAG-3, TIM-3 OR 2B4 DISRUPTION DIFFERENTIALLY REGULATE THE ANTI-TUMOR RESPONSE OF TCR GENE EDITED HUMAN MEMORY STEM T CELLS

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Background: Adoptive immunotherapy with T lymphocytes genetically engineered to overexpress a tumor-specific T cell receptor represents a novel immunotherapeutic option for cancer patients. However, the lack of long-term persistence of infused tumor-reactive T cells and the immunosuppressive tumor microenvironment represent major drawbacks of ACT. Specifically, chronically stimulated tumor-specific lymphocytes become exhausted, a dysfunctional status characterized by loss of effector functions. Exhausted T cells overexpress several inhibitory receptors (IRs), such as PD-1, CTLA-4, Lag-3, Tim-3 and 2B4. The use of monoclonal antibodies targeting IRs (e.g. anti-CTLA-4 and anti-PD-1), can revert T cell exhaustion but proved effective only in a fraction of patients. Also, autoimmune-related adverse events often occur after immune checkpoint blockade, mainly due to the unleashing of autoreactive clones.
Aims: we aim to generate innovative cell therapy products, endowed with long-term persisting capacity and resistance to inhibitory signals and to investigate how the disruption of selected IRs could modulate the resistance to exhaustion in multiple myeloma models.
Methods: CRISPR/Cas9 reagents were used to simultaneously disrupt TIM-3, LAG-3 or 2B4 gene and the TCR alpha chain constant region (TRAC) gene. The frequency of NHEJ was assessed with ddPCR. TRAC-KO-IR-KO T cells were transduced with a lentiviral vector encoding for an HLA-A2-restricted NY-ESO-1-specific TCR. T cells were activated and kept in culture with a protocol to expand long-living early differentiated stem cell memory (T_{SCM}) and central memory (T_{CM}) cells (Cieri et al., Blood 2013). TCR-edited-IR-KO cells and TCR-edited-IR-competent (TCR-edited-IR_{COMP}) cells were challenged in vitro and in vivo with HLA-$A2^{pos}$NY-ESO-1^{pos} multiple myeloma cell lines. HLA-$A2^{neg}$ NYESO-1^{neg} cell lines were used as control.
Results: We efficiently inactivated the endogenous TCR (>98% of NHEJ) and more than 80% of gene disruption was also obtained at LAG-3, Tim-3 or 2B4 locus. TCR disrupted-IR-KO cells were efficiently transduced (> 50%) with the NY-$ESO1_{157-165}$-specific TCR, thus obtaining TCR-edited-IR-KO T cells or TCR-edited-IR_{COMP}T cells. Importantly, TCR-edited-IR-KO T cells retain their expansion capacity and an early differentiated T_{SCM}/T_{CM} phenotype.
Upon chronic stimulation with multiple myeloma cells, TCR-edited-Tim-3-KO and TCR-edited-2B4-KO T cells retained a higher degranulation capacity compared to TCR-edited-LAG-3 KO and TCR-edited-IRCOMP T cells, while TCR-edited-LAG-3-KO T cells showed a limited upregulation of additional inhibitory receptors.
In a preclinical model of aggressive multiple myeloma, TCR-edited-Tim3-KO and TCR-edited-2B4-KO T cells caused higher immunological pressure and were enriched in a higher proportion of highly activated T cells compared to TCR-edited-IR_{COMP}-treated mice. In a similar pre-clinical multiple myeloma model, TCR-edited-LAG-3-KO, but not TCR-edited-IRCOMP, T cells showed a reduced expression of additional IRs and prevented the engraftment of the second infusion of tumor cells, thus indicating an enhanced T cell fitness and resistance to exhaustion of TCR-edited-LAG-3-KO T cells.
Summary/Conclusion: our results show that by combining the versatility of multiplex gene editing by CRISPR/Cas9 with culture conditions designed to engineer T_{SCM} cells, we can generate innovative tumor-specific cellular products redirected against tumor antigens and resistant to different inhibitory signals.

S253 ENGINEERED REGULATORY T CELLS USING ORTHOGONAL IL-2 CYTOKINE-RECEPTOR COMPLEXES PREVENT ACUTE GRAFT-VERSUS-HOST DISEASE.

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Background: The use of regulatory T cells (Treg) has a positive therapeutic potential to ameliorate acute graft-versus-host disease (GvHD), which represents one of the major complications after allogeneic bone marrow transplantation (allo-BMT). One of the remaining obstacles in the clinical practice of Treg administration is the high dose of Treg cells required to prevent GvHD and the difficulty in expanding these cells ex-vivo.
Aims: In this study, we engineered murine Treg cells to express an altered IL-2 receptor β subunit that selectively interacts with an orthogonal

mutant IL-2 (oIL2) without interacting with the natural cytokine or receptor counterparts, thus selectively expand engineered Treg and prevent acute -GvHD.
Methods: $CD4^{+}CD25^{hi}Foxp3^{GFP}$cells were purified from C57Bl/6 $FoxP3^{DRT\text{-}GFP\text{-}luc+}$ mice and transduced with the construct for murine oIL-2 receptor β chain (oTregs) through a retroviral vector. BALB/c mice were lethally irradiated (8.8 Gy) and transplanted with $5x10^{6}$ T cell-depleted bone marrow cells (TCD-BM) from C57Bl/6 mice alone or together with fresh $1x10^{6}$ C57Bl/6 $FoxP3^{DRT\text{-}GFP\text{-}luc+}$ Treg cells (fTreg) or with oTreg ($0.2x10^{6}$ and $1x10^{6}$) on day 0. On day 2, C57Bl/6 Tcon cells ($1x10^{6}$) were injected to induce GvHD. Recipients were treated with PBS or oIL-2 (25K IU/day) for 14 days and then 3 times a week for another 14 days.
Results: By bioluminescence assays, we observed a significant expansion of oTreg (luc+) cells treated with oIL2 at day 7 post-transplant. The expansion of oTreg with PBS and fTreg was observed on day 14 after allo-BMT. The administration of oTreg-oIL2 and fTreg (1:1 Tcon:Treg ratio) significantly increased the survival of the mice compared to Tcon group (P<0.0001 and P=0.0001, respectively). Further, the group oTreg-oIL2 (1:1) showed a significant increase in the survival curve compared to the fTreg group (P=0.03). When decreasing the number of oTreg administrated (5:1 Tcon:Treg ratio) a significant increase in the survival (Tcon vs Tcon:oTreg (5:1)+oIL2; P<0.0001) in the oIL2 group. Similar survival curves were observed between this group and fTreg group (1:1). oIL-2 injection significantly increased the percentage of $Foxp3^{GFP+}$ in $CD4^{+}$ T cells (PBS;14.96±2.4%, oIL-2; 27.76±23.6%, P=0.02) in the peripheral blood (PB) after 7 days post-transplant. oTreg mice group showed a decrease in the percentage of effector T cells after 7 days compared to Tcon group. However, the oIL2 group showed a significant decrease of $ICOS^{+}CD8^{+}$ cells compared to the PBS group in the PB and spleen (P=0.04 and P=0.006, respectively).
Summary/Conclusion: The administration of a reduced number of oTreg and the selective IL-2 stimulation in vivo early after transplant showed a capacity to ameliorate GvHD, representing a novel approach to the utilization of Treg in allo-BMT.

S254 CORD-BLOOD-DERIVED T AND NATURAL KILLER CELLS ENGINEERED VIA THE PIGGYBAC TRANSPOSON SYSTEM TO EXPRESS A LIGAND-BASED CAR TARGETING THE CD116/CD131 COMPLEX

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Background: Chimeric antigen receptor (CAR)-T cell therapy redirected to specific antigens on tumor cells is a promising immunotherapy strategy for various cancers. However, CAR-T cells can induce substantial toxic effects, and it is sometimes difficult to manufacture them because they are produced on an individual-patient basis. Using a non-viral gene delivery, the *piggyBac*-transposon system, we have developed a ligand-based CAR-T cells redirected to the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor (GMR, CD116/CD131 complex), highly expressed in subtypes of myeloid malignancies. *PiggyBac* transposon-mediated, peripheral blood-derived GMR CAR-T cells are abundant in a native or stem cell-like memory T cells, showing a persistent antitumor effect in a xenograft mouse model. Cord blood (CB) offers an attractive, allogeneic, off-the shelf source for immunotherapy and is widely used as an alternative source of stem cell for allogeneic hematopoietic stem cell transplantation. Additionally, administration of CAR-natural killer (NK) cells has been shown to have antitumor effects without major toxic effects, such as cytokine release syndrome, neurotoxicity, or graft-versus-host disease.
Aims: In this study, we engineered CB-derived GMR CAR-T and CAR-NK cells via the *piggyBac* transposon system for more effective and safer cellular therapeutics.
Methods: Mononuclear cells from frozen CB were electroporated with both GMR CAR-transposon and *piggyBac*-transposase plasmids. The electroporated cells were cultured in a defined T-cell medium supplemented with recombinant interleukin (IL)-7 and IL-15, or in a NK-cell medium supplemented with recombinant IL-2 and IL-15. The cells were collected after 14 days of culture. The GMR CAR-T and CAR-NK cells were counted, and CAR expression and immunophenotype were characterized. To examine the anti-tumor activity, CAR-T and CAR-NK cells were co-cultured with the human acute myeloid leukemia cell line MV4-11 at an E:T ratio of 1:1, 1:2, or 1:4.
Results: We obtained GMR CAR-T and CAR-NK cells from CB via the *piggyBac* transposon system. Most CAR-positive T cells exhibited the CD45RA+ CCR7+ phenotype, suggesting that they exhibited the native or stem-cell memory T-cell phenotype. CAR-T and CAR-NK cells eradicated almost all the MV4-11 cells in culture. The results of additional analyses ongoing at the time of the abstract submission will be disclosed at the annual meeting.
Summary/Conclusion: GMR CAR-T and CAR-NK cells can be successfully generated non-virally from CB via the *piggyBac* transposon system. This approach can greatly improve the limitations of current CAR-T therapies.

Cellular immunotherapy and gene therapy - Clinical

S255 POLATUZUMAB VEDODTIN VS. CAR-T CELL FOR PATIENTS WITH RELAPSED/ REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA - A PROPENSITY SCORE MATCHED ANALYSIS

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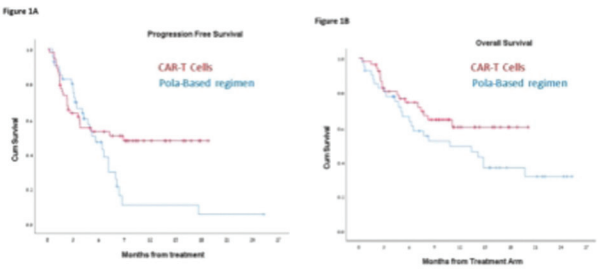
Background: Introduction –Pola –BR (Polatuzumab –bendamustin-rituximab) and chimeric antigen receptor (CAR)-T cells provide superior outcome compared to conventional chemotherapy in patients with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL). However, how to sequence these strategies remains controversial.
Aims: compare the outcome of CAR-T CELLS VS pola- based therapy in R/R DLBCL
Methods: Methods: The study included R/R DLBCL patients, treated between 01/2019-08/2020 with commercial CAR-T or Pola/Pola BR after failing ≥2 lines of treatment. Propensity score analysis, matching patients based on age, lymphoma category (*de-novo*/ transformed), cell of origin, number of prior therapy lines, ECOG performance status and LDH level, was performed. Response rate, progression free survival (PFS) and overall survival (OS) were analyzed.
Results: Results: 98 patients, treated with CAR-T (n=49; 35 with Tisagenlecleucel, and 14 with Axicabtagene ciloleucel) or Pola-based regimen (n=49) were included (patient characteristics are presented in Table 1). Median time from progressive disease to CAR-T infusion was 52 days and mostly immediate for Pola/Pola-BR. Non-relapse mortality was 0 in the CAR-T cohort vs 6% (3/49) in the Pola arm. The overall and complete response rates were 73% and 53% for the CAR-T cohort vs 63% and 20% in the Pola arm. Within a median follow-up period of 9.6 (range, 1-19.1) and 7.7 (range, 0.7-26) months for CAR-T and Pola patients, respectively, median PFS were 8.9 month (95% CI n/a) vs. 5.6 months (95% CI 3.7-7.6) (p=0.08) and median OS was not reached vs. 10.8 (2.2-19.4) months, (p=0.12), respectively(Figures 1A, 1B).

Table 1: Patient characteristics

P value	Pola group (n=49)	CAR-T Group (n=49)*	Domain
.38	67 (23-92)	70 (20-85)	Age
.68	21	23	Sex, female
.48	16	14	Transformed vs *De Novo* DLBCL
.53	27	30	Non-GCB
.43	3 (2-7	2 (2-8)	No prior lines
.1	23	31	ECOG PS >1
.8	38	39	Elevated LDH

CAR-T- Chimeric Antigen Receptor- T cell;DLBCL- diffuse large cell B cell lymphoma; ECOG PS- Eastern Cooperative Oncology Group performance status; LDH-; lactic dehydrogenase; No-number Pola-polatuzumab vedotinAxicabtagene ciloleucel, N=14; Tisagenlecleucel, N=35*

Figure 1: Outcome of patients treated with CAR-T cells vs Pola-Based regimen



Summary/Conclusion: Conclusions - In the lack of prospective randomized trials evaluating CAR-T s vs chemo-immunotherapy, a propensity score, comparing CAR-T with Pola-based regimen was performed, demonstrating a tendency for prolonged PFS and OS in R/R DLBCL patients treated with CAR-T.

S256 26 WEEK EFFICACY AND SAFETY OF ETRANACOGENE DEZAPARVOVEC (AAV5-PADUA HFIX VARIANT; AMT-061) IN ADULTS WITH SEVERE OR MODERATE-SEVERE HEMOPHILIA B TREATED IN THE PHASE 3 HOPE-B CLINICAL TRIAL

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Background: Etranacogene dezaparvovec is an investigational gene therapy for hemophilia B (HB) comprising an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) gene with a liver specific promoter. Early clinical studies and nonhuman primate data suggest that generally prevalent titers of anti-AAV5 NAbs may not preclude successful transduction with etranacogene dezaparvovec.
Aims: A Phase 3, **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (HOPE-B; NCT03569891) trial is ongoing to further assess efficacy and safety of etranacogene dezaparvovec in adults with HB with a wide range of pre-existing NAbs to AAV5. Here we report outcomes at 26 weeks (wks).
Methods: HOPE-B is a Phase 3, open-label, single-dose, single-arm, multi-national trial in adult males with severe or moderate-severe HB (FIX≤2%). All participants (pts) received routine FIX prophylaxis prior to study and were not excluded based on pre-existing NAbs to AAV5. A 6 month prospective lead-in period was followed by a single intravenous dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg) without prophylactic immunosuppression. Pts will be followed for 5yrs. The co-primary endpoints are change in FIX activity at 26 and 52wks and 52wk annualized bleeding rate compared to lead in. Secondary endpoints include factor replacement use, adverse events (AEs), and reactive use of corticosteroids.
Results: 54 pts were dosed and completed 26wks of follow-up. Mean age (±SD) was 41.5 (15.8) yrs. 38/54 pts (70.4%) had bleeds (n=123) during the lead-in despite prophylaxis, and 23/54 (42.6%) had NAbs to AAV5 at baseline. Following treatment, FIX activity increased rapidly to a mean (SD; min,max) of 37.2% (±19.6; 1.0, 97.1) at wk26, representing a mean (SD; min,max) change from baseline of 36.0% (±19.7; 0, 96.1 $p<0.0001$, confirmed by per-protocol sensitivity analysis). No correlation of pre-existing NAbs with FIX activity was identified up to a titer of 678.2; n=52, $R^2 = 0.078$); one individual had a NAb titer of 3212.3 and did not respond. One additional pt received a partial dose and remained on prophylaxis; all other pts (52/54; 96.3%) successfully discontinued routine prophylaxis. 39/54 (72.2%) pts reported 0 bleeds in the first 26wks post-treatment; 15 pts reported a total of 21 bleeds. Mean (SD) annualized FIX consumption (IU/yr/pt) was 292,304 (±171,079) during lead-in, decreasing to 12,622 (±36,466) at wk26 (96.0% reduction, N=54). Overall, 37/54 (68.5%) pts experienced any treatment-related AE post-treatment, the majority of which (81.5%) were mild. No deaths occurred and no treatment-related SAEs were reported. 7 pts had infusion-related reactions; the infusion was discontinued in 1 pt. Treatment-related elevations in liver enzymes were reported in 9 pts who received steroids per protocol. All discontinued steroid use prior to wk26 and FIX activity was preserved in the mild range. Additionally, the most frequent treatment-related AEs were headache (13.0%) and influenza-like illness (13.0%). No inhibitors to FIX were reported and no relationship between safety and NAbs was observed.
Summary/Conclusion: Following a single dose of etranacogene dezaparvovec, FIX activity increased, without the need for prophylactic immunosuppression, into the mild-to-normal range at 26wks in pts with severe/moderately severe HB. Pts were able to discontinue prophylaxis and bleeding was abolished in the majority. Safety was consistent with early phase AAV5 studies and together these data support a favorable safety and efficacy profile.

S257 BETIBEGLOGENE AUTOTEMCEL GENE THERAPY FOR THE TREATMENT OF TRANSFUSION-DEPENDENT B-THALASSEMIA: UPDATED LONG-TERM EFFICACY AND SAFETY RESULTS

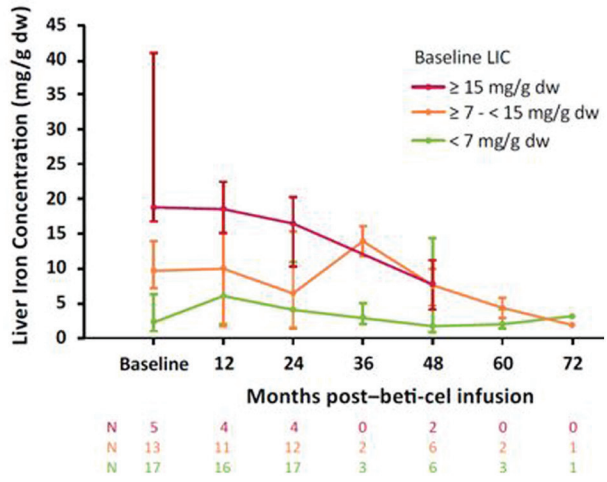
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Background: Betibeglogene autotemcel (beti-cel) is a one-time ex vivo gene therapy for transfusion-dependent β-thalassemia (TDT) that adds functional copies of a modified *HBB* gene, $\beta^{A\text{-}T87Q}$, into patients' hematopoietic stem cells. Gene therapy with beti-cel corrects the underlying cause of TDT to enable lifelong, stable production of functional adult hemoglobin (Hb) sufficient for transfusion independence (TI) and reduction of ineffective erythropoiesis. A total of 63 patients were treated with beti-cel in 2 completed phase 1/2 (Ph1/2; HGB-204, HGB-205) and 2 ongoing phase 3 (Ph3; HGB-207, HGB-212) studies. After 2 years of follow-up, patients could be enrolled in a 13-year long-term follow-up study (LTF-303; NCT02633943). We report LTF-303 interim results in 44 patients with up to 6.4 years' follow-up.

Aims: Assess long-term safety and efficacy of beti-cel in patients with TDT.
Methods: Autologous CD34+ cells were transduced with BB305 lentiviral vector and infused into patients after single-agent, pharmacokinetic-adjusted, busulfan-based myeloablation. In Ph3 studies, transduction used a refined manufacturing process compared with Ph1/2 studies. LTF-303 assessments include Hb, erythropoiesis, iron, and safety. Data are reported as median (min–max).
Results: As of 30 November 2020, 44 patients had enrolled in LTF-303 (age at enrollment in parent studies: 19.5 [7–35] y; Ph1/2: n=22, Ph3: n=22); follow-up was 45.6 (22.9–76.4) mo.
Among patients enrolled in LTF-303, TI (weighted average Hb ≥9 g/dL without packed red blood cell transfusions for ≥12 mo) was achieved and maintained over time in 15/22 (68.2%) patients treated in Ph1/2 and 20/22 (90.9%) patients treated in Ph3. Weighted average Hb during TI was 10.3 and 11.8 g/dL in patients in Ph1/2 and Ph3, respectively. In patients who achieved TI, total Hb over time without transfusion support was maintained from 24 mo (Ph1/2: 10.3 [8.6–13.7] g/dL [n=14]; Ph3: 12.5 [9.7–14.0] g/dL [n=19]) to 36 mo (Ph1/2: 10.5 [8.5–13.5] g/dL [n=15]; Ph3: 12.3 [11.7–13.5] g/dL [n=4]). This was driven by beti-cel–derived HbA^{T87Q} levels and remained stable from 24 mo (Ph1/2: 7.3 [2.9–10.1] g/dL [n=15]; Ph3: 9.4 [5.0–12.4] g/dL [n=19]) to 36 mo (Ph1/2: 7.6 [3.7–10.1] g/dL [n=15]; Ph3: 10.6 [8.6–13.0] g/dL [n=7]). In patients achieving TI in Ph3, soluble transferrin receptor decreased from baseline (129.4 [65.9–235.3] nmol/L, n=20; no patient within normal range) to 24 mo (60.0 [17.7–121.2] nmol/L, n=19; 6 patients within normal range).
Iron removal therapy was managed at the discretion of the investigator and did not target an optimal liver iron concentration (LIC). While the LIC increased just after beti-cel infusion, levels decreased over time in patients who achieved TI, particularly in those who had an elevated LIC at baseline (**Figure**).
No drug product–related AEs were reported >2 years post–beti-cel infusion. Serious AEs occurring after 2 years of follow-up included gonadotropic insufficiency, ectopic pregnancy, fetal death, gallbladder wall thickening/polyp, bacteremia with neutropenia, and major depression (all n=1). No deaths, replication competent lentivirus, or insertional oncogenesis were reported in these patients.

Figure. Liver iron concentration (LIC) over time by baseline value in patients who achieved transfusion independence and enrolled in LTF-303



Summary/Conclusion: These results demonstrate durability and stability of response after beti-cel gene therapy in patients with TDT with no AEs considered related to beti-cel by the investigator >2 years post-infusion. Sustained levels of HbA^{T87Q} and effective iron reduction improved hematologic parameters and lowered iron burden.

S258 RETROVIRAL GENE THERAPY FOR THE TREATMENT OF ADA-SCID: LONG-TERM FOLLOW UP AND FIRST CASE OF T-CELL ACUTE LEUKAEMIA DUE TO INSERTIONAL MUTAGENESIS

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Background: Haematopoietic stem cell (HSC) gene therapy (GT) using a γ-retroviral vector (γ-RV) (Strimvelis®) has been authorised in the EU for the treatment of Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID) in patients with no suitable human leukocyte antigen (HLA)-matched related HSC donor.
Aims: We summarise our experience with ADA-SCID γ-RV GT during clinical development and post-marketing and report the occurrence of the first case of T-cell acute lymphoblastic leukaemia (T-ALL) after GT.
Methods: Since 2000, 40 patients have been infused with autologous CD34+ cells engineered with a γ-RV encoding ADA following low dose busulfan. Patients were monitored long-term with annual visits. Eighteen patients were treated within the Clinical Development Program, 4 in a Named Patient Program (NPP), and 16 with the commercial product. Two patients were treated under Hospital Exemption with mobilised CD34+ peripheral blood cells, instead of bone marrow derived used for Strimvelis. Efficacy was evaluated in the first 36 patients with a sufficient follow-up (FU) up to March 5, 2020; serious adverse events were reported on the entire cohort until November 30, 2020.
Results: All evaluable patients are alive with a median FU of 7.2 years (range 0.3-19.2) with an intervention-free survival of 83.3% (30/36). Of the 6 patients in whom GT failed, 4 underwent allogeneic HSCT and 2 were on long-term enzyme replacement therapy. In all 30 patients with successful outcomes, engraftment of gene corrected cells persisted long-term in multiple haematopoietic lineages, at higher levels in lymphocytes. ADA activity in mononuclear cells was sustained in most patients with adequate systemic detoxification. Immune reconstitution was accompanied in most patients by increased immunoglobulin production, decreased Ig use and antibody response to vaccines. Long-term FU data revealed a decreased rate of severe infections after treatment. Most adverse events were related to disease background, conditioning or immune reconstitution. A drug-related event recently emerged in an NPP patient of 5.75 years of age, who developed T-ALL 4.7 years after GT. Routine FU 3 months earlier did not reveal abnormalities and a polyclonal insertion site profile was present at 1, 1.5 and 3 years post-GT. Clinical onset consisted of haemorrhagic diathesis and weakness. Blood tests showed WBC 291.300/uL and immature lymphocytes (93%) with phenotype CD7+, CD34het, CD2+, CD56-, CD4-, CD8dim, sCD3dim/neg, cyCD3+. There was no CNS or mediastinal involvement. The blast population was transduced (1.18 VCN/genome) and expressed low ADA activity. Integration site analysis identified a single highly dominant clone harboring a vector integration ~40kb upstream the LMO2 gene, which was overexpressed by RT-PCR. Retrospectively, the insertion was found in mature peripheral blood CD4+ T cells at 1 year (7%), stable over time. Whole genome analyses in blasts revealed loss of a large part of chr. 6 and two large LOH regions on chr. 9. The patient showed poor prednisone response, while morphological complete remission was obtained at the end of induction therapy of the AIEOP-BFM ALL 2017 protocol. Further studies are ongoing to better characterize the factors contributing to leukaemogenesis in this patient.
Summary/Conclusion: Efficacy of γ-RV-GT in ADA-SCID is sustained with a FU up to 19.2 years. Due to the identified risk of leukaemogenesis, patients will continue long-term FU to closely monitor the safety of the product. EMA CHMP confirmed that the risk/benefit balance remains favorable for Strimvelis in its approved indication.

S259 A PHASE I-IIA STUDY OF GENETICALLY MODIFIED TIE-2 EXPRESSING MONOCYTES IN PATIENTS WITH GLIOBLASTOMA MULTIFORME (TEM-GBM STUDY)

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Background: Genetically modified cell-based therapies are relevant in immunooncology due to their potential for tumor specificity and potential durability. We developed a cell-based treatment, Temferon, relying on ex-vivo transduction of autologous hematopietic stem and progenitors cells (HSPCs) to express therapeutic payloads within the tumor microenvironment. Temferon targets IFNa to Tie-2 expressing macrophages (TEMs).
Aims: The aim of TEM-GBM study is to evaluate the safety and the efficacy of Temferon in up to 21 newly diagnosed patients with glioblastoma and unmethylated MGMT promoter.
Methods: TEM-GBM is an open-label, Phase I/IIa dose-escalation study. Autologous HSPCs are transduced *ex-vivo* with a lentiviral vector encoding for IFN-α. The transgene expression is confined to TEMs due to the Tie2 promoter and the posttranscriptional regulation by miRNA-126.
Results: As of January 17 2021, 15 patients have been enrolled; 9 received Temferon (D+0) with follow-up of 61 – 559 days. There was rapid engraftment and hematological recovery after the conditioning regimen. Median neutrophil and platelet engraftment occurred at D+13 and D+12, respectively. Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA of peripheral blood and bone marrow cells, were found within 14 days post treatment and persisted subsequently, albeit at lower levels (up to 18 months). We also detected very low concentrations of IFNa in the plasma (median 5pg/ml at D+30; baseline < LLOQ) and in the cerebrospinal fluid, suggesting tight regulation of transgene expression. Three deaths occurred: two at D+343 and +402 after Temferon administration due to disease progression, and one at D+60 due to complications following the conditioning regimen. Seven patients had progressive disease (PD; range D+27-239) as expected for this tumor type. SAEs include infections, venous thromboembolism, brain abscess, hemiparesis, GGT elevation and poor performance status compatible with autologous stem cell transplantation, concomitant medications and PD. Four patients underwent second surgery. These recurrent tumors had gene-marked cells present and increased expression of IFN-responsive gene signatures compared to diagnosis, indicative of local IFNa release by TEMs. In one patient a stable lesion (as defined by MRI) had a higher proportion of T cells and TEMs within the myeloid infiltrate and an increased IFN-response signature than in a progressing lesion. The T-cell immune repertoire changed with evidence for expansion of tumor-associated clones. Tumor microenvironment characterization by scRNA and TCR sequencing is ongoing.
Summary/Conclusion: Our interim results show that Temferon is well tolerated by patients, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon potential to modulate the TME of GBM patients, as predicted by preclinical studies.

Changing the scene on sickle cell disease

S260 SAFETY AND EFFICACY OF VOXELOTOR IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE AGED 4-11 YEARS

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Background: Sickle cell disease (SCD) is an inherited, lifelong disorder characterized by polymerization of deoxygenated sickle hemoglobin (HbS), chronic hemolytic anemia, and vaso-occlusive crises (VOCs). Lifelong ischemic injury and inflammation that begins during childhood in patients with SCD is associated with progressive end-organ damage, substantial morbidity, and early mortality. Voxelotor, an oral, once-daily HbS polymerization inhibitor, is approved in the United States for the treatment of SCD in adults and pediatric patients aged ≥12 years. Here we report the evaluation of safety and efficacy of voxelotor in pediatric patients with SCD aged 4 to 11 years.
Aims: To assess the safety and efficacy of weight-based, 1500-mg-equivalent, once-daily doses of voxelotor in pediatric patients with SCD (HbSS or HbSβ^0-thalassemia) aged 4 to 11 years.
Methods: Patients with SCD aged 4 to 11 years received once-daily voxelotor 1500 mg or 1500-mg weight-based-equivalent dosing for up to 48 weeks. Patients were included if they had a hemoglobin (Hb) concentration of 5.5 to 10.5 g/dL at baseline. Concomitant hydroxyurea was allowed if the dose was stable for ≥3 months at enrollment. Study outcomes included the change from baseline to week 24 in Hb and changes in markers of hemolysis (indirect bilirubin, lactate dehydrogenase, and reticulocyte count). Other outcomes included safety as assessed by adverse events (AEs).
Results: A total of 45 pediatric patients (median [range] age, 7.0 [4-11] years; median [range] weight, 24.0 [12-41] kg; 51.1% female) were enrolled to receive the weight-based dosing of voxelotor equivalent to 1500 mg. Of these patients, 95.6% had HbSS and 4.4% had HbSβ^0 genotypes. At baseline, 84.4% were receiving hydroxyurea, and 53.3% had ≥1 VOC in the year prior to enrollment. At baseline, the mean (SD) Hb level was 8.6 (1.0) g/dL. At week 24, the mean change (SD) in Hb from baseline was +1.0 (1.1) g/dL, and 47.1% (95% CI, 29.8%>64.9%) of patients achieved a Hb response, defined as a >1 g/dL increase in Hb. Reductions in markers of hemolysis, as measured by mean percent change from baseline, were observed for indirect bilirubin (–38.6%), lactate dehydrogenase (–2.6%), and reticulocytes (–3.3%). Improvements in Hb and markers of hemolysis were also observed in those who were managed at the maximally tolerated dose of hydroxyurea. Correlation of Hb response with observed pharmacokinetics and percent Hb occupancy will be presented. Treatment-related AEs not related to SCD were reported in 48.9% of patients; most were grade 1 or 2, and treatment discontinuation rates due to treatment-related AEs were low (9%). The most commonly reported treatment-related AEs were diarrhea (11%), vomiting (11%), and rash (grouped term; 11%).
Summary/Conclusion: Voxelotor increased Hb and decreased markers of hemolysis in pediatric patients with SCD aged 4 to 11 years, the majority of whom were receiving stable hydroxyurea. Additionally, the drug was well tolerated, and no new adverse safety signals were detected. These results were consistent with those in adults and adolescent patients aged ≥12 years treated with voxelotor 1500 mg once daily in the HOPE trial. Overall, these results support the use of voxelotor in pediatric patients with SCD ≥4 years of age as a potential strategy for early mitigation of the morbidity and mortality associated with SCD.

S261 COMPLETE RESOLUTION OF SEVERE VASO-OCCLUSIVE EVENTS AND IMPROVED PATHOPHYSIOLOGY WITH LENTIGLOBIN GENE THERAPY IN SICKLE CELL DISEASE (SCD): ONGOING PHASE 1/2 HGB-206 GROUP C STUDY

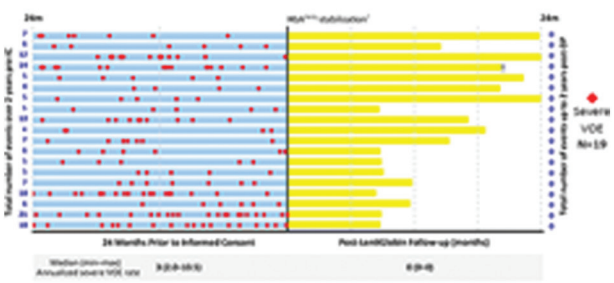
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Background: SCD is a progressive disease caused by a single point mutation in the β-globin gene. Despite lifelong treatment (tx) options, SCD results in painful vaso-occlusive events (VOEs), progressive vasculopathy, and chronic hemolytic anemia, leading to significant morbidity and early mortality. LentiGlobin for SCD (bb1111) gene therapy (GT) utilizes a modified human β-globin gene that produces GT-derived anti-sickling hemoglobin (Hb)A^{T87Q}.
Aims: The ongoing Phase 1/2 HGB-206 study is the largest clinical trial of GT in SCD to date. Data from Group C are presented here.
Methods: Patients (pts; ≥12–≤50 yrs) with SCD and recurrent severe VOEs, including acute episodes of pain and acute chest syndrome, were enrolled. CD34+ cells were collected by plerixafor mobilization/apheresis and transduced with BB305 lentiviral vector. LentiGlobin was infused after myeloablative busulfan conditioning. Lab evaluations, SCD-related outcomes, pain intensity using Patient Reported Outcomes Measurement Information System (PROMIS)-57, and safety were assessed; data are median (min–max) unless otherwise stated.
Results: As of August 20, 2020, 43 pts (24 [12–38] yrs) had initiated cell collection, 32 of whom were treated with LentiGlobin and followed for 13.0 (1.1–30.9) months. Neutrophil and platelet engraftment were achieved at 19.5 (12–35) and 30 (18–136) days, respectively; all pts stopped RBC transfusions by 90 days post-tx. Near pancellular expression of HbA^{T87Q} was observed ≥6 months post-tx with ~90% of RBCs containing $\beta^{A\text{-}T87Q}$ by 18 months (n=10). At last visit in evaluable pts with ≥6 months follow-up (n=22), total Hb was 12.0 (9.6–15.1) g/dL; HbA^{T87Q} and HbS contribution to total Hb were 5.6 (2.7–8.9) and 6.1 (4.8–7.8) g/dL, respectively. At last visit in adolescents with ≥6 months follow-up (n=6), median total Hb and HbA^{T87Q} were 13.5 and 6.1 g/dL, respectively. At last visit, lactate dehydrogenase, indirect bilirubin, and reticulocytes (n=32) approached normalization along with reductions in nucleated RBCs and serum transferrin receptor levels (n=23).
In 19 pts with a history of ≥4 severe VOEs and 6 months of follow-up, complete resolution of VOEs was observed after 6 months, with no reports of severe VOEs in the 24 months post-tx compared with an annualized severe VOE rate of 3 (2.0–10.5) in the 24 months prior to informed consent (**Fig.**). Overall mean PROMIS-57 pain intensity scores decreased from 4.5 at baseline (n=19) to 1.3 at Month 24 (n=4).
Tx-emergent serious adverse events (TESAEs) reported in 2 pts were abdominal pain, opioid withdrawal syndrome, nausea, and vomiting. All other TESAEs were reported in 1 pt. No SAEs were considered related to LentiGlobin. One pt had a nonserious Grade 2 event of febrile neutropenia considered to be LentiGlobin-related by the investigator. One death, unlikely related to LentiGlobin, occurred >18 months post-tx in a pt with significant baseline SCD-related cardiopulmonary disease. Beyond the August 20, 2020 data cutoff, one pt in Group C with persistent anemia 6 months after transplant was found to have trisomy 8 by fluorescence *in situ* hybridization on a 6-month bone marrow aspirate; the case is currently being investigated for myelodysplastic syndrome.

Figure. Complete resolution of severe VOEs post-LentiGlobin treatment



Protocol severe VOEs are shown; patients with ≥4 severe VOE at baseline before IC and with ≥6 months of follow-up post-DP infusion are included. A severe VOE was defined as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or ER observation unit visit, or ≥2 visits to a day unit or ER over ≥2 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration. In the last dataset, one patient had a non-serious VOC at Day 107; this event was recorded as an investigator reported VOE but did not meet the definition of a protocol VOE.
*HbA^{T87Q} expression stabilizes within 6 months; *One death, unlikely related to LentiGlobin, >18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
DP, drug product; ER, emergency room; IC, informed consent; max, maximum; min, minimum; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event.

Summary/Conclusion: LentiGlobin tx resulted in complete resolution of severe VOEs up to 24 months post-tx and decreased patient-reported pain intensity from baseline. There was near pancellular HbA^{T87Q} expression and improved SCD pathophysiology after tx. The safety profile of LentiGlobin tx regimen remains generally consistent with myeloablative single-agent busulfan conditioning and underlying SCD.

S262 ISCHEMIC WHITE MATTER LESIONS ARE ASSOCIATED WITH COGNITIVE DYSFUNCTION IN ADULTS WITH SICKLE CELL DISEASE

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Background: At least 33% of adults with sickle cell disease (SCD) have neurocognitive deficits and up to 50% show radiological signs of ischemia on cerebral imaging. In adults, evidence about the possible association between ischemic white matter lesions (IWML) and cognitive function remains controversial.
Aims: 1) Describe the prevalence of neuroradiological abnormalities on routine screening magnetic resonance imaging and angiography (MRI/A) in a contemporary Canadian cohort of adults with SCD. 2) Test for associations between the presence and severity of brain lesions on MRI/MRA, and performance on cognitive screening using the Rowland Universal Dementia Assessment Scale (RUDAS). We hypothesized that the presence and severity of IWML on screening MRI/A is associated with lower RUDAS performance in SCD adults.
Methods: *Design:* cross-sectional study, two Canadian comprehensive SCD centers (CHUM, Montréal and UHN, Toronto). *Inclusion criteria:* adult out-patients, all SCD phenotypes, tested with RUDAS. *Patient characteristics/outcomes:* Patient information was extracted from electronic patient records. Brain MRI/A reports <1 year from date of cognitive screening were reviewed. Findings were categorized: white matter hyperintensities (WMH), lacunae, cortical infarct (CI), atrophy, Moya-Moya, arterial stenosis or aneurysm. IWML was defined as a WMH and/or lacunae and its burden was graded with an adapted Fazekas score. Previous literature defined a RUDAS score of <23 as suggestive of dementia. *Statistics:* T-test and Fisher exact were used to test for association between RUDAS performance and brain MRI/A findings. The effect of genotype subgroup on the association was assessed using Mantel-Haenszel test. Statistical significance was established at $p<0.05$.
Results: Between July 2018 and September 2019, 252 patients were screened (CHUM 92, UHN 160) with the RUDAS. Contemporary screening MRI/A was available for 166 (65.9%) patients. Mean age was 31.0 [range 18-75] and 83 (50.0%) were female. Phenotype distribution was 108 (65.1%) with SS or Sb^0 and 58 (34.9%) with SC or Sb^+. A history of stroke was recorded in 17 (10.2%). WMH were reported in 71 (42.8%) patients, lacunae in 31 (18.7%), aneurysms in 20 (12.0%), stenosis in 12 (7.2%), atrophy in 8 (4.8%), CI in 4 (2.4%) and Moya Moya in 4 (2.4%). An IWML was described in 92 (55.4%). A RUDAS score <23 was found in 13 (7.8%) patients with recent MRI/MRA, compared to 29 (11.5%) in the overall cohort. Patients with IWML had significantly lower RUDAS scores (t= -2.66, p= 0.009). The odds of having RUDAS <23 was 4.9 times higher in patients with IWML than those without. A significant interaction between genotype subgroup and the association was found. In the presence of IWML, the SC and Sb^+ subgroup had 5.2 times higher odds of low RUDAS score than SS and Sb^0 subgroup (Table).

Table: Distribution of suspected dementia in adults with sickle cell disease, according to the presence or absence of ischemic white matter lesions on routine screening MRI/A. Results are also presented according to phenotype strata.

	N (%)	RUDAS		Odds ratio [95% confidence interval], p-value
		< 23	23 - 30	
All phenotypes	**166**			
Presence of IWML	92 (55.4)	11 (12.0)	81 (88.0)	OR=4.9 [1.0-22.8], p=0.04*
Absence of IWML	74 (44.6)	2 (2.7)	72 (97.3)	
SS and $Sβ^0$	**108**			
Presence of IWML	64 (59.3)	6 (9.4)	58 (90.6)	OR=5.2 [1.1-24.6], p=0.04**
Absence of IWML	44 (40.7)	1 (0.9)	43 (99.1)	
SC and $Sβ^+$	**58**			
Presence of IWML	28 (48.3)	5 (17.9)	23 (82.1)	
Absence of IWML	30 (51.7)	1 (3.3)	29 (96.7)	

*Fisher exact test
** Mantel-Haenszel test
Abbreviations: IWML= ischemic white matter lesion, MRI/A= magnetic resonance imaging and angiography, OR= odds ratio, RUDAS= Rowland Universal Dementia Assessment Scale

Summary/Conclusion: This is the largest study reporting on results from concurrent systematic cognitive screening and MRI/A surveillance in adults with SCD, with all major phenotypes represented. These data confirm the high prevalence of neurologic lesions in a contemporary cohort. The presence of IWML on screening MRI/A is associated with neurocognitive deficits. Independent radiological assessment is under way to grade the severity of the radiological lesions and correlate these findings with dementia. Multivariable analysis will be presented at the meeting. These findings highlight an area of unmet need in the management of neurocognitive morbidity in SCD.

S263 THE SAFETY, PHARMACOKINETICS & PHARMACODYNAMIC EFFECTS OF IMR-687, A HIGHLY-SELECTIVE PDE9 INHIBITOR, IN ADULTS WITH SICKLE CELL DISEASE: PHASE-2A PLACEBO-CONTROLLED & OPEN-LABEL EXTENSION STUDIES

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Background: IMR-687 is a highly-selective phosphodiesterase 9 (PDE9) inhibitor being developed as an orally-administered therapy for patients with sickle cell disease (SCD) and beta-thalassemia. IMR-687 increases intracellular cGMP levels by activating the NO-cGMP pathway and has been shown in preclinical studies to increase fetal hemoglobin (HbF) expression and reduce hemolysis and sickling of RBCs, pivotal to the reduction of sickle cell crisis.
Aims: The objective of this Phase 2a study is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of IMR-687 as a monotherapy and in combination with hydroxyurea (HU) when administered to subjects with SCD. An open label extension (OLE) of the Phase 2a study is ongoing to assess the long-term safety and benefit of IMR-687 administered for up to 4 years.
Methods: This Phase 2a, randomized, double-blind, placebo-controlled study (IMR-SCD-102) of IMR-687 was conducted in adult subjects with SCD as a monotherapy or in combination with HU. Subjects received placebo or IMR-687 (50 mg escalated to 100 mg or 100 mg escalated to 200 mg) once daily for 4-6 months. On the OLE, subjects received 200 mg IMR-687 once daily. PK, PD parameters [e.g., HbF, F-cells, hemoglobin (Hb) and markers of hemolysis] and vaso-occlusive crises (VOCs) were measured. In preliminary post-hoc analyses of Phase 2a results, longitudinal data of absolute change from baseline in PD parameters were analyzed using mixed model repeated measures (MMRM) with fixed effect of treatment, visit week, treatment-by-visit-week interaction and covariates of baseline value and baseline-by-visit-week interaction.
Results: A total of 93 subjects were randomized and treated in the 'parent' Phase 2a study. As of data cut-off (31-Dec-2021), 24 subjects from the parent study enrolled in the OLE, with ~12 subjects with evaluable PD data at 4 months. Results to date indicate that IMR-687 was generally safe and well-tolerated as a monotherapy and in combination with HU and had no substantial PK effect on HU. No treatment-related serious adverse events were reported, and the most frequent adverse events (≥10%) were sickle cell anemia with crisis, headache and nausea. In subjects treated with IMR-687 without HU (parent study), the LS mean (SEM) absolute change from baseline to Week 24 in F-cells (%) was +5.66 (2.87) in the 100/200 mg group (N=13), compared with -6.00 (3.77) in the placebo group (N=7), for an LS mean difference of 11.66 (SEM=4.72; p=0.0190). A trend for improvement in HbF (%) was observed in active groups without HU (compared to placebo group). Absolute changes in F-cells (%) and HbF (%) were highly-correlated in the IMR-687 groups without HU after 24 weeks (N=19, r=0.75, p<0.0001). In subjects on the OLE, at month 4, HbF (%) and F-cells (%) showed a mean absolute change of +1.9 and +7.3, respectively, with minimal changes in Hb. Two patients with the longest time on study (18 and 8 months) showed a 64% and 69% reduction, respectively, in rate of VOCs (relative to same time prior to treatment) as well as sustained changes in HbF, F-cells and markers of hemolysis.
Summary/Conclusion: Results from the Phase 2a and OLE studies (as of data cut-off) demonstrate that daily dosing of up to 200 mg IMR-687 was safe and well-tolerated as a monotherapy or in combination with HU. Treatment with 200 mg IMR-687 was shown to increase F-cells (%) with trends for improved HbF, markers of hemolysis and rate of VOCs. Based on these encouraging data, a Phase 2b study testing IMR-687 at higher doses was initiated to further explore IMR-687 as a disease-modifying therapy for SCD.

S264 DIFFERENTIAL ENDOTHELIAL VCAM1 EXPRESSION AND IMPLICATIONS FOR SICKLE CELL ANEMIA VASCULOPATHY

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Background: Vascular disease is systemic in sickle cell anemia (SCA), with profound effects in organs like the brain, where stroke is the most severe end of the cerebral vasculopathy spectrum. Endothelial dysfunction is an important pathobiological mechanism in SCA systemic vasculopathy, with upregulation of adhesion molecules (e.g., VCAM-1), lower nitric oxide bioavailability, and increased oxidative stress. In previous association studies, we found positive associations between the presence of three specific *VCAM1* gene promoter haplotypes and i) high blood flow velocities in the median cerebral artery, and ii) a chronic hemolysis biochemical marker.
Aims: The aims of our work were: a) to investigate the functional role of those *VCAM1* promoter haplotypes in endothelial cell response following endothelial activation through TNF-α stimulation; b) to assess the modulation role of proinflammatory and/or pro-oxidative stimuli on endothelial *VCAM1* expression; and, finally, to evaluate how hydroxyurea (HU) treatment would affect that expression.
Methods: After molecular cloning of three *VCAM1* promoter haplotype constructs, using pGL4 promoterless vectors, haplotype sequence was confirmed, by Sanger sequencing, prior to transfection. Transfection experiments for each construct were performed, with or without TNF-α stimulation, using EAhy926, and HBEC as macrovascular and microvascular endothelial cell models, respectively. Differences in promoter activity were assessed by luciferase reporter assay. RNA was extracted from non-transfected EAhy926 and HBEC cell cultures stimulated or not with TNF-a and/or hemin, and with or without HU treatment. RT-qPCR was performed to analyze *VCAM1* expression. *HMOX1* and *NOS3* were also analyzed for comparison purposes.
Results: Our results showed that two *VCAM1* promoter haplotypes, previously associated with pediatric cerebral vasculopathy and hemolysis in SCA, increased promoter activity in transfected and TNF-α-stimulated EA.hy926 and HBEC cells, consistent with a higher *VCAM1* expression in macro and microvascular settings. In non-transfected cells, we also observed TNF-a-induced *VCAM1* overexpression as well as heme-induced overexpression of *HMOX1* in both cell models. Heme did not affect *VCAM1* nor *NOS3* expression and the latter was also not affected by TNF-a stimulus. Hydroxyurea treatment lowered TNF-a-induced *VCAM1* and *NOS3* expression but did not affect heme-induced *HMOX1* expression.
Summary/Conclusion: These data further indicate that *VCAM1* haplotypes we previously associated with pediatric cerebral vasculopathy and hemolysis in SCA, induce higher *VCAM1* expression potentially affecting both cerebral and systemic vasculopathy risk. The differential endothelial expression of *VCAM1*, *NOS3*, and *HMOX1* after proinflammatory and/or pro-oxidative stimuli also reinforces their genetic modulation role in SCA systemic vasculopathy.

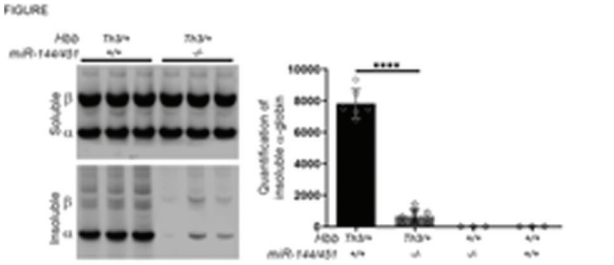
Changing the scene on thalassemias

S265 MIR-451 FUNCTION ON ULK1-MEDIATED AUTOPHAGY OF FREE ALPHA-GLOBIN IN BETA-THALASSEMIA

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Background: β-Thalassemia is a common, frequently debilitating, inherited anemia caused by *HBB* gene mutations that reduce or eliminate the expression of the β-globin subunit of adult hemoglobin (HbA, α2β2). Consequently, excess free α-globin forms toxic precipitates during erythropoiesis, causing destruction of red blood cells (hemolysis) and apoptosis of their precursors (ineffective erythropoiesis [IE]). In many respects, β-thalassemia resembles other protein aggregation disorders in which the accumulation of unstable misfolded proteins leads to tissue destruction. Previously, we showed that free α-globin is eliminated by protein quality-control pathways, including the ubiquitin-proteasome system and autophagy (Khandros *et al.*, Blood 2012). Recently, we identified that free α-globin is eliminated by ULK1-dependent, ATG5-independent autophagy that is suppressed by mTORC1 (Lechauve *et al.* Sci Transl Med 2019). We measured an elevated mTORC1 activity in β-thalassemic erythroid cells and the administration of the mTORC1 inhibitor rapamycin to β-thalassemic mice (strain $Hbb^{Th3/+}$) caused a reduction in α-globin precipitates with lessening of anemia and IE.
Aims: Our overall hypothesis is that inhibition of mTORC1 can alleviate β-thalassemia by stimulating ULK1-mediated autophagy of free α-globin. We will determine how disruption of the *miR-144/451* locus impacts AMPK and mTORC1 activity in erythoird cells and how ablation of miR-144/451 mitigates β-thalassemia.
Methods: Our initial step has been to cross our mouse strains $miR\text{-}144/451^{-/-}$ and $Hbb^{Th3/+}$. miR-451, the most abundant erythroid microRNA, targets the mRNA encoding CAB39/MO25, a cofactor for the LKB1 kinase, which activates AMPK (Fang *et al.* Hematologica 2018). Moreover, activated-AMPK indirectly inhibits mTORC1 by phosphorylating TSC1/2. mTORC1 activity has been analyzed in maturation stage-matched erythroid precursors by immuno-flow cytometry and Western blotting. Afterwards we used mutliple readouts to assess β-thalassemia pathology including complete blood counts, electron microscopy of FACS-purified reticulocytes, RBC fractionation followed by gel electrophoresis to quantify α-globin precipitates, and assessment of extramedullary erythropoiesis in the spleen.
Results: Here we show that genetic elimination of miR-451 alleviates β-thalassemia. Loss of miR-144/451 decreased erythroid mTORC1 activity in β-thalassemic erythroblasts by 33%, as measured by reduction of ribosomal protein S6 phosphorylation ($P<0.01$). In β-thalassemic mice, elimination of miR-144/451 resulted in a 92% reduction of red blood cell α-globin precipitates ($P<0.0001$; figure), with lessening of hemolysis and IE, as evidenced by 27% increased RBC count ($P<0.0001$), 3-fold decreased reticulocyte count ($P<0.0001$), and decreased spleen weight (0.52 ± 0.05 vs 0.22 ± 0.05 g, n=7; $P<0.0001$) compared to β-thalassemic mice with intact *miR-144/451* alleles. Importantly, the beneficial effects of miR-144/451 ablation were significantly reduced by genetic ablation of *Ulk1* or *Cab39*, indicating that loss of miR-451 stimulates ULK1-mediated autophagy of free α-globin through the AMPK/mTORC1 pathway.



Legend: Analysis of soluble and insoluble globin chains by triton–acetic acid–urea gel electrophoresis and insoluble α-globin chain quantification. Results are presented as mean ± SD; ****$p < 0.0001$ by t-test.

Summary/Conclusion: Advances in medical management and hematopoietic stem cell transplantation have improved and extended the lives of β-thalassemia patients significantly, however, new therapies are still required to further optimize care. Our findings suggest two novel therapeutic strategies to treat β-thalassemia by enhancing ULK1-mediated autophagy of free α-globin: pharmacological inhibition of mTORC1 or suppression of miR-451 by antagomirs.

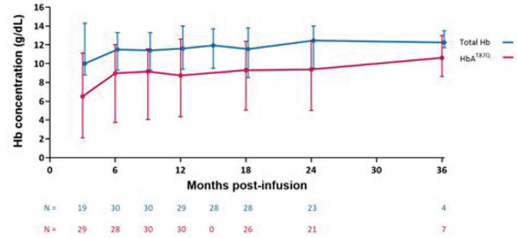
S266 BETIBEGLOGENE AUTOTEMCEL IN PATIENTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA: UPDATED RESULTS FROM HGB-207 (NORTHSTAR-2) AND HGB-212 (NORTHSTAR-3)

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Background: Transfusion-dependent β-thalassemia (TDT) is a genetic disease requiring lifelong packed red blood cell (pRBC) transfusions and regular iron chelation. Betibeglogene autotemcel (beti-cel) is a one-time ex vivo gene therapy that adds functional copies of a modified *HBB* gene, $\beta^{A\text{-}T87Q}$, into patients' hematopoietic stem cells to correct the underlying genetic cause of TDT and enable lifelong, stable production of functional adult hemoglobin (Hb) sufficient for transfusion independence (TI).
Aims: To evaluate updated efficacy and safety of beti-cel in patients with TDT in ongoing, fully enrolled phase 3 studies, HGB-207 (Northstar-2; non-β^0/β^0 genotypes; NCT02906202) and HGB-212 (Northstar-3; β^0/β^0, $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$, and $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$ genotypes; NCT03207009).
Methods: CD34+ cells are mobilized using granulocyte-colony stimulating factor and plerixafor, collected via apheresis, transduced with BB305 lentiviral vector, and infused back into patients after single-agent, pharmacokinetic-adjusted busulfan-based myeloablation. Primary endpoint in both studies is TI (weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 mo; the primary endpoint for HGB-212 is the result of a protocol amendment dated October 2020). Patients are followed for 2 y and, upon study completion, are eligible for a long-term follow-up study for an additional 13 y. Data are median (min–max).
Results: As of 30 November 2020, 41 patients (29 non-β^0/β^0, 12 β^0/β^0 genotype) had been treated with beti-cel and followed for 24.3 (0.9–42.2) mo. Age at informed consent was 13 (4–34) y. All patients with >1.3 mo follow-up (n=40) achieved neutrophil and platelet engraftment 25.5 (13–39) and 46.0 (13–94) d after infusion, respectively. Lymphocyte nadir within the first mo post-infusion was 0.47 x 10^9/L (0.02–1.81 x 10^9/L; n=41; reference range, 0.9–6.5 x 10^9/L [range varies by laboratory]).
Transfusion independence was achieved by 30/34 (88.2%) evaluable patients, including 6/7 (85.7%) patients with β^0/β^0 genotypes and 24/27 (88.9%) patients with non-β^0/β^0 genotypes (including 10/11 β^+/β^0, 5/6 β^E/β^0, 3/3 β^+/β^+, 2/3 $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$, 2/2 $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$, and 2/2 $\beta^+/\beta^{+IVS\text{-}I\text{-}110}$ genotypes). Weighted average Hb during TI was 11.5 (9.5–13.6) g/dL. At last follow-up, all 30 patients had maintained TI for 20.6 (12.3–39.4) mo. All patients who achieved TI had Hb ≥9 g/dL at 6 mo post-infusion. Unsupported total Hb and HbA^{T87Q} over time are shown in the **Figure.**
Adverse events in ≥2 patients considered by the investigator to be related or possibly related to beti-cel included abdominal pain (n=3) and thrombocytopenia (n=3; 1 serious event). Serious adverse events that occurred in ≥2 patients included pyrexia (n=4), thrombocytopenia (n=3), veno-occlusive liver disease (n=3), febrile neutropenia (n=2), neutropenia (n=2), and stomatitis (n=2). There were no deaths and no evidence of clonal dominance or insertional oncogenesis in these studies. Fertility preservation was performed in 30/41 (73.2%) patients. A pregnancy after in vitro fertilization was reported in the partner of a male patient who had banked sperm prior to beti-cel infusion. The pregnancy was ongoing at last follow-up.

Figure. Unsupported Total hemoglobin (Hb) and HbA^{T87Q} Levels Over Time in Patients Who Achieved Transfusion Independence. Unsupported total Hb is defined as the total Hb level without any packed red blood cell transfusions within 60 days prior. Median (min–max) depicted.



Summary/Conclusion: In this analysis, 88% of treated evaluable patients in HGB-207 and HGB-212 achieved TI and demonstrated stable HbA^{T87Q}. The safety profile was consistent with that of busulfan-based myeloablative conditioning. Beti-cel–related events were consistent with side effects of DMSO, a cryoprotectant used in the drug product.

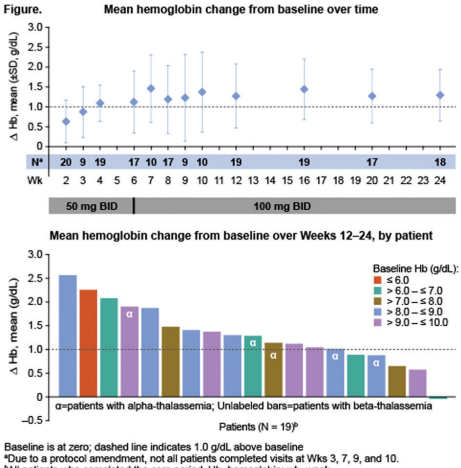
S267 RESULTS FROM A PHASE 2, OPEN-LABEL, MULTICENTER STUDY OF THE ORAL PYRUVATE KINASE ACTIVATOR MITAPIVAT IN ADULTS WITH NON–TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

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Background: Thalassemias are characterized by ineffective erythropoiesis and hemolysis due to imbalanced production and precipitation of globin chains. Adenosine triphosphate (ATP) levels are reduced in thalassemic red blood cells (RBCs), despite increased energy demands to maintain RBC cell integrity. Mitapivat (AG-348) is an oral activator of RBC pyruvate kinase (PKR), an enzyme regulating ATP production via glycolysis. In mice, mitapivat increased ATP synthesis and survival of thalassemic RBCs. Mitapivat has been shown to increase hemoglobin (Hb) in patients (pts) with PK deficiency and sickle cell disease.
Aims: To report the results of the 24-week (wk) core period of a phase 2 open-label trial of mitapivat in adults with α- or β-non–transfusion-dependent thalassemia (NTDT; NCT03692052).
Methods: Key inclusion criteria: β-thalassemia ± α-globin gene mutations, Hb E β-thalassemia, or α-thalassemia (Hb H disease); Hb ≤10.0 g/dL; ≤5 RBC units transfused in prior 24 wks and none in 8 wks prior to study drug. Pts received mitapivat 50 mg orally twice daily (BID), then increased to 100 mg BID at Wk 6 visit, if tolerated. Primary endpoint was % pts who achieved a Hb response (increase ≥1.0 g/dL from baseline [BL] at any time between Wks 4–12, inclusive). Secondary endpoints included sustained Hb response (≥2 Hb increases of ≥1.0 g/dL vs BL during Wks 12–24 after achieving a primary Hb response), time to first ≥1.0 g/dL Hb increase, markers of hemolysis and erythropoiesis, and safety.
Results: Of 20 pts (15 female) who received mitapivat, the mean age (SD) was 45.3 (11.8) yrs (range 29–67); mean (SD) BL Hb was 7.9 (1.4) g/dL (range 5.1–9.8). At Wk 6, all pts were escalated to 100 mg BID. Nineteen pts (95.0%) completed the core period, one discontinued due to adverse event (AE);17 pts continued to the extension period. Sixteen pts (80.0%, 90% CI 59.9, 92.9; p<0.0001) achieved a Hb response, including 5/5 pts with α-thalassemia and 11/15 pts with β-thalassemia. Mean (SD) time to first Hb increase >1.0 g/dL was 4.5 (3.2) wks, and mean Hb (SD) increase from BL during Wks 12–24 was 1.3 (0.6) g/dL. A sustained response was achieved in 65% of pts, including 5/5 pts with α-thalassemia and 8/15 pts with β-thalassemia. Mean Hb change from BL over time and average Hb increase from BL by patient are shown (Figure). Hb increases occurred across the spectrum of BL levels. Directional improvements in markers of erythropoiesis and hemolysis were also observed. The safety profile was consistent with that of previously published mitapivat studies. There was one serious grade 3 unrelated AE of renal impairment which led to treatment discontinuation. There were three non-serious grade 3 AEs leading to dose reduction: 1 resulted in a permanent dose reduction to 50 mg BID, and 2 were successfully rechallenged at 100 mg BID. The most common non-serious AEs occurring in ≥25% of pts were initial insomnia (10/20), dizziness (6/20), and headache (5/20). Dose escalation to 100 mg BID was well tolerated and not associated with any increase in AEs. Twelve pts had DXA scans at BL and 6 months; no notable trends for changes in bone mineral density were observed.

Figure. Mean hemoglobin change from baseline over time



Baseline is at zero; dashed line indicates 1.0 g/dL above baseline
[a]Due to a protocol amendment, not all patients completed visits at Wks 3, 7, 9, and 10.
[b]All patients who completed the core period. Hb=hemoglobin; wk=week.

Summary/Conclusion: These results demonstrate that PKR activation with mitapivat was well tolerated and improved anemia, hemolysis, and ineffective erythropoiesis, and may represent a novel therapeutic approach for pts with α- or β-thalassemia. Pivotal trials will be initiated in 2021.

S268 INHIBITION OF FIBROBLAST GROWTH FACTOR-23 (FGF-23) AS A NOVEL STRATEGY TO TARGET BONE AND HEMATOPOIETIC STEM CELL NICHE DEFECTS IN BETA-THALASSEMIA

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Background: Over decades the research on beta-thalassemia (BT) has been mostly focused on erythropoiesis, leaving the study of the bone marrow (BM) environment and hematopoietic stem cells (HSC) underexplored. We have recently demonstrated that HSC function in BT is negatively affected by an altered BM microenvironment and that targeting of the defective HSC-BM stromal niche crosstalk rescues the impaired quiescence and self-renewal of HSC (*Aprile et al., Blood 2020*). BT can be cured by HSC transplantation from healthy donors or autologous HSC upon gene therapy. Since the quality of HSC and the conditions for engraftment depend on the presence of a healthy BM microenvironment, niche-HSC crosstalk plays a crucial role for post-transplant outcome.
Consistently with the common finding of osteoporosis in BT patients, we found in *Hbb*$^{th3/+}$ (*th3*) BT mice reduced bone deposition and low levels of parathyroid hormone (PTH), negatively affecting stem cell number, quiescence and self-renewal. Fibroblast growth factor-23 (FGF-23) is a hormone mainly secreted by osteocytes, which acts as negative regulator of bone metabolism and PTH production. Since FGF-23 is positively modulated by the anemia-related factor erythropoietin (EPO), we hypothesized that the high EPO levels in BT, subsequent to ineffective erythropoiesis, might contribute to FGF-23 increase, thus affecting bone and BM niche homeostasis.
Aims: We investigated the mechanisms underlying bone and HSC niche defects in BT and we focused on FGF-23. We also explored the role of EPO on enhancing FGF-23 levels.
Methods: We measured levels of FGF-23 in *th3* mice and BT patients by ELISA. We inhibited FGF-23 signaling in *th3* mice by *in vivo* administration of FGF-23 blocking peptide and we analyzed bone density by pQCT, HSC and erythroid populations upon treatment. We neutralized *in vivo* the EPO axis and analyzed FGF-23 levels.
Results: We measured high levels of circulating FGF-23 in BT mice (*n*=10) and patients (*n*=17). To provide proof of concept data of the causative role of FGF-23 on BT bone and stromal niche defects, we inhibited FGF-23 signaling. FGF-23 inhibition rescued the bone defect in *th3* mice, by increasing trabecular bone mineral density. Importantly, the treatment restored the frequency of HSC to levels comparable to wild-type controls by expanding the pool of quiescent cells. FGF-23 inhibition had also a positive anti-apoptotic effect on the expanded BM erythroid compartment, promoting the maturation of erythroid precursors, confirming results obtained in models of secondary anemias. *In vivo* neutralization of EPO axis demonstrated the causative role of EPO on enhancing FGF-23 levels in BT.
Preliminary evidence in BT patients showed negative correlations between FGF-23 and markers of bone homeostasis (e.g. osteocalcin and VitD), whereas positive correlations with ineffective erythropoiesis (e.g. reticulocytes).
Further analysis will unravel the negative impact of high FGF-23 on bone mineralization and BM stromal niche-HSC interactions in BT.
Summary/Conclusion: Our findings uncover an underexplored role of FGF-23 in bone and BM niche defects in BT, as a condition of severe anemia and chronic EPO stimulation, thus proposing FGF-23 as the molecule at the crossroads of erythropoiesis and bone metabolism. The inhibition of FGF-23 signaling might provide a novel strategy to ameliorate bone compartment and restore HSC-BM niche interactions in BT, with a potential translational relevance in improving HSC transplantation and gene therapy/editing approaches.

S269 TGF-BETA SIGNALING CONTROLS THE LINEAGE CELL FATE OF HEMATOPOIETIC STEM CELLS TOWARDS ERYTHROID BRANCHING IN BETA-THALASSEMIA

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Background: Beta-thalassemia (Bthal) is a genetic disorder due to mutations in the ß-globin gene, leading to a reduced or absent production of HbA, which interferes with erythroid cell maturation and limits normal red cell production. Patients are affected by severe anemia, hepatosplenomegaly, and skeletal abnormalities due to rapid expansion of the erythroid compartment in bone marrow (BM) caused by ineffective erythropoiesis. In a classical view of hematopoiesis, the blood cell lineages arise via a hierarchical scheme starting with multipotent stem cells that become increasingly restricted in their differentiation potential through oligopotent and then unipotent progenitors. In human, novel purification strategies based on differential expression of CD49f and CD90 enrich for long-term (49f+) and short-term (49f–) repopulating HSCs, with similar myeloid (My) and lymphoid (Ly) potential. In this view, it has been proposed that erythroid (Ery) and megakaryocytic (Mk) fates branch off directly from 49f– cell. Recently, in a new study the use of CLEC9A marker highlighted the separation between multipotent (Ery/My/Ly) long-term repopulating cells (Subset1, defined as CLEC9A^{high}CD34^{low}) and cells with only My/Ly and no Ery potential (Subset2, defined as CLEC9A^{low}CD34^{high}) within the HSC/MPP compartment.
Aims: Recent evidence showed that the BM microenvironment is perturbed in Bthal. Our aim is to understand how the priming and kinetics of HSC undergoing lineage specification and differentiation are changed under this stress environment.
Methods: Immunophenotype and functional analysis of the lineage commitment allowed to characterize of most primitive Bthal HSC/MPP cells. Gene expression profiling of hematopoietic subpopulations sorted from BM samples of Bthal patients and healthy donors (HDs) delineated the transcriptional networks governing hematopoiesis. We evaluated the expression levels of niche factors involved in the regulation of hematopoiesis/erythropoiesis by ddPCR on RNA purified from Bthal mesenchymal stromal cells. Their protein levels in the BM plasma were analyzed by ELISA. Confirmation experiments are ongoing *in vivo* in Bthal murine model (*Hbb*$^{th3/+}$ strain).
Results: An increased proportion of MPPs was observed in Bthal patients compared to HDs. The Subset1 compartment was actually endowed with an enhanced Ery potential. Focusing on progenitors (CD34$^+$ CD38$^+$) and using a new sorting scheme that resolved My, Ery, and Mk lineage fates, we found a reduction of Ery (CD71$^+$ BAH1$^{-/+}$) subsets in Bthal samples. By gene expression profiling of Bthal HSC/MPP, we observed down-regulation of TGFß signaling-induced gene expression and enrichment in erythroid signature. The levels of TGFß molecules were altered in Bthal BM micro-environment and treatment of HD Subset 1 cells demonstrates how TGFß/BMP pathway is instrumental for the erythroid cell lineage specification of HSCs. The analysis of molecular pathways driven by TGFß signaling led to the identification of druggable targets with the potential to improve thalassemic hematopoiesis and to normalize erythropoiesis. Ongoing *in vivo* studies with specific drugs will provide cues to rescue the unbalanced hematopoietic primitive compartment
Summary/Conclusion: Overall, these findings show that Bthal HSCs are exiting from the quiescent state towards a preferential erythroid differentiation. The drivers are likely specific niche signals, linked to the TGFß, and chronic BM stimulation or, alternatively, a specific regulation of the '*erythroid branching*', naturally present in the HSC pool, which is exacerbated by the pathophysiology of the disease.

Changing the scene on congenital anemias

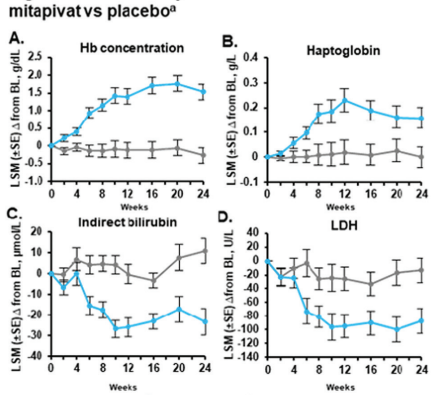
S270 ACTIVATE: A PHASE 3, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MITAPIVAT IN ADULTS WITH PYRUVATE KINASE DEFICIENCY WHO ARE NOT REGULARLY TRANSFUSED

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Background: Pyruvate kinase (PK) deficiency is a rare hereditary disease caused by reduced red blood cell PK (PKR) enzyme activity leading to defective glycolysis. The resulting lifelong hemolytic anemia is associated with serious complications, regardless of transfusion status. Management is limited to supportive therapies. Mitapivat (AG-348) is an investigational, first-in-class, oral, allosteric activator of PKR, which was shown to improve hemolysis for up to 42 months in a phase (Ph.) 2 study of patients (pts) with PK deficiency.
Aims: The ACTIVATE study (NCT03548220) evaluated the efficacy and safety of mitapivat in adult pts with PK deficiency who were not regularly transfused.
Methods: ACTIVATE was a Ph. 3, randomized, double-blind, placebo (PBO)-controlled study. A 12-week (wk) dose escalation (5, 20, 50 mg twice daily) period (Part 1) was followed by a 12-wk fixed-dose period (Part 2). Primary endpoint was hemoglobin (Hb) response, defined as ≥1.5 g/dL increase in Hb from baseline (BL), sustained at ≥2 scheduled assessments at Wks 16, 20, or 24 during Part 2. Secondary endpoints were prespecified and tested in a hierarchical order at a 2-sided α=0.05 as follows: change from BL in Hb concentration, indirect bilirubin, reticulocyte percentage (%), and Hochberg testing for change from BL in lactate dehydrogenase (LDH), haptoglobin, and PK deficiency diary (PKDD) and PK deficiency impact assessment (PKDIA). The PKDD and PKDIA are disease-specific patient-reported outcomes (PROs) in which a higher score indicates more severe disease impact.
Results: Eighty pts were randomized (mitapivat n=40; PBO n=40). The population was balanced between the mitapivat and PBO arms: mean age 36.0 vs 37.2 years, 40% vs 40% male, 70% vs 80% white, mean BL Hb 8.6 vs 8.5 g/dL. The primary endpoint was met, with 16 mitapivat pts (40%) achieving a sustained Hb response vs 0 PBO pts (p<0.0001). Secondary endpoints were met, including significant improvements with mitapivat compared with PBO in BL Hb, hemolysis markers, and PROs: average change from BL (difference in least squares mean [95% CI]) in Hb concentration, 1.8 g/dL (1.2, 2.4; p<0.0001), indirect bilirubin, –26.26 µmol/L (–37.82, –14.70; p<0.0001), reticulocyte %, –0.1011 (–0.1391, –0.0632; p<0.0001), LDH, –70.81 U/L (–115.88, –25.74; p=0.0027), haptoglobin 0.158 g/L (0.043, 0.273; p=0.0079), and PKDD –3.11 (–5.80, –0.41; p=0.0247) and PKDIA –3.25 (–6.39, –0.12; p=0.0421). The Hb and hemolysis marker improvements in the mitapivat group were rapid and maintained over time (Figure). Treatment-emergent adverse events (TEAEs) occurred in 35 pts in each arm. TEAEs grade ≥3 occurred in 10 (25.0%) mitapivat vs 5 (12.8%) PBO pts. The most common TEAEs with mitapivat were nausea and headache, which were less frequent for mitapivat vs PBO (n=7; 17.5% vs n=9; 23.1% and n=6; 15.0% vs n=13; 33.3%, respectively). The most common TEAEs grade ≥3 with mitapivat were hypertriglyceridemia and hypertension (both n=2; 5.0%). Transaminase increases any grade/grade ≥3 occurred in 1 (2.5%)/0 (0%) mitapivat pt vs 6 (15.4%)/2 (5.1%) PBO pts. No TEAEs led to discontinuation.

Figure: Hb and hemolysis marker outcomes for mitapivat vs placebo[a]



[a]Difference in LSM for secondary endpoints comparing BL to average change at Weeks 16, 20, and 24; p-values are based on the MMRM method: Hb concentration, p<0.0001; haptoglobin, p=0.0079; indirect bilirubin, p<0.0001; LDH, p=0.0027;. BL=baseline; Hb=hemoglobin; LDH=lactate dehydrogenase; LSM=least squares mean; MMRM=mixed-effect model repeated measure; SE=standard error

Summary/Conclusion: ACTIVATE is the first PBO-controlled study in PK deficiency. Primary and secondary endpoints were met, indicating clinically meaningful benefit for pts treated with mitapivat. No new safety signals were identified. Mitapivat has the potential to be the first disease-modifying drug therapy approved for PK deficiency.

S271 ACTIVATE-T: A PHASE 3, OPEN-LABEL, MULTICENTER STUDY OF MITAPIVAT IN ADULTS WITH PYRUVATE KINASE DEFICIENCY WHO ARE REGULARLY TRANSFUSED

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Background: Pyruvate kinase (PK) deficiency is a rare hereditary disease caused by reduced red blood cell PK (PKR) enzyme activity leading to defective glycolysis and decreased red blood cell (RBC) lifespan, resulting in lifelong hemolytic anemia and associated comorbidities. In a natural history study, 12% of adult patients (pts) with PK deficiency were found to require regular transfusions, which have been associated with chronic complications, including iron overload and end organ damage. There are currently no approved disease-modifying drug therapies for this condition. Mitapivat (AG-348) is an investigational, first-in-class, oral, allosteric activator of PKR. In a phase (Ph.) 2 study of PK deficiency pts that were not regularly transfused, mitapivat improved hemoglobin (Hb) and hemolysis markers for up to 42 months. This current study was designed to further evaluate mitapivat in the regularly transfused PK deficiency population.
Aims: The ACTIVATE-T study (NCT03559699) evaluated the efficacy and safety of mitapivat in adult pts with PK deficiency who were regularly transfused.
Methods: ACTIVATE-T was a global, multicenter, open-label, Ph. 3 study in regularly transfused adults with PK deficiency. A 16-week (wk) dose escalation (5, 20, 50 mg twice daily) period (Part 1) was followed by a 24-wk fixed-dose period (Part 2). Key inclusion criteria: age ≥18 years (yrs), documented presence of ≥2 mutant alleles in *PKLR* (of which ≥1 was a missense mutation) and ≥6 transfusion episodes in the past 52 wks. Primary endpoint: reduction in transfusion burden, defined as ≥33% reduction in number of RBC units transfused during Part 2 compared with the pt's individual historical transfusion burden standardized to 24 wks. The p-value calculation was based on the binomial exact test of H0: transfusion reduction response rate ≤10% vs H1: transfusion reduction response rate >10% at a 1-sided α=0.025. Pts who discontinued the study before completing 12 wks of treatment in Part 2 were considered non-responders. Secondary endpoints included transfusion-free responders (defined as no transfusions during Part 2) and annualized RBC units transfused.
Results: Twenty-seven pts were enrolled: mean age 36.6 yrs, 26% male, 74% white, mean baseline Hb 9.2 g/dL. Of the 27 pts treated in the study, 20 (74%) completed Part 2, 6 (22%) discontinued treatment, and 1 was lost to follow-up. Ten (37%) pts treated with mitapivat achieved a ≥33% reduction in transfusion burden (1-sided p=0.0002; Table). Mean number of RBC units transfused (annualized) was 11.38 up to the end of the study, compared with 16.63 historically; relative reduction=39%. Six (22%) pts were transfusion-free during Part 2. Treatment-emergent adverse events (TEAEs) occurred in all pts. TEAEs grade ≥3 occurred in 8 (30%) pts. The most common TEAEs (any grade) were increased alanine aminotransferase (n=10; 37%) and headache (n=10; 37%). No TEAEs led to discontinuation of treatment.

Table: Primary and secondary efficacy endpoint outcomes with mitapivat (N=27)

Primary endpoint	Responders, n[d]	Responders, %	95% CI	1-sided p-value[e]
Reduction in transfusion burden[a]	10	37%	19–58%	0.0002
Secondary endpoint	**Responders, n[d]**	**Responders, %**	**95% CI**	
Transfusion-free[b]	6	22%	9–42%	
Secondary endpoint	**Historical mean, n**	**During study mean, n**	**Relative reduction**	
Annualized RBC units transfused[c]	16.63	11.38	39%	

[a]Defined as ≥33% reduction in number of RBC units transfused during Part 2, standardized to 24 wks, compared with historical transfusion burden standardized to 24 wks; [b]Defined as no transfusions during Part 2; [c]Defined as total number of RBC units standardized to 52 wks; [d]Pts who discontinued before completing 12 wks of treatment in Part 2 were considered non-responders; [e]Based on binomial exact test of H0: transfusion reduction response rate ≤10% vs. H1: transfusion reduction response rate >10% at a 1-sided α=0.025.
CI=confidence interval; pts=patients; RBC=red blood cell; wks=weeks

Summary/Conclusion: ACTIVATE-T is the first Ph. 3 clinical study in pts with PK deficiency who are regularly transfused. The study demonstrated a significant decrease in transfusion burden, and 22% of pts were transfusion-free. No new safety signals were identified. These results support that mitapivat, through the novel mechanism of PKR activation, provides meaningful benefit to regularly transfused pts with PK deficiency. Mitapivat has the potential to become the first disease-modifying drug therapy approved for PK deficiency.

S272 IDENTIFICATION OF A NOVEL GENE CAUSING AN AUTOSOMAL RECESSIVE FORM OF CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE III

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Background: Congenital Dyserythropoietic Anemia (CDA) Type III was first described in a Swedish family as a disease with a dominant hereditary pattern caused by mutations in the *KIF23* gene, whose protein product is involved in cytokinesis. Despite this, there are several reports of an autosomal recessive inheritance form of CDA III with no identified genetic cause.
Aims: To identify the genetic origin of the recessive forms of Congenital Dyserythropoietic Anemia (CDA) Type III
Methods: Gene variant analysis using WES sequencing coupled with siRNA silencing and microscopy studies. CRISPR/Cas9 technology to generate knock-in models in zebrafish and knock-out cellular models.
Results: Here we report a young Spanish case clinically diagnosed of CDA III with no mutations in any of the known CDA genes, including *KIF23* gene. His bone marrow aspirate showed the typical phenotype of CDA III with giant multinucleated erythroblasts, giant hyperlobulated erythroblast, inter-cytoplasmatic bridges and chromatin bridges. The rest of the family was unaffected pointing to a possible recessive form of CDA III. The family was analyzed by WES and a pathogenic rare missense mutation was identified in homozygosis in the proband; while the rest of the family (father, mother and unaffected sister) were heterozygous. Silencing of the identified gene in HeLa cells mimics the phenotype observed in the bone marrow of our patient. Complete abrogation of this gene in zebrafish shows defects in cytokinesis and erythropoiesis and showing a clear anemic phenotype. The protein product of this gene has a role in cytokinesis and it is highly expressed in erythroid cells.
Summary/Conclusion: All these evidences indicate that we have identified a new gene responsible for an autosomal recessive form of CDA type III. We are currently generating a knock-in zebrafish models with the same mutation as the one presented in our patient, as well as sequencing additional possible CDA type III cases.

S273 ESTABLISHMENT AND PHENOTYPING OF VIABLE MOUSE MODELS OF X-LINKED SIDEROBLASTIC ANEMIA AND PROTOPORPHYRIA USING CRISPR-CAS9 EDITING

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Background: 5-aminolevulinic acid synthase 2 (ALAS2) is the first and rate-limiting enzyme of erythroid heme biosynthesis. It combines glycine

and succinyl-coA to form 5-aminolevulinic acid (ALA), the precursor of porphyrins and heme. ALAS2 is essential in mammals, its expression being precisely regulated during erythropoiesis. Inherited ALAS2 defects cause two rare diseases: X-linked Sideroblastic Anemia (XLSA) and X-linked Protoporphyria (XLPP), due to loss-of-function and gain-of-function mutations, respectively. Male XLSA patients have a microcytic hypochromic anemia of variable severity, characterized by abnormal mitochondrial iron deposits in nucleated and enucleated erythroid cells, termed ring sideroblasts and siderocytes. In two-thirds of patients, the anemia responds to pyridoxine (B6) supplementation. Both male and female XLPP patients develop acute photosensitivity, due to accumulation of free protoporphyrin (PP) in erythrocytes. No curative treatment, other than hematopoietic stem cell transplantation, is available for XLSA or XLPP.
Aims: The lack of ALAS2 mouse models has limited both our understanding of physiopathology, and potential treatment of XLSA and XLPP. We aimed to establish XLSA and XLPP mouse models.
Methods: Employing CRISPR/Cas9 gene targeting technology, we established 3 common XLSA (ALAS2 p.R170H, p.R411H and p.R452H) and 1 XLPP (ALAS2 p.Q548X) mutations in mice. The natural history of the disease was determined for each strain, focusing on blood parameters, free PP levels, and erythropoiesis. We also examined the consequences of vitamin B6 deficient and supplemented diets on each of these parameters.
Results: Four independent injections were performed in E0.5 blastocysts (C57BL/6N) generating a total of founder 45 animals. Animals harboring the expected allele were identified (p.R170H: 3 of 13; p.R411H: 1 of 2; p.R452H: 1 of 14 and Q548X: 4 of 16 animals) and transmitted through the germline. Mutant and control littermate animals have been phenotyped up to one-year of age.
XLSA: Variable numbers of siderocytes are present in peripheral blood smears of animals of all three XLSA lineages as early as 1 week of age and each develops a progressive microcytic, hypochromic anemia.As expected male phenotypes were more severe than female phenotypes, but siderocytes and erythroid defects are also observed in female XLSA carriers. The p.R411H strain has the most severe phenotype. B6 depletion in the p.R411H strain results in a severe ineffective erythropoiesis manifest as extreme splenomegaly and a block in erythroid differentiation.
XLPP: Both XLPP p.Q548X males and females accumulate free PP in erythrocytes. Compared to the Fech^{m1Pas} model (C57BL/6J) of erythroid protoporphyria due to a severe recessive loss-of-function mutation in ferrochelatase, the peak of free PP accumulation occurs earlier in age in XLPP mice. In early stages of the disease (8 weeks), XLPP mice do not develop liver fibrosis.
Summary/Conclusion: For the first time, knock-in ALAS2 mouse strains with viable loss and gain of function mutations have been obtained and each expresses the key features of the corresponding human diseases.

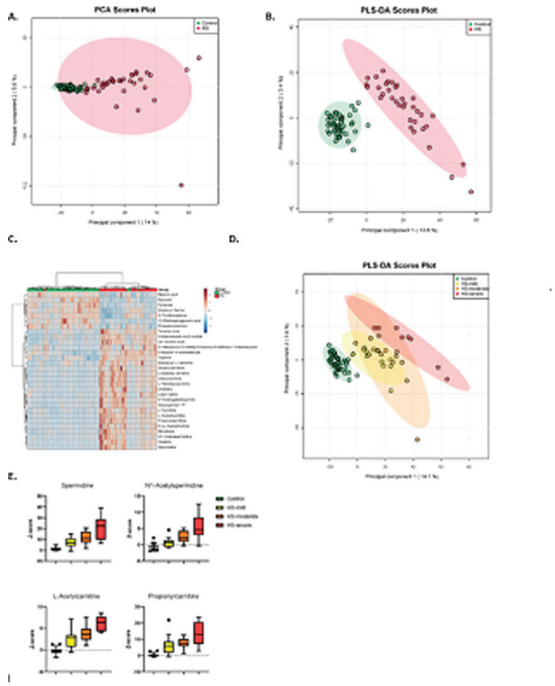
S274 METABOLIC FINGERPRINT IN HEREDITARY SPHEROCYTOSIS CORRELATES WITH RED BLOOD CELL CHARACTERISTICS AND CLINICAL SEVERITY

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Background: Hereditary spherocytosis (HS) is one of the most common forms of hereditary hemolytic anemia in people of northern European descent (1:2000-3000). It is characterized by altered red blood cell (RBC) membrane integrity due to disruption of the (vertical) association between the cytoskeleton and the lipid bilayer. The disorder is highly heterogeneous, both clinically and molecularly, and genotype-phenotype correlations are largely unclear. The mechanistic basis of decreased red blood cell (RBC) deformability in HS has been well established but little is known about the metabolic consequences of reduced membrane-cytoskeleton integrity in HS. This question is especially relevant since RBC membrane proteins are implicated in cellular metabolism. In this study we investigated the metabolic impact of membrane defects using untargeted metabolomics in dried blood spots (DBS) and established a metabolic fingerprint for HS.
Aims: Investigating broad metabolic changes in HS by defining a metabolic signature for HS could **1.** contribute to increased understanding of clinical heterogeneity, and **2.** provide new leads for studying pathophysiological mechanisms in HS.
Methods: Untargeted metabolomics was applied on DBS samples obtained from 35 HS patients and 50 healthy controls by direct infusion high resolution mass spectrometry using a previously established protocol. (1,2) Statistical analyses were performed using MetaboAnalyst and Graphpad Prism (Version 8.3.0;538). Red blood cell deformability was evaluated by osmotic ektacytometry on the Laser Optical Rotational Red Cell Analyzer (Lorrca, RR Mechatronics, Zwaag, Netherlands)
Results: In total, 1770 unique metabolite features were identified in the respective DBS samples from patients and controls. Distinct metabolic profiles between groups were identified by principal component analysis and partial least square discriminant analysis (Figure 1A-B). Distinctive increased metabolites in the HS-fingerprint include polyamines and (acyl) carnitines. Vitamin B6 intermediates, 2,3-diphosphoglyceric acid and glyceraldehyde 3-phosphate were significantly decreased in HS ($p<0.0001$) (Figure 1C). Interestingly, when exploring phenotypic heterogeneity, subgroups of mildly, moderately and severely affected patients could be identified, revealing discrete differences in metabolic profiles for especially the mildly and severely affected patients (Figure 1D). Furthermore, the most discriminating metabolites in these metabolic profiles showed a gradient that relates with clinical disease severity (Figure 1E), and they correlated inversely and statistically significant with red cell characteristics. In addition, a trend to significance was observed for these metabolites and red blood cell deformability as measured by osmotic gradient ektacytometry.

Figure 1.



Summary/Conclusion: In this study we identified a metabolic fingerprint for patients with HS using untargeted metabolomics in dried blood spots. The metabolic disturbances include altered levels of 2,3-DPG and polyamines, that correlate with red cell characteristics and clinical severity. Hence, our data show that untargeted metabolomics in DBS is instrumental in investigating phenotypic heterogeneity and it provides promising leads for studying pathophysiological mechanisms in HS.

Focus on iron metabolism

S275 HEPATOCYTES INSTRUCT LIVER SINUSOIDAL ENDOTHELIAL CELLS TO INDUCE BMP6 IN RESPONSE TO IRON

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Background: Iron availability is essential for erythropoiesis and needs to be maintained within the physiological range to prevent hematological disorders. The liver hormone hepcidin is the master regulator of systemic

iron homeostasis. It binds and triggers degradation of the sole cellular iron exporter ferroportin (Fpn), blocking dietary iron absorption and iron release from cellular stores. Hepatic iron levels control hepcidin mRNA expression in hepatocytes (HCs) by modulating the BMP signaling pathway. Conditions of iron overload induce the growth factor BMP6 that is released from liver sinusoidal endothelial cells (LSECs), the most relevant cell type of the liver for sensing of iron availability. LSECs account for only a very small percentage of total liver cells and primary cultures are difficult to generate as these cells easily transdifferentiate. Therefore detailed molecular insights into how LSECs sense iron levels and the signaling pathways controlling BMP6 production in response to iron levels are challenging to obtain.
Aims: Our aim is to understand the molecular mechanisms of how the liver senses iron availability, controls BMP6 production and hepcidin synthesis. Results are expected to be translated to new therapeutic strategies for iron-related disorders.
Methods: Murine liver cell suspensions were prepared by *in vivo* liver perfusion and digestion. HCs and LSECs were isolated combining cell gradient isolation and exclusion adherence steps or immunoselection with antibodies conjugated to magnetic beads. The quality of the LSEC preparations was assessed by FACS analysis and Scanning Electron Microscopy. Ferritin protein levels and *Transferrin Receptor 1* mRNA expression served as markers to determine the intracellular iron content of isolated liver cells. RNA-seq of HCs and LSECs isolated from FpnC326S mice was performed with Illumina NextSeq500.
Results: We established highly pure primary murine LSEC cultures with 95% of cells positive for LSEC markers. Analyses of the LSEC ultrastructure indicated the presence of fenestrae - a unique LSEC feature that confirms the absence of transdifferentiation. We show that primary LSECs fail to modulate BMP6 expression in response to iron treatment, but require a co-culture with iron-loaded primary HCs to significantly increase BMP6 expression. These data are supported by findings from a genetic mouse model of systemic iron overload (FpnC326S), hallmarked by iron-loaded HCs and elevated BMP6 levels despite a lack of increased iron content in LSECs. RNA-seq analysis of primary HCs and LSECs isolated from FpnC326S mice identified altered signaling pathways. Experiments are ongoing to combine these results with *in silico* ligand-receptor interaction analysis and experiments in primary cell cultures to unravel the hepatocytic factor essential for the iron-dependent regulation of BMP6.
Summary/Conclusion: We established a high quality preparation of primary LSECs as a fundamental tool to investigate how these cells sense iron to modulate BMP6 expression. Our *ex vivo* data reveal that, contrary to former belief, the LSEC-secreted growth factor BMP6 is not regulated by changes in the LSEC intracellular iron content. Accordingly, we show that LSECs isolated from a mouse model of iron overload are not iron-loaded, despite increased BMP6 expression. Importantly, co-culture of primary LSECs with HCs demonstrates that the latter are essential to induce BMP6 expression when iron levels are increased. These data support a model in which cell-to-cell communication between HCs and LSECs is essential to sense iron availability and activate BMP6 transcription.

S276 NEW INSIGHTS INTO PATHOGENIC MECHANISMS OF HEPATIC IRON METABOLISM DUE TO PIEZO1 GAIN OF FUNCTION VARIANTS.

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Background: Dehydrated hereditary stomatocytosis (DHS) is an autosomal dominant condition characterized by alterations in red blood cell membrane permeability to the cations. The most frequently mutated gene in DHS is *PIEZO1* that encodes a mechanoreceptor, a cation channel activated by mechanical stimuli. Pathogenic variants in PIEZO1 result in a gain-of-function (GOF) phenotype with delayed inactivation of the cation channel that leads to erythrocyte dehydration. The most harmful complication is the hepatic iron overload (Andolfo et al, AJH 2018; Picard et al Haematologica 2019). We already demonstrated the involvement of PIEZO1 at hepatic level by alterations of ERK1/2 and BMP/SMADs pathways that led to the suppression of hepcidin (Andolfo et al, AJH 2020). This finding was recently confirmed and extended by the study of the mouse model carrying a GOF variant of PIEZO1 that develop age-onset iron overload and specific alterations of the macrophage phagocytic activity (Ma et al, Cell 2021). These recent studies suggest that *PIEZO1* is an important genetic factor involved in iron metabolism but the molecular mechanism by which it regulates iron metabolism in the interplay among RBCs, hepatocytes and macrophage is still unknown.
Aims: This study aims to dissect the mechanism that links *PIEZO1* GOF variants to the suppression of hepcidin by investigation of new players of intracellular signaling pathways.
Methods: Creation of Hep3b engineered R2456H-PIEZO1 knock-in (KI) cells by CRISPR/Cas9; qRT-PCR and western blotting analysis; calcium and potassium ion channel assay; differential proteomics analysis, and RNA sequencing.
Results: To study the involvement of PIEZO1 in the regulation of iron homeostasis we established a KI Hep3b cell model heterozygous for the most frequent variant of PIEZO1, R2456H, by CRISPR/Cas9 technology (Hep3b-GOF-PIEZO1). Hep3b-GOF-PIEZO1 cells showed (i) no alteration of PIEZO1 gene and protein expression; (ii) increased intracellular calcium concentration compared to Hep3b-WT cells; (iii) hyper activation of the potassium channels activity compared to Hep3b-WT; (iv) reduced *HAMP* expression, according to the decreased phosphorylation of the BMP/SMADs pathway. To further dissect the alteration of the transcriptome and proteome of Hep3b-GOF-PIEZO1 model, we performed both differential proteomics and RNA-Seq. Differential proteomics identified 225 total proteins differentially regulated in Hep3b-GOF-PIEZO1 cells compared to Hep3b-WT ones (Protein with Log2 Difference ≥ ± 1 and -Log p-value > 1.3 were considered significantly enriched), 147 upregulated and 78 downregulated. RNA-Seq identified 5689 genes differentially regulated in Hep3b-GOF-PIEZO1 cells compared to Hep3b-WT ones ($p<0.05$, post-hoc correction by FDR), 1695 up-regulated and 1823 down-regulated ($-0.5 \leq$fold change≤ 0.5). Using this *multiomics* integrated approach, Hep3b-GOF-PIEZO1 cells showed alterations in several proteins belonging to MAPK pathways, and revealed new genes and proteins that links the increased calcium concentration to the activation of the intracellular pathways as TGF-b signaling and R-RAS.
Summary/Conclusion: We herein deeply dissected the mechanism by which PIEZO1 GOF mutations cause hepatic iron overload in DHS. The creation of a hepatic engineered cell line for PIEZO1 R2456H variant confirmed the effect on the cation flux and the deregulation of iron status. Proteomic and transcriptomic data give us the opportunity to improve our knowledge identifying new actors in the regulation of the complex landscape of iron metabolism.

S277 ANEMIA OF CHRONIC KIDNEY DISEASE IS PREVENTED THROUGH TRANSFERRIN RECEPTOR 2 INHIBITION

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Background: Chronic Kidney Disease (CKD) is characterized by progressive kidney failure, low erythropoietin (EPO) levels, inflammation and iron deficiency, factors that contribute to anemia development.
Current EPO-based therapies, often with iron supplementation, are effective but frequently lead to side effects, mainly cardio-vascular. Thus, more specific approaches are needed.
Transferrin Receptor 2 (TFR2) in hepatocytes regulates hepcidin and iron homeostasis, and in erythroid cells interacts with EPO receptor, adjusting EPO sensitivity. In mice, total and hepatic *Tfr2* inactivation causes iron overload, while its ablation in the erythroid compartment boosts erythropoiesis.
Aims: We investigated whether *Tfr2* may be a therapeutic target for renal anemia. Our approach is expected to simultaneously increase iron availability and erythroid EPO responsiveness. Moreover, given the restricted expression of TFR2, off-target effects should be limited.
Methods: Feeding mice an adenine-rich diet for 8 weeks we induced CKD in:
(1) mice with bone marrow (BM)-specific deletion of *Tfr2* ($Tfr2^{BMKO}$) and relative controls, generated through BM transplantation and fed the adenine diet after complete recovery;
(2) mice with reduced *Tfr2* expression in the liver, obtained treating wild type mice twice a week for 6 weeks with antisense oligonucleotides anti-*Tfr2* (*Tfr2*-ASO) after renal damage development;
(3) mice with germline *Tfr2* inactivation in the whole organism ($Tfr2^{KO}$) and relative controls ($Tfr2^{WT}$).
Results: Renal damage and iron restriction were comparable between $Tfr2^{BMKO}$ and control mice, but $Tfr2^{BMKO}$showed enhanced erythropoiesis,

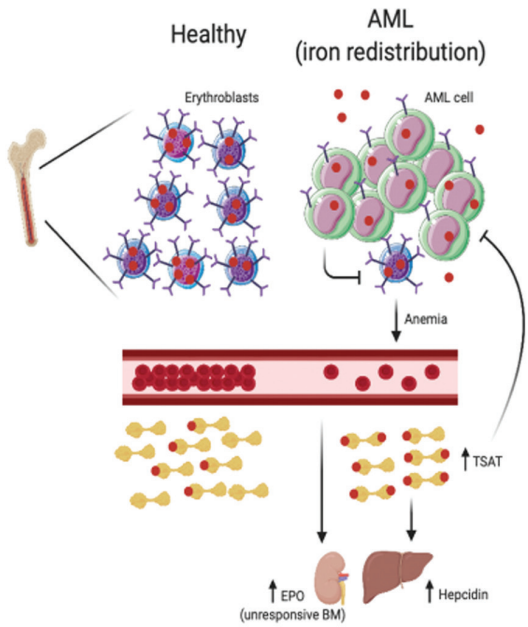
due to the increased EPO responsiveness of erythroid cells lacking *Tfr2*, as suggested by the over-activation of the EPO-EPOR signaling pathway (despite comparable EPO levels). However, anemia was only delayed, since at the end of the 8-week-long protocol iron availability was not adequate to sustain the enhanced erythropoiesis.
Having the proof-of-principle that targeting erythroid *Tfr2* stimulates erythropoiesis in CKD, we moved to *Tfr2*-ASO treatment, which downregulates *Tfr2* in the liver (95-97%), but not in the erythroid compartment. Circulating iron levels were increased in *Tfr2*-ASO mice, that showed also higher red blood cells (RBC) count and hemoglobin (Hb) levels during the first 2 weeks of treatment. However, Hb reverted to control levels before the end of the protocol. Thus, we confirmed that increased iron availability alone, due to hepatic *Tfr2* downregulation, is not sufficient to boost erythropoiesis for a long period.
Finally, despite comparable renal damage, $Tfr2^{KO}$ mice showed higher RBC count and Hb levels compared to $Tfr2^{WT}$ littermates, until the end of the 8-week-long protocol.
Summary/Conclusion: The concomitant targeting of hepatic and erythroid *Tfr2*, here obtained through a total genetic inactivation, is necessary to ameliorate anemia of CKD. Indeed, on one side, selective *Tfr2* inactivation in the BM enhances EPO responsiveness of erythroid cells and stimulates erythropoiesis, without increasing EPO levels per se. On the other side, hepatic *Tfr2* targeting increases iron availability. Therefore, a specific approach able to inhibit both hepatic and erythroid *Tfr2* could adjust iron availability according to the enhanced erythropoiesis, correcting both the drivers of anemia development in CKD. In the future, we will compare this approach to the available therapies and possibly move to a pharmacologic targeting.

S278 LOSS OF ERYTHROBLASTS IN ACUTE MYELOID LEUKEMIA CAUSES IRON REDISTRIBUTION WITH CLINICAL IMPLICATIONS

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Background: Acute myeloid leukemia (AML) is a heterogeneous disease with poor prognosis and limited treatment strategies. Determining the role of cell-extrinsic regulators of leukemic cells is vital to gain clinical insights into the biology of AML. Iron is a key extrinsic regulator of cancer but its systemic regulation remains poorly explored in AML.
Aims: We aimed at studying iron metabolism in AML and the mechanisms involved in its regulation.
Methods: We analyzed AML patients at diagnosis and explored mechanisms involved in the regulation of iron metabolism using the syngeneic MLL-AF9-induced AML mouse model and mouse mutants.
Results: We analyzed serum iron parameters of 84 AML patients at diagnosis and observed a unique profile not associated with inflammation or red blood cell (RBC) transfusions: high ferritin, low transferrin, normal to high serum iron and elevated TSAT (median 51.5%). We also observed that AML patients had very high circulating hepcidin levels (median 152.0 vs. 14.3 ng/ml; $p < 0.001$), albeit a modest increase in inflammatory C-reactive protein (CRP) and interleukin 6 (IL-6). To explore the mechanism underlying the changes of iron metabolism in AML, we used the syngeneic MLL-AF9 AML mouse model. We observed that only infiltrated mice treated with chemotherapy had increased TSAT. Interestingly, AML-burdened mice had hyperleukocytosis with lymphopenia and thrombocytopenia but normal RBC and reticulocyte counts. A key difference between adult mice and humans is the significant contribution of the spleen to mouse erythropoiesis. We observed that bone marrow (BM) erythroblasts were depleted in human and mouse AML but splenic erythropoiesis was enhanced in leukemic mice. We hypothesized that the loss of erythroblasts in AML could also drive iron redistribution and TSAT increase in mice, if not compensated by an increased splenic erythropoiesis. As predicted, splenectomized mice with AML had anemia, reticulocytopenia, increased TSAT and detectable non-transferrin bound iron (NTBI), demonstrating that loss of BM erythroblasts in AML causes iron redistribution. Through direct quantification, protein and transcriptomic analysis, we demonstrated that iron is partially redistributed into AML cells. This led us to hypothesize that iron redistribution may be clinically relevant in AML. Survival analysis revealed that AML patients with higher TSAT at diagnosis had significantly better overall survival (OS), even after multivariate analysis. Experiments using different mouse models (*Hfe*-KO, iron-dextran) confirmed that increased TSAT is associated with better OS in AML.



Summary/Conclusion: Our study shows that AML patients have a unique iron profile independent of RBC transfusions characterized by increased TSAT due to loss of BM erythroblasts. We propose that TSAT at diagnosis may be a relevant independent prognostic factor in AML.

S279 HEPCIDIN IS A MARKER OF COVID-19 SEVERITY AND MORTALITY IN A COHORT OF HOSPITALIZED ITALIAN PATIENTS

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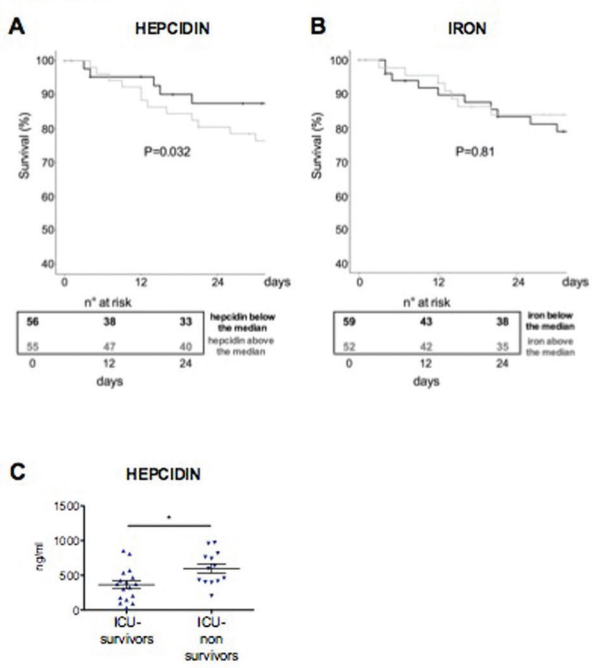
Background: Several risk factors for Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) infection are well established, including advanced age, male gender, strong inflammatory response, neutropenia and lymphopenia, and more recently hypoferremia. Hepcidin, the liver peptide hormone whose role is to regulate plasma iron concentration, is at the crossroad between iron metabolism and inflammation, being positively regulated by iron itself and proinflammatory cytokines. However, its role as potential biomarker of COVID-19 severity has not been explored in depth.
Aims: Aim of the study is to investigate whether plasma hepcidin, measured at admission, can be considered a marker of COVID-19 severity and mortality.
Methods: Plasma hepcidin and iron levels were analyzed in a well-characterized cohort of 111 Italian COVID-19 patients hospitalized between March 18th and May 5th, 2020 at San Raffaele University Hospital

(UH), in Milan, Italy, one regional COVID-19 reference hospital. Diagnosis of COVID-19 was based on a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19. The cohort had a median age of 57.6 (48.5-66.3) years, and included prevalently males (64%). Blood samples were obtained at admission, plasma immediately retrieved and frozen until analyzed for the concentration of iron, hepcidin (ELISA kit from Intrinsic LifeSciences), proinflammatory markers as C-reactive protein (CRP) and ferritin, and cytokines with a role in hepcidin modulation, as interleukin IL6, IL1b, TNFa and Interferon gamma (IFNg).

Results: In this cohort of COVID-19 patients, iron concentration was below normal range in 93.7% of patients, whereas hepcidin levels were significantly increased in 61.3% of patients. However, considering that hypoferremia suppresses hepcidin expression, even normal hepcidin is inappropriately high in most cases. Patients with higher hepcidin levels were significantly older and had higher concentrations of markers of inflammation (CRP and ferritin) and cell damage (AST and LDH). Negative correlations were observed with the severity of respiratory failure, as reflected by the PaO2/FiO2 *ratio*. The role of hepcidin is strengthened by the Kaplan-Meier survival curve (**Figure 1A**) and confirmed by the Regression Tree analysis, which identified hepcidin as the most important predictor of death among the others recognized predictors. On the other hand, iron levels do not affect survival, likely because of the uniformly low levels in all patients (**Figure 1B**).

Interestingly, limiting the analysis to critical patients in ICU, high hepcidin predicts mortality (**Figure 1C**), independently of age lung function, inflammation and tissue damage.

FIGURE 1



Summary/Conclusion: Overall our data suggest that hepcidin can be considered a marker of morbidity and outcome of COVID-19, of special value for severely compromised patients in ICU (Nai et al., AJH 2021). Further studies are needed to verify whether targeting the hepcidin axis may influence the disease outcome.

Fungal, bacterial and viral infections in hematology

S280 DEVELOPMENT OF NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 IN HEALTHY SANITARY WORKERS AND OCTOGENARIANS POST-BNT162B2 MRNA COVID-19 VACCINE: FIRST RESULTS OF A PROSPECTIVE TRIAL IN 366 INDIVIDUALS

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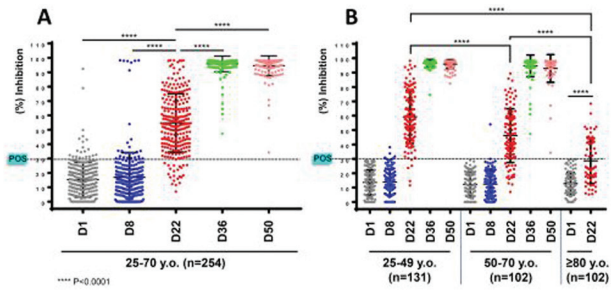
[1]Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, [2]Department of Cell Biology and Biophysics, National and Kapodistrian University of Athens, Faculty of Biology, [3]Department of Clinical Biochemistry, "Aghia Sophia" Children's Hospital, Athens, Greece

Background: Efficacy of vaccines against SARS-CoV-2 virus is of great importance in order to mitigate COVID-19 pandemic. The BNT162b2 mRNA vaccine is the first approved by both FDA and EMA vaccine with confirmed clinical activity in phase 3 trials. However, the immune responses against SARS-CoV-2 after BNT162b2 vaccination have not been fully elucidated in several population subsets including octogenarians and patients with malignancies or autoimmune disorders.

Aims: The aim of this prospective study (study no: NCT04743388) is to evaluate the development of neutralizing (NAbs) and anti-spike RBD IgG antibodies against SARS-CoV-2, as well as the levels of cytokines and the induced B- and T-cells subpopulations following vaccination with BNT162b2 vaccine. Participating groups include healthy sanitary workers, elderly individuals (above the age of 70) and patients with hematological malignancies or solid tumors under different types of treatment. Herein we present preliminary results of the BNT162b2 vaccine effects in the development of anti-SARS-CoV-2 antibodies in healthy sanitary workers and octogenarians.

Methods: Healthy sanitary (i.e., physicians and nurses) workers of Alexandra hospital, Athens, Greece and volunteered octogenarians were included in this study. The inclusion criteria included (*a*) age higher than 18 years and (*b*) the absence of any known auto-immune or malignant disease. NAbs against SARS-CoV-2 and anti-Spike-RBD IgG antibodies were measured using FDA approved methods, i.e., the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript, Piscataway, NJ, USA) and the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics GmbH, Mannheim, Germany), respectively. Time-points for blood collection were day 1 (D1) (first BNT162b2 dose), D8, D22 (second dose), D36 and D50 for healthy sanitary workers and D1, D22 and D50 for octogenarians. The study includes also a follow-up of the antibodies levels every 3 months till month 18 post the delivery of the second dose (D22) of the vaccine.

Results: The study population included 254 healthy sanitary workers (92 males/162 females; median age: 49 years, range: 25-70 years) (group 1) and 112 octogenarians (51 males/61 females; median age: 85 years, range: 80-95 years) (group 2). Twenty-one donors from group one and ten from group two had NAbs inhibition titers >30% (threshold for positivity) at D1; these titers significantly expanded at D8 indicating the presence of sustained rapid anti-SARS-CoV-2 antibody production in COVID-19 healers (Figure, A). NAbs titers (in negative at D1 donors) from group one, were found to increase significantly already at D22 (day of second vaccination), plateaued two weeks (D36) after the second dose of the vaccine (NAbs inhibition ≥90%) and remained at high levels at D50 (NAbs inhibition ≥90%) (Figure, A). Notably, the NAbs titers (in negative at D1 donors) had lower increases in ages 50-70 *vs*. 25-49 at D22; this age-related effect of the vaccine efficacy was confirmed in octogenarians who at D22 developed significantly lower NAbs titers *vs*. all other age groups (Figure, B). Similar kinetics were found in donors of groups one and two for the anti-spike RBD IgG antibodies.



Summary/Conclusion: We conclude that the BNT162b2 mRNA vaccine is exceedingly effective in producing high anti-SARS-CoV-2 antibody (NAbs and anti-spike RBD IgGs) titers in healthy donors. Given however that this readout is seemingly (up to the delivery of the second dose of the vaccine) age-dependent, we suggest that the second timely vaccination is needed, especially in the elderly population.

S281 EHA GUIDELINE: ANTIFUNGAL PROPHYLAXIS IN ACUTE MYELOID LEUKEMIA TREATED WITH NOVEL AGENTS

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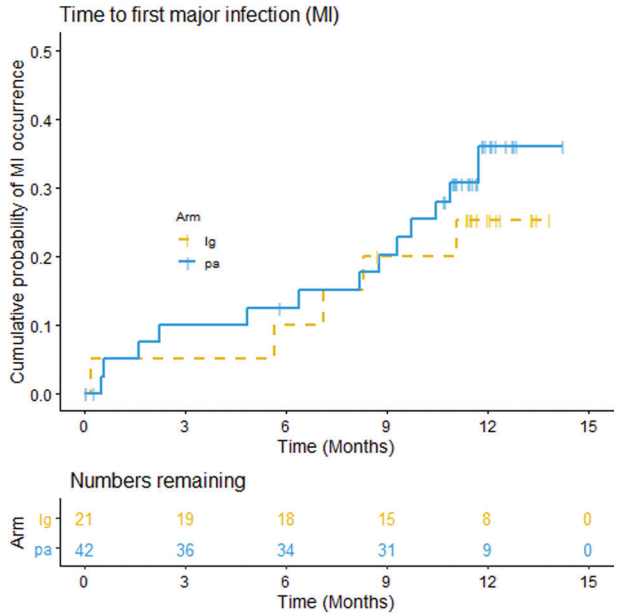
Background: Novel therapeutic agents for acute myeloid leukemia (AML) have become available recently. Antifungal prophylaxis is generally recommended during induction remission chemotherapy, however, treatment settings for AML patients have become diverse and the risk-benefit ratio for antifungal prophylaxis in those settings is not well assessed in clinical trials. Due to cytochrome p450 metabolization and its inhibition by antifungal drugs, there is potential for drug-drug interactions (DDI) between novel AML agents and antifungals.
Aims: To define evidence- or consensus-based recommendations for antifungal prophylaxis for AML patients on treatment with novel agents
Methods: Experts from the European Hematology Association (EHA) Working Group Infections in Hematology and Cochrane Hematology Group develop an evidence and consensus-based guideline according to the GRADE methodology. The following PICO endpoints for each of the novel agents were formulated: occurrence of fungal infection, prolongation of hospitalization, days on intensive-care unit and mortality due to fungal infection, quality-of-life, and potential drug-drug interactions. Systematic literature review was performed. In three consensus-meetings, recommendations for each novel AML drug and specific setting were formulated.
Results: The following novel agents for treatment of AML were identified with not all of them being yet licensed for treatment: Hypomethylating agents (HMA; Azacytidine and decitabine), Midostaurin, Venetoclax (+HMA), Lestaurtinib, Gilteritinib, Sorafenib, Quizartinib, Ivosidenib, Enasidenib, Crenolanib, Glasdegib, Sapacitabine, Custatuzumab, Iomab B, Idanasutlin.
Evidence from the literature was generally scarce since fungal infections and prophylaxis were generally not assessed in randomized controlled trials of the respective AML drug.
Evidence-based recommendations were formulated for HMA, Midostaurin, and Venetoclax/HMA, for all other agents, consensus-based recommendations were given including the patient-specific setting of application of the novel agents (relapsed/refractory AML, single therapy or in combination with chemotherapy, induction treatment or maintenance etc.) into the decision process
Antifungal prophylaxis is not recommended or moderately recommended in most settings, and strongly recommended if the novel AML agent is administered with intensive chemotherapy during induction treatment. Dose adaptations of some of the AML agents (midostaurin, venetoclax, quizartinib, sorafenib, gilteritinib) are moderately recommended with limited evidence if antifungal prophylaxis is administered with a strong CYP3A4 inhibitor due to expected increased exposure
Summary/Conclusion: This guideline document to help supporting the decision if to use antifungal prophylaxis in AML patients under treatment with novel agents will soon become available as the first one assessing this specific setting and will complement existing guidelines for antifungal prophylaxis.

S282 RATIONAL: A RANDOMISED CONTROLLED FEASIBILITY TRIAL COMPARING PROPHYLACTIC IMMUNOGLOBULIN WITH ANTIBIOTICS IN PATIENTS WITH ACQUIRED HYPOGAMMAGLOBULINEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES

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Background: Prophylactic immunoglobulin (Ig) replacement and prophylactic oral antibiotics (PA) are used to prevent infections in patients with haematological malignancies and acquired hypogammaglobulinemia. Ig has been shown to reduce infection risk, but is costly and in limited supply. PA have been shown to reduce infection risk in other patient populations and are less expensive, but have side-effects and can increase antimicrobial resistance rates. Guidelines and clinical practice vary internationally, with some recommending a trial of PA prior to commencing Ig replacement, and others omitting PA. The efficacy, safety and cost-effectiveness of Ig and PA have not been directly compared in a randomised controlled trial (RCT) in patients with acquired hypogammaglobulinemia secondary to haematological malignancies.
Aims: To determine the feasibility of delivering PA as an alternative to Ig replacement in patients with haematological malignancies and acquired hypogammaglobulinemia.
Methods: Phase II, multicentre, feasibility RCT (ACTRN12616001723471). Eligible patients had acquired hypogammaglobulinemia due to a haematological malignancy, a history of recurrent or severe bacterial infections or an IgG level <4g/L (excluding paraprotein), and had a life expectancy more than 12 months. Exclusion criteria included prior allogeneic haematopoietic stem cell transplant and prior Ig replacement in the preceding 3 months. Patients were randomised to receive Ig (0.4g/kg IV every 4 weeks, modified to achieve an IgG trough level ≥ lower limit of reference range; or 0.1g/kg/week SC, modified to achieve an IgG trough level of ≥ lower limit of reference rage) or daily oral prophylactic antibiotics (trimethoprim-sulfamethoxazole 160mg/800mg, with 100mg doxycycline as an alternative for hypersensitivity) for 12 months at a 1:2 ratio. Randomisation was stratified by site. Patients allocated to PA were allowed to cross over to Ig if they experienced a CTCAE ≥ Grade 3 infection. Treatment allocation was not blinded but infectious outcomes were adjudicated by an independent, blinded, outcome adjudication committee. The primary outcome was proportion of patients alive and remaining on assigned treatment arm 12 months following randomisation. Secondary outcomes included time to first major infection (defined as CTCAE ≥ Grade 3 infection).
Results: 63 patients were randomised, 60 received treatment and had primary outcome data available. The median age was 69 years (IQR 66-75), 34 (54%) were female, 12 (19%) had myeloma, 29 (46%) chronic lymphocytic leukaemia, 20 (32%) had non-Hodgkin lymphoma and 2 (3%) other haematological malignancy. For the primary outcome, 76% (95% CI 53-92) in the Ig arm and 71% (95% CI 55-84) in the PA arm were alive and on assigned treatment 12 months following randomisation (p=0.77). The time to first major infection was similar between the two groups (see figure 1), with the lower quartile 11.0 months in Ig arm vs 9.7 months in PA arm, (log rank test p=0.54). 74% of patients in the Ig arm and 64% in the antibiotic arm were free of major infection during the 12 months.



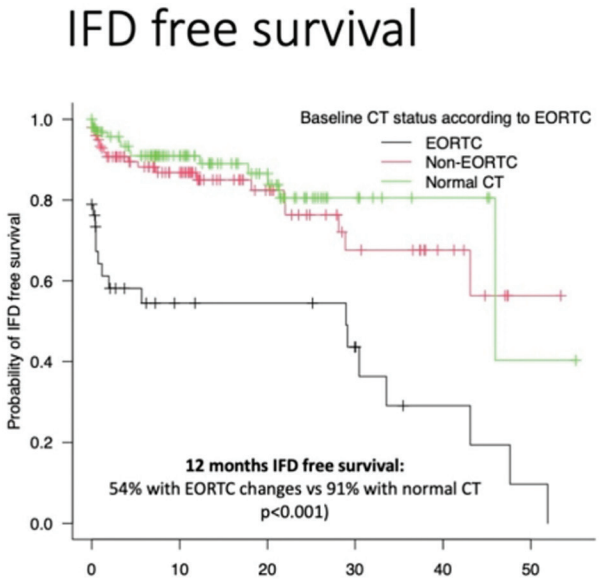
Summary/Conclusion: In this phase II trial, a similar proportion of patients allocated to Ig and to PA remained alive and on their assigned treatment arm at 12 months. There was no significant difference in time to first major infection between the two treatment arms. These findings support the feasibility of proceeding with a phase III trial to compare efficacy, safety and cost-effectiveness of Ig replacement to PA in patients with acquired hypogammaglobulinemia.

S283 BASELINE CT THORAX AND RISK OF INVASIVE FUNGAL DISEASE IN ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: Invasive fungal lung disease (IFD) is a well-recognised complication post haematopoietic stem-cell transplant (HSCT), occurring in approximately 5-21% of patients, despite tri-azole anti-fungal prophylaxis. Baseline CT thorax (BCT) pre-HSCT is increasingly considered as standard practise to evaluate lung disease, however evidence on outcomes from previous studies has been limited by either small or heterogenous cohorts (Ceesay et al 2018, Bitterman et al 2019).
Aims: A number of smaller heterogenous retrospective studies including our centre's previous study by Ceesay et al, BJH 2018, have been published reporting outcomes and risk factors for IFD associated with abnormal baseline CT chest prior to induction chemnotherapy or transplantation,. Based on these findings, we implemented baseline CT chest in all our high-risk group patients due to undergo allogeneic stem cell transplantation and induction chemotherapies from 2015. Routine biomarkr screening and diagnostic clinical algorithm was implemented. This study then set out to prospectively evaluate utility of baseline CT chest in a homogenous cohort of allo HSCTs and its correlation of different morphological imaging changes and baseline patient related factors associated with risk for IFD.
Methods: We conducted a single centre prospective analysis of patients with myeloid malignancies and aplastic anaemia (n=350) who underwent T-cell deplete allogeneic HSCT between Jan 2015 and April 2019. BCT was performed in 235 (67%) patients within 4 weeks of planned HSCT with biomarker driven IFD screening & diagnostic strategy as standard. IFD was defined as probable/proven disease by European Organisation for Research & Treatment of Cancer(EORTC)-2008 criteria.
Results: Baseline CT was abnormal in 58% of patients (136/235). EORTC defined abnormalities were present in 28% of abnormal CT's (38/136). Post HSCT, IFD developed in 9.1% of total patients (n=32/350) and in 12.3% (n=29/235) of those who had BCT. Patients with EORTC defined changes on BCT developed more IFD compared to those with normal BCT findings (34.2% vs 9.4%, p=<0.01). Univariate analysis of baseline characteristics identified that a significantly higher proportion of those with history of previous IFD developed post-HSCT IFD (33.3% vs 8.3%; P=<0.01). Reduced intensity conditioning, poor baseline performance status and co-morbidities, and gas transfer (TLCO <70%) significantly influenced the development of IFD. Risk factors for baseline abnormal CT were Age >60 years, higher HCT-CI, pre-existing lung disease and prior history of IFD.
Although presence of abnormal BCT did not influence overall survival, there was a significant reduction in overall survival at 12 months post HSCT in those who developed IFD(62% vs 76%, p=0.001, log rank). Among patients with EORTC defined changes on BCT, there was a significant reduction in median IFD-free survival (30.5 months vs 47 months, p=0.009) when compared to non-EORTC and normal CT findings (see Figure attached). There was a significant reduction in overall survival at 12 months post HSCT in those who developed IFD(62% vs 76%, p=0.001, log rank).



Summary/Conclusion: Previous IFD history, EORTC changes & multiple non-EORTC changes at baseline CT and abnormal TLCO pre-HSCT influenced IFD related outcomes with a significant reduction survival post IFD event. We suggest early respiratory optimisation including focussed diagnostics in patients with abnormal pre-HSCT chest imaging, to reduce risk of IFD-related mortality. Further evaluation of impact of interventions in patients with abnormal BCT is warranted.

S284 EARLY INFECTIONS FOLLOWING COMMERCIAL ANTI-CD19 CAR-T CELLS INFIRM POPULATION – A SINGLE CENTER RETROSPECTIVE STUDY

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Background: Chimeric antigen receptor T cells (CAR-T) cells targeting CD19, demonstrate highly effective anti-tumor response in Diffuse Large B Cell Lymphoma (DLBCL). However, can result in significant side effects such as prolong neutropenia and infections. The incidence of infections in the setting of real world data hasn't been completely identified.
Aims: To perform a comprehensive analysis of infection rate and profile in the first month after CAR-T cells in a cohort of infirm patients treated with commercially available CAR-T cells.
Methods: This is a retrospective, single center study conducted in the Bone marrow transplant unit, Tel Aviv, analyzing the infection rate in consecutive patients with DLBCL who were treated with commercially available axicabtagene ciloleucel or tisagenlecleucel. Following a local protocol, all patients were treated with prophylaxis with ciprofloxacin and fluconazole when neutrophil counts decreased below $0.5*10^3$/µl. Acyclovir was administered at conditioning initiation. Microbiology and clinical documented infections (MDI and CDI, respectively) were defined according to the ECIL guidelines. Following white blood cell recovery, patients carried out weekly full blood count, and

monthly CMV and HHV-6. A logistic regression was performed for the association between baseline characteristics and documented infections.
Results: From June 2019 to December 2020, we included 60 consecutive patients with DLBCL treated with axicabtagene ciloleucel (n=16, 27%) or tisagenlecleucel (n=44, 73%). The median age was 69.3 (range, 19.8-85.2) years and ECOG-Performance status(PS) was 2-3 in most patients (58%). Broad spectrum antibiotics was administered to patients experiencing neutropenic fever (n=53, 88%). Overall infections were noted in 27/60 patients (45%).Bacterial infections were seen in 16 patients (27%) and included CDI in 7 (Pneumonia, n=5; periodontal infection, n=1 and cellulitis, n=1) and MDI in 9 patients (Gram negative rod bacteremia (GNR), n= 5; Gram positive cocci(GPC) bacteremia, n= 3; Both GNR and GPC, n=1). Viral infection was described in 14 patients (23%). The most common viral infection was CMV reactivation (n=10, 17%) leading to initiation of anti-CMV treatment in 6 among these patients. None had CMV disease. HHV-6 was positive in 3 patients (5%) with one of these patients presenting with acute encephalitis. Other viral infections reported were RSV (n=2)COVID-19 (n=1). No fungal infection was documented. Incidence of documented infections was higher in patients with CRS/ICANS compared with patients without [23/44 (52%) vs 4/16 (25%), p=0.005]. While CRP levels predicted documented infections (p= 0.041), ferritin blood levels did not (p=0.130).
In univariate analysis, ICANS (OR= 4.5, p = 0.018) was associated with higher incidence of bacterial infection while there was a trend for lower incidence of bacterial infections in patients with chemo-sensitive disease to bridging therapy (OR= 0.375, p= 0.074)(Table 1). Age or ECOG-PS were not associated with increased risk of bacterial infection. Patients with documented infection had an increase in hospitalization days compared to those without documented infection (26.44 vs 21.7 days, p= 0.085).

Table 1: Risk factor for bacterial infection one months following CAR-T cell infusion using univariate analysis:

Variable	Odds ratio	P value
Age	0.990	0.618
ECOG PS	N/A	0.960
Bridging therapy	1.259	0.738
Chemo-sensitive disease	0.375	0.074
CRS	3.267	0.150
ICANS	4.5	0.018
hypogammaglobulinemia	1.944	0.574
CRP prior to CAR-T cells infusion	1.004	0.331
Ferritin prior to CAR-T cells infusion	1	0.717

CRS; Cytokine release syndrome, ICANS; Immune effector cell-associated neurotoxicity syndrome

Summary/Conclusion: Infections were common in the first month following CAR-T cell administration, however were not increased in elderly patients or those presenting with poorer PS. Patients refractory to bridging therapy and ICANS should be monitored cautiously for the occurrence of infections. CMV monitoring should also be considered.

COVID-19 impact on hematology: How it started - How it's going

S285 SAFETY AND EFFICACY OF THE BNT162B2 MRNA COVID-19 VACCINE IN PATIENTS AFTER ALLOGENEIC HCT AND CD19-BASED CAR-T THERAPY – A SINGLE CENTER PROSPECTIVE COHORT STUDY

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Background: The Pfizer/BioNTech BNT162b2 vaccine, employing mRNA technology, has been recently approved by both the FDA and EMA for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, demonstrating a 94.6% protection rate in a phase 3 study. While this vaccine is recommended by the FDA, EBMT and ASH-ASTCT for immunosuppressed patients, data regarding protection efficacy and safety in patients undergoing immunologic cell therapy are scarce.

Aims: We aimed to evaluate efficacy and toxicity of the BNT162b2 vaccine in patients that underwent hematopoietic cell transplantation and CAR-T therapy.
Methods: All patients under active treatment at the long-term follow-up HCT clinic (n=124) at the Tel Aviv Sourasky Medical Center, were evaluated for immunologic recovery (CD19+, CD4+, and CD8+ cell blood levels) pre-vaccination and were recommended to receive the commercial vaccination based on the EBMT recommendations. Patients were prospectively followed for vaccination-safety profile (laboratory tests, GVHD monitoring, and symptom-based questionnaire). We evaluated the humoral immune response to vaccine, 7-14 days after the second vaccine dose, by *in vitro* quantitative determination of anti-SARS-CoV-2S antibodies using Elecsys® assay and cellular immune response by ELISpot, estimating IL-2 and IFN-gamma secretion in response to a pool of lyophilized SARS-COV-2 S and M peptides (PepTivator; Miltenyi). The trial was approved by the local Ethics Committee and was registered by the clinical trials network (NCT04724642).
Results: From 23-Dec-2020 all sequential patients (allogeneic, n=101 and CAR-T, n=23) were assessed for eligibility based on the EBMT recommendations (Version 5.0, Feb 21, 2021). Of those, 100 patients were eligible and 79 patients (allogeneic, n=65 and CAR-T, n=14) were vaccinated per-protocol. Characteristics of patients are depicted in **Table 1**. Overall, the 2 vaccine doses were well tolerated. Adverse events were reported in 39% of allogeneic HCT recipients (4.6% grade ≥3) and 32% of CART recipients (7% grade ≥3). All events resolved within few days, with the exception of 1 secondary graft rejection which is still under investigation. Among the CAR-T group, 5 patients (36%) had humoral antibody response. Patients with CD19+ lymphocytes >0 had a higher likelihood to develop antibodies compared to those with B cell aplasia (67% vs. 12.5%, p=.036). Among the allogeneic HCT group - 47 patients (81%) had a humoral antibody response. Incidence of positive serology was lower in patients with concomitant high intensity immunosuppressive therapy (IST) compared to those with low intensity IST (69% vs. 94%, p=.016). Linear regressions identified that male sex (beta=-.380, p=.012) and high intensity IST (beta=-.497, p=.014) were associated with lower antibody titer, while age, months from HCT, intensity of conditioning, low CD19 cell count, and active GVHD did not predict response. Analysis of peptide induced cytokine release by ELISpot is ongoing and will be presented at the EHA meeting.

Table 1 – Characteristics of patients

Datum	All cohort (n=79)
Age in years (median, range)	66 (23-82)
Sex, female (n, %)	35 (44%)
Months from infusion (median, range)	
Allogeneic HCT	22 (3-162)
CART	9 (3-17)
Status of disease	
Remission	76 (96%)
Relapse	3 (4%)
Base line disease	
AML	36 (46%)
MDS	7 (9%)
ALL	8 (10%)
DLBCL	12 (15%)
Other lymphoma	8 (10%)
Myeloproliferative neoplasm	7 (9%)
Other	1 (1%)
Preparative regimen (allogeneic pts only)	
Myeloablative	40 (62%)
Reduced intensity/non myeloablative	25 (38%)
Donor (allogeneic pts only, n=65)	
Matched-sibling	17 (26%)
Mismatched-family donor	5 (5%)
Matched unrelated donor	44 (68%)
Mismatched unrelated donor	1 (1%)
Graft-vs-host disease (allogeneic pts only, n=65)	
Active acute GVHD	0 (0%)
Active chronic GVHD	40 (62%)
Previous chronic GVHD	3 (5%)
Concurrent immunosuppressive therapy	(58%) 38
Patients on active chemotherapy	(8%) 8
Total lymphocyte count – cell/microL (median, range)	1100 (100-6500)
Total CD19-positive lymphocyte (median, range)	60 (0-1078)
Total CD4-positive lymphocyte (median, range)	325 (10-1375)
Total CD8-positive lymphocyte (median, range)	766 (48-4258)
CD4/CD8	0.48 (0.14-2.9)

Summary/Conclusion: Humoral response to the BNT162b2 mRNA COVID-19 vaccine in CAR-T patients with B cell aplasia is significantly impaired, while overall response in patients after allogeneic HCT is encouraging. Patients on concomitant high intensity IST had impaired humoral response to BNT162b2. Longer follow-up is mandatory to test persistence of antibodies, and general preventive practices should be continued until more data are available.

S286 OUTCOMES IN PATIENTS WITH ACUTE LEUKAEMIA AND COVID-19: RESULTS OF SUBGROUP ANALYSIS OF CHRONOS19 REGISTRY

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Background: Patients (pts) with acute leukemia (AL) are at high risk of COVID-19 severe and lethal course. Intensive chemotherapy and immunosuppression in these patients are the possible causes of high mortality. Emerging data on risk factors and outcomes in this vulnerable patient population is aimed to support strategies of their medical care.
Aims: To evaluate treatment outcomes and risk factors in pts with AL and COVID-19 in a real-world setting.
Methods: CHRONOS19 [NCT04422470] is an ongoing nationwide observational cohort study of adult (≥18 y) pts with hematologic disease (both malignant and non-malignant) and lab-confirmed or suspected (based on clinical and/or CT findings) COVID-19. We performed a subgroup analysis of pts with AL and COVID-19. Primary objective was to evaluate treatment outcomes and identify risk factors associated with higher mortality in this group of pts. Primary endpoint was 30-day all-cause mortality. Long-term follow-up was performed at 90 and 180 days. Data from 14 centers was collected on a web-based platform and managed in a deidentified manner.
Results: As of data cutoff on January 27, 2021, 575 pts were included in the registry, 132 of them with AL were eligible for primary endpoint assessment n(%): AML – 86(65%), ALL – 37(28%), APL – 9(7%); M/F 55(42%)/77(58%), median age 45 [18-79] years, induction phase/R/R/ treatment in remission 49(37%)/27(21%)/ 54(42%), agranulocytosis in 55(42%) pts, 68(53%) pts were transfusion dependent, comorbidities – in 58(45%) pts. Complications developed in 98(74%) pts: pneumonia (71%), sepsis (9%), CRS (8%), ARDS (6%). One-third of pts had severe COVID-19, 30% were admitted to ICU, 26% required mechanical ventilation. We performed comparative analysis of characteristics between a group of pts with AL and other hematologic diseases (lymphomas, chronic leukemia, multiple myeloma, and other malignant and non-malignant diseases): pts with AL had significantly more frequent agranulocytosis (42% vs 20%, p<0,001), transfusion dependence (53% vs 33%, p<0,001), and a higher rate of admission to ICU (30% vs 20%, p=0,036). All-cause mortality at 30 days was 24% in pts with AL vs. 15% in pts with other hematologic diseases (p=0,03); 70% of deaths were due to COVID-19 complications in pts with AL. At 90 days, one additional death due to COVID-19 occurred. At 180 days, 5 more deaths due to leukemia progression were registered. Risk factors that were significantly associated with overall survival (OS) are listed in Table 1. In multivariate analysis, ICU + mechanical ventilation, HR, 70.258 (19.5-270.0) and age >60 years HR, 3.340 (1.08-10.9) were the most significant risk factors of death. Overall, AL were associated with a higher risk of death, HR, 2.40 (1.28-4.51), compared to less aggressive diseases (CML, CLL, MM, lymphomas, non-malignant), HR, 0.54 (0.37-0.80). COVID-19 affected treatment of AL in 65% of pts, 58% experienced treatment delay for a median of 4 [1-10] weeks. In 11 of 103 (10,7%) pts with AL early relapse/refractory disease was detected, but the association of relapses with affected treatment is unknown. COVID-19 re-infection was described in 2 patients.

Table 1. Univariate analysis of factors associated with lower OS

Risk Factor	HR (95CI)	p
ICU + mechanical ventilation	70.258 (19.5-270.0)	<0.0001
ECOG 4 vs. ≤3	6.83 (3.28-14.21)	<0.00013
Admission to ICU	5.41 (1.46-20.10)	<0.0001
COVID-19 severity	6.83 (3.28-14.21)	<0.0001
COVID-19 complications	2.99 (1.16-7.68)	0.0162
Transfusion dependence	4.31 (1.96-9.50)	0.0004
R/R disease	2.18 (0.97-4.86)	0.151
Age ≥60 vs. <60 y	1.92 (1.00-3.68)	0.0451
MTA	1.62 (0.85-3.09)	0.0389
Male vs. female	1.48 (0.78-2.80)	0.2224
Comorbidities	1.63 (0.85-3.12)	0.1235

Summary/Conclusion: Thirty-day all-cause mortality was significantly higher in SARS-CoV-2-infected pts with AL than in those with other hematologic diseases. Longer-term follow-up (180 days) for AL outcomes and OS will be presented.

S287 KINETICS OF ANTIBODIES AGAINST SARS-COV-2 IN CONVALESCENT PLASMA DONORS AFTER EIGHT MONTHS FROM COVID-19: PERSISTENCE OF SPIKE ANTIBODIES BUT LOSS OF NEUTRALIZING ANTIBODIES IN 24% OF DONORS

E. Terpos [1,*], D. Stellas [2], M. Rosati [2], T. N. Sergentanis [1], X. Hu [3], M. Politou [4], V. Pappa [5], I. Ntanasis-Stathopoulos [1], S. Karaliota [2], J. Bear [3], M. Pagoni [6], E. Grouzi [7], E. Korompoki [1], A. Antoniadou [8], A. Kotanidou [9], G. Panayiotakopoulos [10], G. N. Pavlakis [2], B. K. Felber [3], M. A. Dimopoulos [1]

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Background: Elucidating the characteristics of human immune response against SARS-CoV-2 is of high priority for determining vaccine strategies. The duration of the persistence of anti-SARS-CoV-2 antibodies in individuals who suffered from COVID-19 is not clearly defined yet.
Aims: The aim of this study was to assess the kinetics of anti-SARS-CoV-2 antibodies and neutralizing antibodies among convalescent plasma donors during an 8-month period from their first symptoms of COVID-19.
Methods: Participants were enrolled in a phase 2 study of plasma donors (NCT04408209) for the use of convalescent plasma for the treatment of COVID-19 in Greece. For the detection of anti-SARS-CoV-2 antibodies, we used four in-house ELISA assays measuring antibodies to (i) trimeric Spike (S), (ii) Spike Receptor Binding Domain (Spike-RBD), (iii) Nucleocapsid, and (ii) Nucleocapsid RNA Binding Domain (N-RBD). For the Neutralizing Antibody (NAb) assay using SARS-CoV-2 pseudotyped virus, serial dilutions of heat-inactivated sera were incubated with an equal volume of the pseudotyped virions (pHIVNLEnv-Nanoluc) and the virion-Ab mixture was used to transduce HEK293T/ACE2wt cells. Two days later, the luciferase levels were measured in the cell extracts and the ID50 (50% Inhibitory Dose) was calculated using GraphPad Prism version 8.0 for MacOS X (GraphPad Software, Inc, La Jolla, CA) with nonlinear regression curve fit using inhibitor vs responses variable slope (four parameters).
Results: In total, 148 convalescent plasma donors (median age: 50 years, range: 18-65) with a median follow-up of 8.3 (range 6.8-10.5) months post their first disease symptoms were included in this analysis. Ninety-one patients did not need hospitalization and 57 were hospitalized due to COVID-19. At the initial screen, all patients showed positive antibody responses recognizing trimeric Spike, Spike-RBD, Nucleocapsid and N-RBD. At the 6-month follow-up, we continue to detect positive responses to Spike, Spike-RBD, Nucleocapsid and N-RBD in all plasma donors but at lower levels compared to screening (p<0.001). At the 8-month follow-up, no significant reduction was observed compared to 6-month values. A piecewise, random-effects, generalized least squares multivariate regression analysis showed a two-phase pattern of antibody responses, with more pronounced decrease during the first 6 months and a plateau phase after the 6th month post-symptoms onset. Spike antibodies showed better persistence than Nucleocapsid antibodies, whereas antibodies recognizing only the Spike-RBD or N-RBD persisted less than the mixture of antibodies recognizing the respective complete proteins. Neutralization ability contracted faster, since neutralizing antibodies persisted in 76% of patients at the last time point. In the multivariate analysis, older age and hospitalization were independently associated with higher antibody Spike, Spike-RBD, Nucleocapsid, N-RBD and NAb levels.
Summary/Conclusion: We found persistence of anti-SARS-CoV-2 antibodies, especially against Spike and Spike-RBD, up to 8 months post-symptoms onset. However, a loss of neutralizing antibodies became

evident in 24% of convalescent donors at 8 months from initial symptoms of COVID-19. A prolonged follow-up of the donors is necessary to further characterize the kinetics of anti-SARS-CoV-2 B-cell mediated immunity over time and to establish a link between the presence of antibodies and the level of protection against re-infection. Such data should help to optimize vaccination strategies and public health decisions.

S288 COVID-19 AMONG PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: A NATIONAL ISRAELI RETROSPECTIVE ANALYSIS

I. Levy [1,2,*], A. Lavi [2], E. Zimran [3,4], S. Grisariu [3,4], S. Aumann [3,4], G. Itchaki [5,6], T. Berger [5,6], P. Raanani [5,6], N. Lavi [2,7], T. Zuckerman [2,7], L. Shvidel [3,8], O. Jarchowsky [5,9], M. Ellis [5,9], K. Herzog Tzarfati [5,10], M. Koren-Michowitz [5,10], Y. Sherf [11,12], I. Levi [11,12], O. Sofer [2,13], N. Dally [14,15], C. Suriu [14,16], A. Braester [14,16], S. Ben Barouch [11,17], M. Leiba [11,17], D. Goldstein [5,18], N. Sarid [5,18], S. Yeganeh [14,19], M. Mittelman [5,20], J. Halloun [1], T. Tadmor [1,2]

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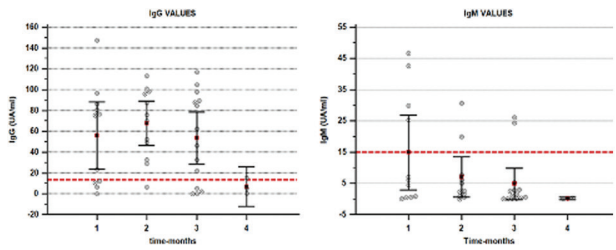
Background: The first COVID-19 patient was diagnosed in Israel in February 2020. It is of importance to evaluate outcomes across patients with hematological malignancies which are generally immunosuppressed and more susceptible to infectious complications.
Aims: We aimed to characterize the clinical course of COVID-19 infection among patients with various lymphoid or myeloid malignancies and determine which of these patients were most at risk of severe infection or mortality.
Methods: This was a national Israeli multicenter retrospective study. Patients with hematological malignancies who were diagnosed with COVID-19 from February 20, 2020 until January 31, 2021 were centrally reported and included in the retrospective analysis with no need for informed consent signing. Clinical and laboratory data regarding baseline characteristics, hematological management, and course and treatment of the COVID-19 disease were collected. Multivariate regression analyses were used to determine the variables associated with severe disease, hospitalization and mortality.
Results: In total, 272 patients from 14 medical centers were included in the analysis. Among them, 140 (51.5%) were men, and the median age was 70yrs. The most frequent malignancies included lymphoma (44.5%), multiple myeloma (22.8%), and chronic lymphocytic leukemia (12.1%). 90 (33.1%) patients developed a severe or critical respiratory infection, and 58 (21.3%) died. According to multivariate regression analyses, both age > 70yrs (OR=2.26; 95% CI: 1.04; 4.95; p=0.041) and current steroid treatment (OR=3.23; 95% CI: 1.06, 9.90; p=0.040) at time of COVID-19 diagnosis were associated with severe to critical disease, while current treatment with monoclonal antibodies was associated with mild to moderate disease (OR=2.86; 95% CI: 1.17, 6.99; p=0.022). Among the 159 hospitalized patients, the hospitalization was longer in patients with severe to critical respiratory infection (IRR=1.53; 95% CI: 1.36, 1.72; p<0.001), or treated with dexamethasone (IRR=1.22; 95% CI: 1.08, 1.38; p=0.002), with enoxaparin (IRR=1.18; 95% CI: 1.06, 1.33; p=0.004) or convalescent plasma (IRR=1.17; 95% CI: 1.04, 1.32, p=0.012); while the hospitalization was shorter in patients treated with remdesivir (IRR=0.78; 95% CI: 0.69, 0.89; p<0.001). The mortality rate was higher in patients > 70yrs (OR=3.41; 95% CI: 1.13, 10.34; p=0.030), with severe to critical infection (OR=27.27; 95% CI: 7.40, 100.48, p<0.001), or in those treated with dexamethasone (OR=5.89; 95% CI: 1.47, 23.63; p=0.012) for COVID-19 respiratory condition, and lower in patients treated with remdesivir (OR=0.19, 95% CI: 0.04, 0.82, p=0.026).
Summary/Conclusion: Respiratory infection with COVID-19 seems to be particularly severe in patients with hematological malignancies. While steroids seem to increase both baseline severity of the infection and mortality, it seems that treatment with remdesivir was associated with reduced mortality and duration of hospitalization. These particularities of haemato-oncological patients may be explained by a remarkably severe COVID-19 viremia that might cause the high mortality rate, while the cytokine release syndrome which generally responds to steroid treatment may be milder in these patients. The management of hematological malignancies during acute COVID-19 infection should be individualized and further investigated.

S289 SEROCONVERSION AND LONGEVITY OF ANTI SARS-COV-2 ANTIBODIES IN ONCO-HEMATOLOGIC PATIENTS WHO EXPERIENCED SARS-COV-2 INFECTION.

A. Candoni [1,*], U. Pizzano [1], M. Fabris [2], C. Marcon [1], R. Stella [1], S. Volpetti [1], R. Stocchi [1], M. E. Zannier [1], J. Olivieri [1], A. Sperotto [1], F. Curcio [2], R. Fanin [1]

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Background: Data on the dynamics and duration of immune response to SARS-CoV-2 infection in hematologic patients are still lacking. Preliminary studies, in non immunocompromised subjects with COVID-19, reported that seroconversion was observed 7 to 14 days following symptom onset with an increase of the IgM and IgG titers during the first month. IgM levels, after peaking by day 30, gradually decreased and can be undetectable by day 180 post-onset. The long-lasting persistence of IgG is not clearly confirmed.
Aims: We evaluate the seroconversion and the kinetics of IgM and IgG against SARS-CoV-2 in hematologic patients who were followed after reverse-transcription quantitative polymerase chain reaction (RT-qPCR) confirmation of SARS-CoV-2 infection.
Methods: Here we report the preliminary data regarding the first 25 COVID-19 positive hematologic patients that were tested for humoral response. The median age was 59 years (range 21-85). The underling hematologic diseases were: lymphoma (10/25), myeloma (7/25), chronic lymphoproliferative diseases (5/25) and acute leukemia (3/25). SARS-CoV-2 infection was mild symptomatic in 5/25 cases and symptomatic in 20/25. Four of these 20 patients had pneumonia that required hospitalization. The median value of IgG, IgM and IgA, at onset of the SARS-CoV-2 infection, was 832 mg/dl (167-2210), 54,5 mg/dl (6-2510) and 54 mg/dl (8-605), respectively. The median value of lymphocytes was 1100/mmc (250-3300). The IgM and IgG antibodies against SARS-CoV-2 spike protein (subunity S1 and S2) were tested by chemiluminescence immunoassay (CLIA) with a positive cut-off value of 15 UA/ml for both IgG and IgM. To assess the kinetics of antibody titers, in our convalescent COVID-19 patients, serum IgM and IgG levels were longitudinally measured at established time points: one month (T1) two months (T2), three months (T3) and four months (T4) after their first positive nasopharyngeal swab test.
Results: Among these first 25 COVID-19 cases, 21/25 (84%) developed specific anti SARS-CoV-2 antibodies with a titer > 15 UA/ml in almost one of the specific time points. However, as reported in Figure *A and B*, after a peak of the IgG and an overall mild increase of IgM, the antibody titer declined from 4 months after the disease onset under the positive cut-off value, although variation between patients was detected. In detail the mean and median titers were: 1) at T1: 56 UA/ml and 75,5 UA/ml for IgG, 15 UA/ml and 6 UI/ml for IgM; 2) at T2: 68 UA/ml and 73 UA/ml for IgG, 7 UA/ml and 2,6 UA/ml for IgM; 3) at T3: 54 UA/ml and 55 UA/ml for IgG and 5 UA/ml and 1,35 UA/ml for IgM; 4) at T4: 7 UA/ml and 5,3 UA/ml for IgG and 0,2 UA/ml and 0,2 UA/ml for IgM.



Summary/Conclusion: Although the number of patients is still limited, our preliminary results show a short lifespan of antibody response in hematologic patients, suggesting a short duration of antibody-mediated

protection against re-infection with SARS-CoV-2. If confirmed in a larger number of cases, these results would suggest to maintain infection prevention and control measures even for hematologic patients who have recovered from COVID-19. In addition, this population should get vaccinated periodically. Additional studies, exploring both humoral and cellular immunity (T cells and memory B cells), will be require to better understand the overall immunologic response against SARS-CoV-2 (and its duration) in hematologic patients.

Transfusion medicine

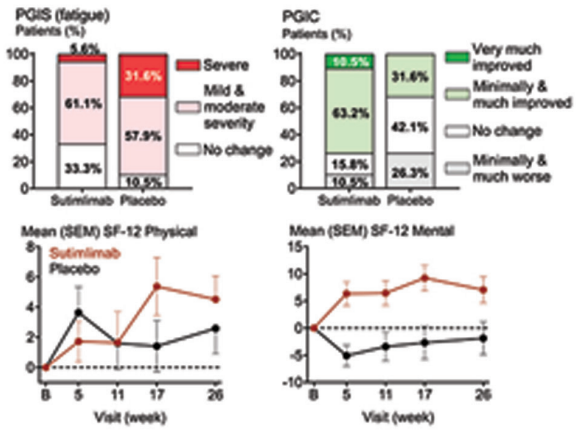
S290 SUTIMLIMAB, A TARGETED COMPLEMENT C1S INHIBITOR, IMPROVES QUALITY OF LIFE (QOL) IN PATIENTS WITH COLD AGGLUTININ DISEASE (CAD): RESULTS FROM THE RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 CADENZA STUDY

A. Röth [1,*], C. M. Broome [2], W. Barcellini [3], B. Jilma [4], Q. A. Hill [5], D. Cella [6], T. H. A. Tvedt [7], M. Yamaguchi [8], M. Lee [9], F. Shafer [9], M. Wardecki [10], B. Schaible [9], X. Jiang [9], P. Patel [9], F. Joly [11], I. C. Weitz [12]

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Background: CAD is chronic autoimmune hemolytic anemia mediated by classical complement pathway activation. CAD patients also may experience profound fatigue (secondary to the anemia and chronic inflammation) (Weitz et al. *Blood*. 2020), anxiety, and depression (Patel et al. *Blood*. 2020). Sutimlimab (formerly BIVV009), a first-in-class humanized monoclonal G_4 antibody, selectively inhibits C1s of the C1 complex, preventing classical pathway activation. In the single-arm CARDINAL study (NCT03347396), sutimlimab rapidly improved all patient-reported outcomes (PROs) in CAD patients and recent transfusion history. CADENZA (NCT03347422) is a randomized, double-blind, placebo (PBO)-controlled Phase 3 study to assess sutimlimab in CAD patients without history of recent transfusion.
Aims: To report the effects of sutimlimab versus PBO on QOL PROs from CADENZA Part A (initial 26-week treatment period).
Methods: Adult patients with confirmed CAD diagnosis, baseline hemoglobin ≤10 g/dL, total bilirubin above normal, ≥1 recent CAD-related symptom, and no recent transfusion were enrolled. Patients were randomized 1:1 to receive sutimlimab (<75 kg, 6.5g; ≥75 kg, 7.5 g; N=22) or PBO (N=20) on Days 0 and 7, then biweekly infusions. A secondary objective is to evaluate QOL using the PROs, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, Patient Global Impression of (fatigue) Severity (PGIS), Patient Global Impression of Change (PGIC), EuroQol 5-dimension 5-level (EQ-5D-5L; index and visual analog scale [VAS] scores) questionnaire, and 12-Item Short Form Health Survey (SF-12; physical and mental components). Treatment assessment time point (TAT) was the mean value for Weeks (W) 23, 25, and 26 for FACIT-Fatigue. FACIT-Fatigue was analyzed by a mixed model for repeated measures; W26 change from baseline for other PROs was analyzed by analysis of covariance with baseline as the covariate.
Results: Baseline QOL (mean FACIT-Fatigue, 32.3) was comparable to other hemolytic anemias, such as paroxysmal nocturnal hemoglobinuria (Schrezenmeier et al. *Haematologica*. 2014), and cancer (Escalente et al. *Cancer Med*. 2019). As early as W1, sutimlimab, but not PBO, elicited a clinically meaningful increase (≥5 points) in mean FACIT-Fatigue. At TAT, the least squares (LS) mean (standard error of the mean [SEM]) difference in FACIT-Fatigue between sutimlimab and PBO groups was 8.9 (2.5) (P<0.001). At W26, severe fatigue was present in 5.6% of patients in the sutimlimab group compared with 31.6% in PBO (PGIS; **Figure**). W26 overall health (PGIC) was assessed as "improved" by 73.7% of patients receiving sutimlimab compared with 31.6% on PBO (**Figure**). Strong trends were present for improved (higher) W26 SF-12 physical and mental scores in the sutimlimab group compared with PBO (LS mean [SEM] difference physical: 4.0 [2.1], P=0.064; mental: 6.1 [3.2], P=0.065) (**Figure**). A strong trend also existed for improved (higher) W26 EQ-5D-5L VAS in the sutimlimab versus PBO groups (LS mean [SEM] difference: 10.8 [5.3], P=0.052). W26 change in EQ-5D-5L index score was not different between groups.

Effects of sutimlimab and placebo on fatigue severity (PGIS), overall health (PGIC), and SF-12 physical and mental components



B, baseline; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; SF-12, 12-item Short Form Health Survey; SEM, standard error of the mean.

Summary/Conclusion: Classical complement pathway inhibition by sutimlimab elicited a rapid, clinically meaningful and significant improvement in fatigue. Nearly three-quarters of patients on sutimlimab considered their overall health improved compared with approximately one-third on PBO. Improvements in some other PROs were also observed. In addition to the single-arm CARDINAL study, these PBO-controlled results support targeting the classical pathway via C1s inhibition in CAD.

S291 C1S-TARGETED INHIBITION OF CLASSICAL COMPLEMENT PATHWAY BY SUTIMLIMAB IN COLD AGGLUTININ DISEASE (CAD): EFFICACY AND SAFETY RESULTS FROM THE RANDOMIZED, PLACEBO (PBO)-CONTROLLED PHASE 3 CADENZA STUDY

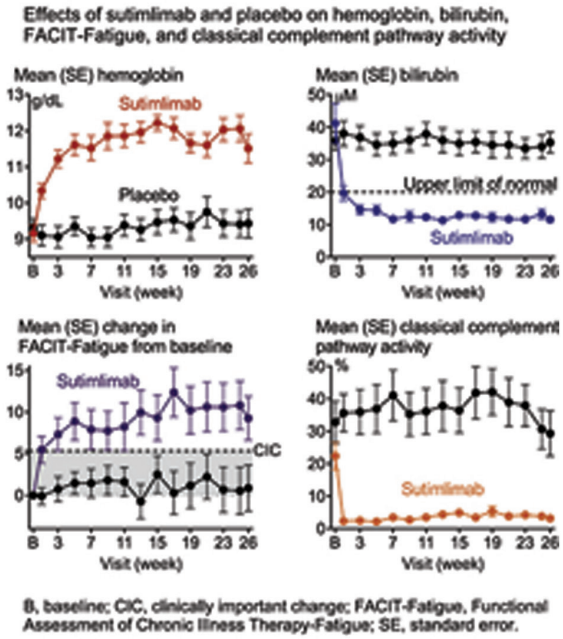
A. Röth [1,*], S. Berentsen [2], W. Barcellini [3], S. D'Sa [4], B. Jilma [5], M. Michel [6], I. C. Weitz [7], M. Yamaguchi [8], J. -I. Nishimura [9], J. Vos [10], P. Patel [11], B. Schaible [11], X. Jiang [11], D. Vagge [12], M. Wardecki [13], F. Shafer [11], M. Lee [11], C. M. Broome [14]

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Background: CAD is a rare autoimmune hemolytic anemia mediated by classical complement pathway activation. Sutimlimab, a first-in-class humanized monoclonal anti-C1s G_4 antibody, selectively inhibits this pathway, halts hemolysis, and improves hemoglobin (Hb) and quality of life (QOL) in CAD patients with recent transfusion history (pivotal single-arm CARDINAL study [NCT03347396]). CADENZA (NCT03347422) is a 26-week (Part A) randomized, double-blind, PBO-controlled Phase 3 study with open-label extension (Part B) to assess sutimlimab in CAD patients without recent transfusion history.
Aims: To report efficacy and safety results from CADENZA Part A.
Methods: Confirmed CAD-diagnosed patients with baseline Hb ≤10 g/dL, abnormally high bilirubin, transfusion independence, and ≥1 CAD symptom were enrolled after informed consent. Patients were

randomized 1:1 to receive sutimlimab (<75 kg, 6.5 g; ≥75 kg, 7.5 g; N=22) or PBO (N=20) on Days 0 and 7, then biweekly infusions. The composite primary endpoint (sutimlimab vs PBO compared using the Cochran-Mantel-Haenszel method) was the proportion of patients with Hb increase ≥1.5 g/dL at the treatment assessment time point (TAT; mean of Weeks 23, 25, and 26), and avoidance of transfusion and study-prohibited CAD therapy (Weeks 5–26). Secondary endpoints (analyzed with mixed model for repeated measures and summary statistics) included TAT change from baseline in Hb, bilirubin, and Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue. Safety was evaluated.

Results: Baseline mean (standard deviation) g/dL Hb was 9.2 (1.1) for sutimlimab and 9.3 (1.0) for PBO. Composite primary endpoint criteria were met by 16 (73%) patients in sutimlimab and 3 (15%) in PBO (odds ratio, 15.9 [95% confidence interval, 2.9–88.0; *P*<0.001]). Sutimlimab, but not PBO, increased mean Hb and QOL (FACIT-Fatigue) and normalized mean bilirubin by Week 1, which were sustained to TAT (**Figure**). At TAT, the least squares mean (standard error) difference in Hb and FACIT-Fatigue between sutimlimab and PBO was 2.6 (0.4) g/dL (*P*<0.001) and 8.9 (2.5) points (*P*<0.001). Improvements coincided with near-complete classical pathway inhibition and C4 normalization. One (5%) patient in sutimlimab and 4 (20%) in PBO received transfusions from Weeks 5 to 26. There were 146 (62% of events) treatment-emergent adverse events (TEAE) in sutimlimab and 90 (38%) in PBO. Three (14%) sutimlimab and 1 (5%) PBO patients had ≥1 serious TEAE (TESAE). One TESAE of cerebral venous thrombosis was related to sutimlimab as assessed by the investigator. Serious infections were reported but none were meningococcal. No TESAE of hypersensitivity or anaphylaxis were reported. No TEAE was suggestive of the development/worsening of autoimmune disease or systemic lupus erythematosus. All PBO and 86% of sutimlimab patients completed Part A and entered Part B; 3 sutimlimab patients discontinued study due to TEAE (acrocyanosis and Raynaud's phenomenon [n=1], infusion-related reactions [n=1], increased blood immunoglobulin M [n=1]). Acrocyanosis and infusion-related reactions were assessed as related to sutimlimab by the investigator. Hypertension (23% vs 0%), Raynaud's phenomenon (18% vs 0%), and acrocyanosis (14% vs 0%) were reported more often in the sutimlimab vs PBO group. No deaths were reported in either group.



Summary/Conclusion: Sutimlimab, but not PBO, rapidly halted hemolysis, markedly increased Hb, and improved QOL (fatigue). In addition to the single-arm CARDINAL study, the CADENZA PBO-controlled results support targeting C1s in CAD.

S292 HEMOSTATIC CHARACTERIZATION OF POST-COVID-19 CONVALESCENT PLASMA DONORS: THE BERGAMO EXPERIENCE

C. J. Tartari [1,*], G. Milani [1], F. Salvetti [1], M. Marchetti [1], L. Russo [1], A. Vignoli [1], M. Vitali [1], L. Barcella [1], M. Cefis [1], P. Gomez-Rosas [1], F. Schieppati [1], G. Ravasio [1], L. Castellani [1], G. Marchesi [1], E. Sanga [1], D. Romeo [1], A. Falanga [1,2]

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Background: Severe COVID-19 is associated with a profound derangement of the hemostatic system characterized by hypercoagulability, complement activation and endothelial cell perturbation. After disease resolution, some convalescent subjects still experience post-COVID-19 symptoms. No information is available on persistence of hemostatic alterations in this setting. Bergamo city, represents one of the first and most affected area by SARS-CoV-2 infection in the world. For this reason, since the beginning we were actively involved in hyperimmune plasma collection from COVID-19 convalescent subjects.

Aims: In this study, in a large cohort of convalescent donors of hyperimmune plasma, we aimed to characterize select hemostatic parameters of hypercoagulability and endothelial cell perturbation and their association with disease severity, demographic characteristics, and antibody levels.

Methods: Recovered COVID-19 patients eligible to plasma donation were tested for the SARS-CoV-2 antibodies by the anti-N IgG SARS-CoV-2 antibodies (Abbott Laboratories, IL, USA, Anti-N Abs), and/or the anti-S IgG SARS-CoV-2 antibodies (Liaison-Diasorin, Sallugia-VC, Italy, Anti-S Abs), according to the manufacturer's instructions. Fibrinogen, protein C, protein S, factor V, factor VIII, factor XIII, D-dimer, and von Willebrand factor (vWF) were assessed.

Results: 425 subjects have been included (275M/150F) with a median age of 48 years (range: 19-67 years). Among convalescent subjects admitted to the donation, male gender, age > 40 years, and previous hospitalization for COVID-19, were identified as independent predictive factors for significantly ($p<0.001$) higher levels of SARS-CoV-2 IgG (both anti-S and anti-N). Hemostatic parameters including fibrinogen, protein S, factor V, factor VIII, factor XIII, and D-dimer were not different between severe and non-severe COVID-19. Differently, convalescent subjects with previous severe COVID-19 showed significantly higher levels of vWF (124±40 vs 121±41 %, $p<0.001$) and PC (119±19 vs 109±19 %, $p<0.001$) compared with non-severe COVID-19 subjects. In addition, significant positive correlations were found between vWF levels and anti-S Abs (vWF antigen $r=0.216$; vWF activity $r=0.257$ and vWF RiCof $r=0.226$, $p<0.01$).

Summary/Conclusion: Our data show that gender, age and severe disease can be potential predictors of an increased immunological response. Furthermore, convalescent subjects show a persistently high vWF levels, suggesting a persistence of the endothelial activation, despite of clinical disease remission.

S293 DESCRIPTION OF THE INFLAMMATORY PROFILE WITH 45 CYTOKINES ACCORDING TO ABO BLOOD GROUP IN COVID-19 AND ITS IMPLICATIONS ON SEVERITY AND MORTALITY.

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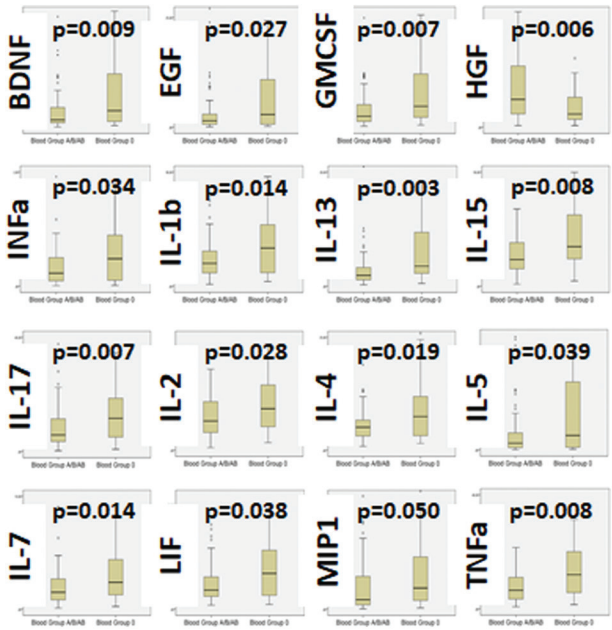
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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently one of the worst pandemics ever. ABO blood groups are associated with different risk of viral infections and they could also play a role in COVID-19 disease. In vitro, studies demonstrated how anti-A and B antibodies neutralized the infectious capacity of SARS-CoV-2. Both SARS-CoV-2 and antibodies let a strong competitive inhibition of angiotensin converting enzyme 2 (ACE2). Those biological mechanisms could be associated with the lower risk of severity and mortality in blood group O patients.

Aims: Prospectively perform a cytokine array in plasma samples from COVID-19 patients who were stratified based on their bloody type, in order to describe the inflammatory response and provide a further insight about the possible protective mechanisms elicited by the blood type O.

Methods: Prospective and consecutive study including blood samples from 108 adult patients diagnosed with COVID-19 and admitted to the "Hospital Clínico Universitario" (Valladolid, Spain) between March 24 to April 11,

2020. Percentage distribution of ABO blood type correspond to 54.6%, 9.3%, 3.7% and 32.4% for A, B, AB and O group respectively. Patients were divided into 2 groups: i. Blood type O (n=35); ii. Blood types A/B/AB (n=73). Forty-five Cytokines, Chemokines and Growth Factors were measured in duplicate for each patient using a MAGPIX system (Luminex). Statistical analysis was performed using the R statistical package version 4.0.2.
Results: In both groups, most frequent comorbidities were hypertension, diabetes and chronic obstructive pulmonary disease. According to analytical profile, blood type O displayed higher lymphocytes (p=0.057) and lower total bilirubin (p=0.009) plasma levels than the A/B/AB group. We found a lower risk (2.16 times) of mechanical ventilation or death in patients with blood type O [Log Rank: p=0.042, Hazard Ratio: 0.463, CI 95% (0.213-1.004), p=0.050]. Moreover, 15 cytokines were over-express (and 1 under-expressed) in blood type O (**Image upload. Left box-plots: Group A/B/AB. Right Box-plots: Group O**). Last, a multivariate model found BDNF, IL-13 and IL-27 as the best cytokines able to differentiate the immune profile based on the blood type.
Discussion: In first place, blood type of the general population covered by our hospital are 42%, 9%, 4% and 47% for blood types A, B, AB and O respectively. Nevertheless, our cohort found increase blood type A (54.6%) and decrease in blood type O (32.4%). Therefore, and according our results, blood type O was not only associated to a lower risk of mortality or mechanical ventilation, but also to the need of hospital admission. In second place, a strong ACE2 downregulation – competitive inhibition of ACE2 by SARS-CoV-2 and anti-A and B antibodies – associates high Ang-II plasma levels which allows the production of inflammatory cytokines and, at the same time, a possible lower infectious capacity by SARS-CoV-2 in O blood type patients. Moreover, the existence of a higher activation status of the immune system could also let a rapid activation of the immune response in patients with the O blood type and associate a quicker viral clearance.



Summary/Conclusion: Our cohort showed how blood type O associated with both lower rates of hospital admission and lower risk of intubation or death. Indeed, these patients produced higher amounts of cytokines in response to SARS-CoV-2, hence mounting an effective immune response which allowed them to control the viral infection and therefore decrease the risk of further complications.

S294 LARGE-SCALE PRODUCTION OF CULTURED ERYTHROCYTES USING BIOREACTORS

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Background: Transfusion of donor-derived red blood cells to alleviate anaemia is the oldest and most common form of cellular therapy. In addition, red blood cells hold great promise as delivery agents of e.g. specific drugs of enzymes. However, the source depends on donor availability, and carries a potential risk of alloimmunization and blood borne diseases. In vitro cultured, customizable red blood cells (cRBC) negate these concerns and introduce precision medicine both in transfusion medicine as well as in drug delivery applications.
Aims: Here we investigated the requirements to produce red blood cells from erythroid cultures in stirred bioreactors in order to upscale the process.
Methods: Using inhouse generated serum-free GMP-grade media we optimize a protocol to expand erythroblast and differentiate cultures using 0.5 and 3.0 L stirred bioreactors. Culture parameters, e.g. oxygen availability, shear stress, impellor speed, culture density and perfusion speeds were measured. Sheer stress-induced effects on cells was evaluated by assessing specific signal transduction pathways and globally by RNA-sequencing. Cultured red blood cells were subjected to quality assessment including deformability by Automated Rheoscope and Cell Analyser (ARCA) and oxygen equilibrium curves as measured with a Hemox analyser. Flow cytometry was used to asses enucleation rates and differentiation progression.
Results: In stationary cultures, more than 90% of the cells enucleated and expressed adult haemoglobin as well as the correct blood group antigens. Passaging cRBC through a leukodepletion filter yielded 100% enucleated, stable cRBC. Deformability and oxygen association/dissociation were similar in cRBC and peripheral blood erythrocytes. RNA sequencing and proteomics was performed daily during differentiation and revealed expression dynamics of important erythroid processes, e.g. increased expression of genes involved in blood group expression, globin regulation, erythroid specific metabolic enzymes, and autophage/mitophage degradation of intracellular organels as well as / downregulation of processes involved in cell proliferation. Next, we optimized a protocol to expand erythroblast cultures using 0.5 and 3.0 L stirred bioreactors. Erythroblasts produced in this system showed similar proliferation potential compared to static conditions. Oxygen availability is a critical process parameter and erythroblasts could be cultured at oxygen concentrations as low as 0.7 mg/L, controlled by intermittent sparging. Maximum shear stress at the impeller tip, predicted to be ~1.8 Pa, was mimicked in an orbital shaker setup to evaluate the effect of mixing on the culture. This level of shear stress induced Ca2+-dependent signaling pathways, including the calcineurin/NFAT pathway, and PKC-enhanced STAT5 signaling. As a result, erythroid maturation under differentiation conditions is accelerated by this level of shear stress. Cell erythroblast densities of up to 10 x 106 cells/mL were reached upon continuous media perfusion, 5X higher compared to the current expansion culture systems. Erythroblasts cultured at high density with perfusion maintained high viability and low spontaneous differentiation. This perfusion strategy leads to smaller culture volumes.
Summary/Conclusion: Our culture protocols enable us to culture RBC from adult peripheral blood mononuclear cells both in static and bioreactor settings. The use of bioreactor is projected to be significantly more cost-effective compared to static cultures. Currently we prepare for a clinical trial with cRBC.

ITP: from bench to bedside

S295 A RESERVOIR OF RITUXIMAB-RESISTANT SPLENIC MEMORY B CELLS CONTRIBUTES TO RELAPSES AFTER B-CELL DEPLETION THERAPY

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Background: We previously showed that RTX-resistant, autoreactive plasma cells contribute to primary failures of RTX in patients with immune thrombocytopenia (ITP). Such cells are presumably absent in patients achieving a complete response to RTX. However, many of these patients eventually relapse during B cell reconstitution, suggesting a new generation of autoreactive plasma cells.
Aims: To decipher the contribution of different B-cell subsets in relapses occurring after B cell depletion in ITP.
Methods: We performed flow cytometry, high-throughput sequencing of V(D)J genes, and single-cell RNA-sequencing of B cells and plasma cells from spleen samples of ITP patients with distinct clinical history: 1) Patients that achieved a complete response after a course of RTX and relapsed during B-cell reconstitution (n=8), 2) patients with primary failure of RTX, i.e. who did not respond to treatment at the time of B-cell depletion (n=16), and 3) patients with active ITP that were not treated with RTX (n=7) as controls.
Results: Analysis of B and plasma cells VH gene repertoire at bulk and single-cell antigen-specific level revealed the coexistence of two simultaneous responses in germinal centers, originating from both previously mutated memory B cells that survived RTX treatment and newly generated B cells. We identified memory B cells recognizing GPIIbIIIa, one of the most common auto-antigen in ITP, that harbored a very high number of VH mutations, suggesting they resisted RTX. These memory B cells belonged to clones shared with plasma cells and germinal centers populations, confirming that autoreactive RTX-resistant memory B cells can return in germinal centers and/or differentiate into plasma cells, thus contributing to disease relapse.
In RTX-refractory ITP patients, we further identified by single cell RNA-sequencing a population of quiescent splenic memory B cells, which presents a unique, yet reversible, RTX-shaped phenotype characterized by down-modulation of B cell specific factors including $CD20^-$ and expression of pro-survival genes. These RTX-resistant memory B cells included anti-GPIIbIIIa clones. Importantly, their continued surface expression of CD19 make them efficient targets for current anti-CD19 therapies.
Summary/Conclusion: Overall, our results clearly demonstrate that RTX-resistant autoreactive memory B cells reactivate as RTX is cleared from the organism. This study thus uncovers a new pathogenic entity in ITP that can be targeted by available therapeutic agents.

S296 LONG-TERM SURVIVAL IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNE THROMBOCYTOPENIA - A NATIONWIDE POPULATION-BASED COHORT STUDY

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Background: Immune thrombocytopenia (ITP) exists in a primary form with no underlying cause (pITP), and a secondary form (sITP). Survival in pITP has been found to be reduced compared to background populations. However, only few studies on long-term outcomes and prognosis have been conducted, and prognosis of sITP is to our knowledge unknown.
Aims: In this study, we leverage the unique Danish patient registries to present long-term survival for patients with chronic primary and secondary immune thrombocytopenia.
Methods: Incident chronic ITP patients aged ≥ 18 years were identified as patients with two defined WHO ICD-8 or ICD-10 ITP-diagnosis codes registrations ≥ 12 months apart in any Danish hospital during 1980-2016. Patients with prevalent ITP at the beginning of the study period were excluded (using data from 1977-1979).
Among patients with chronic ITP, sITP cases were identified using the designated ICD10-code (D695) or through registration of an associated diagnosis before or up to 12 months after the first ITP diagnosis.
For each ITP patient, we identified and matched up to 50 individuals from the background population and not previously registered with ITP, matching on age and sex. Patients' index date were the date of the second diagnosis registration after ≥ 12 months, assigning comparison individuals an index date corresponding to the matched ITP patient. Individuals were followed from index date until death, emigration, or end of study, whichever came first.
Results: We identified 3,402 patients fulfilling primary criteria for chronic ITP. Of these, 836 were excluded (210 were prevalent, 506 were <18years of age, 80 had congenital platelet disorders and 40 had Evans syndrome) yielding a total of 2,566 patients with chronic ITP in the period 1980-2016. Comparisons comprised 123,244 individuals.
Among patients with chronic ITP 90.3% (n=2,318) were classified as pITP and 9.7% (n=248) as sITP (associated diagnoses were immunodeficiency (<5), autoimmunity (n=119), infection (n=46), hematological cancer (n=48) or D695 ICD-code only (n=48), with some overlap between groups).
The entire cohort included 60.3% women and mean age at index date was 55.5 [95% CI: 55.4; 55.6], 19.9% (n=511) of all patients with chronic ITP and 0.2% (n=251) of all comparisons were splenectomized. Survival analysis showed that median survival [95%CI] was 17.3 years [15.3; 20.0] for patients with pITP and 25.5 years [25.2; 26.0] for their corresponding comparisons. For patients with sITP, median survival was reduced to 12.3 years [8.9; 15.2], and 25.8 years [24.6; 27.1] for their comparisons (Figure 1).
When performing Cox-regression, hazard ratio (HR) for death between groups was 1.85 [1.74; 1.97] when comparing all patients with chronic ITP to all comparisons (total number of comparisons in the cohort). Risk of death for patients with sITP vs. pITP (adjusted for age) was also elevated with a HR of 1.50 [1.24; 1.81].
Subgroup analyses for both pITP and sITP vs. respective comparisons were also performed. For patients with pITP vs. comparisons HR was 1.77 [1.66; 1.89], and among patients with sITP vs. comparisons HR was 2.79 [2.33; 3.33].

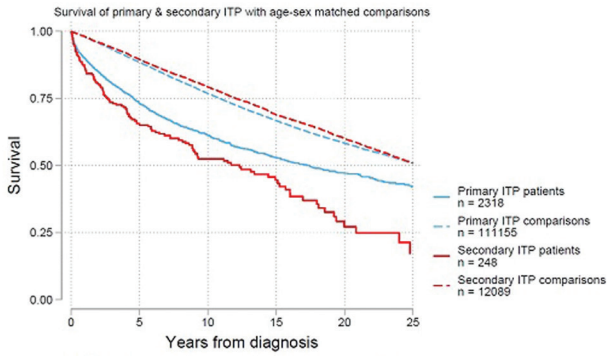


Figure 1 - Kaplan-Meier *survival curves for patients with chronic ITP* Solid lines illustrate patients with primary and secondary ITP while dashed lines show their respective comparisons

Summary/Conclusion: Survival for both pITP and sITP are reduced compared to the general population.
This cohort provides a unique possibility of future outcome studies of patients with pITP and sITP.
Analyses of temporal trends and comorbidity are ongoing and will be presented with the abstract.

S297 FEATURES OF HEMATOPOIETIC STEM AND PROGENITOR CELLS IDENTIFIED THROUGH SINGLE-CELL RNA SEQUENCING IN IMMUNE THROMBOCYTOPENIA

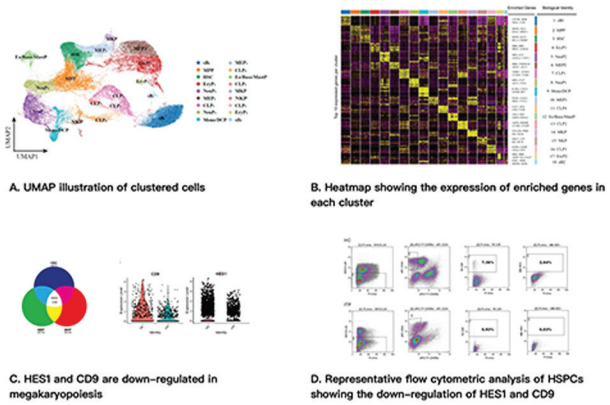
Y. Liu [1,2,*], A. Liu [1,2], J. Peng [1,2]

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Background: Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia. A growing body of emerging evidence indicates that abnormalities during any stage of thrombopoiesis and megakaryocytopoiesis can influence platelet production.
Aims: Our study concentrated on the hematopoietic stem and progenitor cells (HSPCs) in ITP patients from the perspective of single cell transcriptome.
Methods: $CD34^+$ HSPCs were isolated from BM of four newly diagnosed ITP patients and four healthy adults as controls by fluorescence-activated cell sorter (FACS), and Single-cell RNA sequencing (scRNA-seq) data was collected using the recommended protocol for the 3' scRNA-seq 10X genomics platform.
Results: We perform scRNA-seq for 69,178 single $CD34^+$ HSPCs, and detected over 3000 expressed genes per cell on average. Uniform manifold approximation and projection (UMAP), a method for nonlinear dimensionality reduction, showed a visualized image of the cells (Fig 1. A). Heatmap showed the scaled expression of top 10 differentially expressed genes in each cluster (Fig 1. B). Cell clusters expressed established markers of hematopoietic populations, revealed diverse hematopoietic cell

types and implied differentiation trajectories consistent with current views of hematopoiesis. We identified an unambiguous feature of HSPCs in ITP patients with the down-regulation of HES1 and CD9 (Fig 1. C). And the results were verified by flow cytometry (Fig 1. D). Furthermore, through cell culture, we found that lin$^-$CD45ra$^-$CD34$^+$CD9$^+$ cells produced fewer mature megakaryocytes in ITP patients than healthy controls. Our study suggested that HES1 and CD9 were involved in the pathogenesis of ITP.

Fig1. ScRNA-seq analysis of the BM HSPCs from ITP patients and controls



A. UMAP illustration of clustered cells

B. Heatmap showing the expression of enriched genes in each cluster

C. HES1 and CD9 are down-regulated in megakaryopoiesis

D. Representative flow cytometric analysis of HSPCs showing the down-regulation of HES1 and CD9

Summary/Conclusion: Using scRNA-seq, we revealed a hierarchically-structured transcriptional landscape of hematopoietic differentiation of BM CD34+ HSPCs. We observed a significantly descreased expression of HES1 and CD9 in newly diagnosed ITP patients, which might relate with the generation of abnormal MKs and be a biomarker potentially using in diagnosis.

S298 HIGH LEVEL OF ESTRADIOL INDUCES MEGAKARYOCYTE APOPTOSIS AND IMPAIRS PROPLATELET FORMATION VIA MST1-FOXO1 AXIS DURING PREGNANCY IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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Background: Immune thrombocytopenia (ITP) affects 1-10 in 10000 pregnancies. Although most patients were remaining relatively stable throughout pregnancy, the platelet counts may decrease following the prolongation of gestation, especially in the third trimester. The pathogenesis is usually considered to be secondary to physiologic changes during gestation, such as an increase in blood volume, platelet activation, or increased platelet clearance. However, the precise pathogenesis of ITP during pregnancy has not been fully understood.
Aims: It is to explore the relationship between the high level of estradiol (E2) and defective thrombopoiesis in ITP during pregnancy.
Methods: Twenty consecutive successful pregnancies in 20 ITP patients were studied. Blood samples were analyzed to determine the concentration of E2 at different gestational ages using ELISA. BM-derived CD34$^+$ cells from healthy controls (HCs), ITP patients and pregnant ITP (P-ITP) patients were cultured. BM-derived CD34$^+$ cells from ITP patients were treated with different concentrations of E2. he differentiation of megakaryocytes (MKs) and polyploidization were assessed by flow cytometry. Proplatelet formation (PPF) were observed with a phase-contrast microscope and a confocal microscope. MK apoptosis and markers of apoptosis pathways were detected via flow cytometry, and western blotting was used to evaluated the expression of FoxO1 and Mst1.
Results: P-ITP patients experienced significant reduction in platelet counts during gestation, particularly in the late stages. BM-derived CD34$^+$ cells from HCs, ITP patients and P-ITP patients were sorted and cultured. It was observed that the percentage of CD41$^+$CD42b$^+$ MKs and high ploidy MKs were significantly lower in ITP patients than in HCs. In addition, few MKs with proplatelets were observed in ITP patients. A higher percentage of CD41$^+$CD42b$^+$ MKs and high ploidy MKs were found in P-ITP samples than in ITP samples. However, in P-ITP samples, fewer MKs with proplatelets were observed. The results indicated that the thrombopoiesis ability differed between ITP and P-ITP patients.
The concentration of E2 was founded to be sharply increased during pregnancy in ITP. To explore whether there is a link between the levels of E2 during gestation and thrombopoiesis in ITP patients during pregnancy, BM-derived CD34$^+$ cells from ITP patients were treated with different concentrations of E2, which were determined by the serum levels of P-ITP patients. E2 was observed to dose-dependently promote the MKs differentiation and polyploidization. However, at high E2 levels of 10 nM and 100 nM, few proplatelet-generating MKs were observed. In the 10 nM and 100 nM groups, a high percentage of apoptotic MKs was detected. The physiologic concentration of 0.1 nM had no obvious influence on MKs apoptosis. The expression of Bak, Bax, and cleaved caspase-3, which were components of the intrinsic apoptosis pathway, were significantly increased in the 10 nM and 100 nM groups. Increased apoptotic MKs were also observed in BM biopsy samples from P-ITP patients. These findings indicated that a high concentration of E2 could induced activation of the intrinsic apoptosis pathway in ITP MKs and impaired PPF. The activation of the Mst1-FoxO1 axis, which induced activation of the intrinsic apoptosis pathway, was found in ITP MKs treated with a high level of E2.
Summary/Conclusion: For the first time, our study demonstrated that a high level of E2 during pregnancy impaired proplatelet formation by activating the intrinsic apoptosis pathway via the Mst1-FoxO1 axis in ITP.

S299 PHASE I/II UPDATED SAFETY AND EFFICACY RESULTS OF ORAL BRUTON TYROSINE KINASE (BTK) INHIBITOR RILZABRUTINIB IN RELAPSED/REFRACTORY IMMUNE THROMBOCYTOPENIA (ITP)

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Background: Immune thrombocytopenia (ITP) is characterized by immune-mediated platelet destruction and impaired production, triggering thrombocytopenia, and a predisposition to bleeding. Despite recent therapeutic advances, durable remission remains an unmet need for relapsed/refractory ITP patients. Rilzabrutinib is an oral, reversible, covalent inhibitor of BTK that targets immune-mediated ITP activities and has simultaneous rapid anti-inflammatory effects and neutralization and prevention of autoantibody signaling preclinically. The ongoing phase I/II study (NCT03395210) assesses the safety and efficacy of rilzabrutinib in patients with relapsed or refractory ITP who previously responded to ≥1 prior ITP therapy and have no available treatment options. Initial results have shown rapid and durable clinical activity and a well-tolerated safety profile in patients responding to rilzabrutinib.
Aims: Phase II evaluation of rilzabrutinib in the overall study population and patients initiating 400 mg BID rilzabrutinib.
Methods: Eligible patients with 2 baseline platelet counts <30×10^9/L received oral rilzabrutinib at starting doses of 200 mg QD, 400 mg QD, 300 mg BID, or 400 mg BID; intrapatient dose escalation was allowed to improve efficacy. Rilzabrutinib was given for 24 weeks; additional long-term therapy was administered at the 400 mg BID dose in responders only. Stable doses of concomitant ITP medication (corticosteroids and thrombopoietin-receptor agonists) were permitted for patients without adequate platelet response. The primary endpoints are safety and ≥2 consecutive platelet counts ≥50×10^9/L and increased ≥20×10^9/L from baseline without requiring rescue medication. All patients provided informed consent.

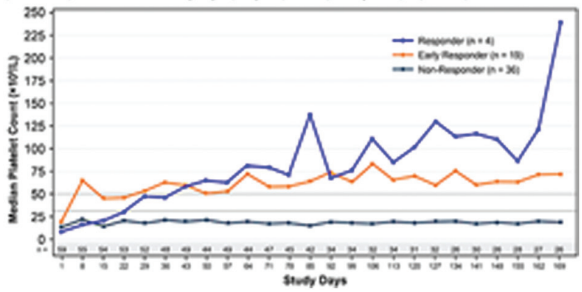
Results: The overall study population comprises 59 patients, of whom 44 had a starting dose of 400 mg BID; data cutoff was 09Nov2020. Overall, patients had a median age 50 years (range, 21-74), median duration of ITP 6.4 years (range, 0.4-52.5), and a median of 6.0 prior therapies (range, 1-53; 25% prior splenectomy). Baseline median platelet counts were 15-16×10^9/L (range, 2-33). Baseline demographics were similar for patients initiating 400 mg BID. A total of 23 patients (39%) overall and 17 (39%) initiating 400 mg BID achieved the primary efficacy endpoint (Table). Primary responses were observed irrespective of prior treatments or responses. Responders maintained platelet counts ≥50×10^9/L for a median of 75% of weeks, as well as increased platelet counts of ≥20×10^9/L above baseline levels for a median of 87% of weeks (Figure). Approximately half of all patients attained platelet counts of ≥30×10^9/L by day 8. Day 8 platelet count was associated with a high negative predictive value for achieving the primary endpoint (>80%) and may assist with identifying patients unlikely to reach the targeted primary platelet response. Related treatment-emergent adverse events (all grade 1/2) were observed in 29 of 59 (49%) patients overall; most common were 31% diarrhea and 25% nausea (all others were <10%). There were no related bleeding/thrombotic events, ECG abnormalities, hypertension, or liver enzyme elevations.

Table. Summary of Platelet Response with Rilzabrutinib in ITP

	All Patients (N = 59)		400 mg BID Starting Dose (n = 44)	
Primary endpoint response*, n (%)	23 (39)		17 (39)	
Prior splenectomy	5/15 (33)		3/11 (27)	
No prior splenectomy	18/44 (41)		14/33 (42)	
TPO-RA naive patients	10/17 (59)		8/14 (57)	
Based on response to prior therapy	Responded	No Response	Responded	No Response
TPO-RA	6/20 (30)	7/22 (32)	3/14 (21)	6/16 (38)
Rituximab	3/9 (33)	3/14 (21)	2/7 (29)	3/14 (21)
Fostamatinib	2/6 (33)	1/2 (50)	2/5 (40)	1/2 (50)
Percent of weeks with target platelet counts, median (range)				
≥50×10^9/L	75% (25%-100%)		75% (37%-100%)	
≥20×10^9/L above baseline	87% (29%-100%)		87% (33%-100%)	
Achieved ≥30×10^9/L by day 8†				
Yes, n (%)	30 (51)		22 (50)	
Positive predictive value	63%		59%	
No, n (%)	29 (47)		22 (50)	
Negative predictive value	86%		82%	

BID, twice daily; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.
*At least 2 consecutive platelet counts ≥50×10^9/L and increased ≥20×10^9/L from baseline without requiring rescue medication.
†In patient-was-enrolled-and-did-not-have-day-8-platelet-counts.

Figure. Median platelet counts during main rilzabrutinib treatment period based on no response or platelet responses of ≥50×10^9/L by day 8 (early responders) or any time (responders)



Summary/Conclusion: Rilzabrutinib was well-tolerated and showed rapid and durable responses, with half of the patients achieving platelet counts ≥30×10^9/L by day 8, potentially providing a tool for predicting early response to treatment, and a durable primary endpoint response. Taken together, these findings support further investigation of the magnitude and durability of rilzabrutinib clinical benefit.

Dilemmas in coagulation and thrombosis

S300 CHIP-ASSOCIATED MUTANT ASXL1 ACTIVATES INNATE IMMUNE PATHWAY IN MYELOID CELLS AND PROMOTES ATHEROSCLEROSIS IN MICE

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Background: Recent epidemiological studies showed the significant association between cardiovascular diseases (CVD) and clonal hematopoiesis of indeterminate potential (CHIP). CHIP is defined as the clonal expansion of blood cells driven by somatic mutations in hematopoietic genes, such as *DNMT3A*, *ASXL1*, *TET2*, or *JAK2*. Previous studies have shown that *TET2*-, *DNMT3A*- and *JAK2*-driven CHIP in fact promote atherosclerosis or worsen heart failure using mice models. In contrast, whether and how ASXL1 mutations contribute to atherosclerosis remains unknown despite the robust clinical association between mutant *ASXL1*-driven CHIP and CVD.
Aims: We aim to investigate the crosstalk between hematopoiesis with mutant ASXL1 and CVDs.
Methods: We previously established knockin (KI) mice expressing a C-terminally truncated form of ASXL1-mutant (ASXL1-MT). Using these mice, we assessed if the high-fat diet (HFD) affects the reconstitution and differentiation of hematopoietic cells with ASXL1-MT. We also assessed the role of hematopoietic cells derived from ASXL1-MT KI mice in the development of atherosclerotic CVDs using the atherosclerosis-prone Ldlr-/- mice. To study the mechanisms underlying the promotive effect of ASXL1 mutation on atherosclerosis, we used mouse and human cell lines (RAW264.7 cells, 293T cells), BaF/3 cells expressing Toll-like receptor (TLR), and bone marrow-derived macrophages derived from the ASXL1-MT KI mice.
Results: The Ldlr$^{-/-}$ mice transplanted with bone marrow from ASXL1-MT KI mice showed significantly larger atherosclerotic lesions in the aorta and aortic valves than the control mice. We also found that HFD conferred growth advantage to ASXL1-MT cells over wild-type cells, particularly in the population of the inflammatory monocytes. Consistent with these findings, RNA-seq of the plaque-macrophages derived from ASXL1-MT KI mice showed more inflammatory signatures than those from control mice. Thus, these data suggest that mutant ASXL1 promotes HFD-induced expansion of inflammatory monocytes and macrophages, thereby accelerates atherosclerosis.
Mechanistically, we found that wild-type and mutant ASXL1 have different effects on the innate immune pathway. NF-κB reporter assay revealed that wild-type ASXL1 suppressed, while mutant ASXL1 promoted, the reporter activation induced by the TLR stimulation. Furthermore, we found that wild-type ASXL1, but not mutant ASXL1, suppresses the activation of TAK1 in TLR-NF-κB signaling pathway through direct interaction with IRAK1 and TRAF6. These results suggest that ASXL1 inhibits the innate immune pathway through interactions with IRAK1/TRAF6/TAK1 in myeloid cells, while mutant ASXL1 loses this regulatory function. Finally, we assessed the effect of IRAK1/4 inhibitor on atherosclerosis in HFD-fed ASXL1-MT mice. As expected, IRAK1/4 inhibition decreased the number of inflammatory monocytes and attenuated the development of atherosclerosis driven by ASXL1-MT.
Summary/Conclusion: Our study demonstrated the causative role of the CHIP-associated *ASXL1* mutation to promote atherosclerosis. Inhibition of the innate immune pathway may prevent the development of CVD associated with CHIP harboring *ASXL1* mutations.

S301 RAVULIZUMAB REDUCES THE RISK OF THROMBOSIS IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND HIGH DISEASE ACTIVITY: 2-YEAR DATA FROM A PHASE 3, OPEN-LABEL STUDY

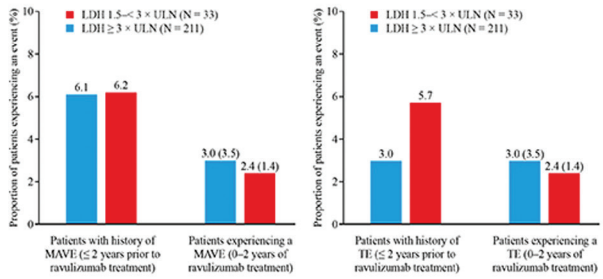
R. Peffault de Latour [1,*], A. Hill [2], W. Füreder [3], C. Piatek [4], M. Griffin [5], M. Ogawa [6], J. Wang [6], K. Usuki [7], A. Röth [8], J. W. Lee [9]

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Background: Patients with paroxysmal nocturnal hemoglobinuria (PNH) are at an increased risk of thromboembolism (TE) which may be fatal. Results of a univariate retrospective analysis from the International PNH Registry showed that patients with intravascular hemolysis, defined as lactate dehydrogenase (LDH) ≥ 1.5 × upper limit of normal (ULN; 246 U/L), and ≥ 2 × ULN, high disease activity (HDA) symptoms, and history of TEs and major adverse vascular events (MAVEs) are at significantly greater risk of experiencing TE. Where available, ravulizumab is the current standard of care for PNH, however, its long-term effectiveness in preventing TEs and MAVEs in patients with HDA is unknown.

Aims: To evaluate the long-term effectiveness of ravulizumab at preventing TEs and MAVES in patients with PNH and HDA in a phase 3 study stratified by baseline LDH levels.
Methods: This ongoing phase 3, multicenter, randomized, open-label study (NCT02946463) enrolled adult patients (aged ≥ 18 years) with PNH and HDA (LDH levels ≥ 1.5 × ULN and presence of 1 or more PNH-related symptoms within 3 months of screening) who were complement-inhibitor-naïve. Patients received weight-based dosing of ravulizumab every 8 weeks or eculizumab (900mg every 2 weeks) during the randomized treatment period and continued or switched to ravulizumab during the extension period (5 years). In this post-hoc analysis, patients who received ravulizumab were stratified by baseline LDH levels into two groups: 1.5 – < 3 × ULN (Group A) or ≥ 3 × ULN (Group B). Proportion of patients experiencing MAVE or TE in 2 years prior to enrollment and after receiving ravulizumab during 2 years of the study were compared for each group. TEs included thrombophlebitis/deep vein thrombosis (DVT), renal vein thrombosis, renal arterial thrombosis, mesenteric/visceral vein thrombosis, mesenteric/visceral arterial thrombosis, hepatic/portal vein thrombosis, dermal thrombosis, acute peripheral vascular disease occlusion, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, and pulmonary embolus. MAVEs include both TEs and non-TEs (amputation [nontraumatic, nondiabetic], myocardial infarction, transient ischemic attack, unstable angina, gangrene [nontraumatic, nondiabetic], and specified if other).
Results: Patients were stratified to Group A (n = 33) or Group B (n = 211), respectively. Patient demographics were comparable between the two groups, with mean (SD) age at first infusion of 48.2 (15.5) years for Group A and 44.9 (15.6) years for Group B. However, more patients in Group A were white compared with Group B (51.5% and 36.5%, respectively). Over the 2 years of study, patients in Group A and Group B underwent 56.7 and 361.2 patient-years of exposure to ravulizumab, respectively. Treatment with ravulizumab resulted in fewer reported MAVEs and TEs compared with the 2 years prior to enrollment in both groups (**Figure 1**). MAVEs reported during the 2 years of treatment with ravulizumab were all TEs. Only 1 patient (3.0%) in Group A experienced TE, which was classified as a pulmonary embolism event. In Group B, 5 patients (2.4%) experienced TE, including 2 DVT events, and 1 event each of thrombosis, jugular vein thrombosis and peripheral artery thrombosis. Ravulizumab was well-tolerated in all patients for up to 2 years with no new safety signals.

Figure 1 Summary of MAVEs and TE events in patients with PNH and high disease activity



Data label values in parentheses represent the MAVE or TE event rate per 100 patient-years during the 2 years of ravulizumab treatment.
LDH, lactate dehydrogenase; MAVE, major adverse vascular events; PNH, paroxysmal nocturnal hemoglobinuria; TE, thromboembolism; ULN, upper limit of normal.

Summary/Conclusion: Ravulizumab reduces the risk of thrombosis in patients with PNH and HDA, who are at an increased risk of TE.

S302 HALF-LIFE PROLONGATION OF VON WILLEBRAND FACTOR: A NEW THERAPEUTIC STRATEGY FOR HAEMOPHILIA A AND VON WILLEBRAND DISEASE

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Background: Von Willebrand Factor (VWF) and coagulation Factor VIII (FVIII) circulate in a noncovalent complex in blood and promote primary haemostasis and clotting respectively. As well as mediating platelet adhesion, VWF reduces the clearance of FVIII. VWF deficiency causes mucocutaneous bleeding, and FVIII deficiency mainly causes spontaneous joint bleedings. Both of them can result in life-threatening bleeding during surgery or after trauma, and may necessitate VWF or factor VIII replacement therapy in severe cases. Only recently, VWF has become a target for therapeutic interventions in prothrombotic diseases. However, intravenous infusion of the A1 domain blocking aptamer ARC1779 was also effective in patients with hyperactive VWF (VWD type IIb), and increased their plasma levels of VWF, FVIII and platelet counts pointing towards a potential hemostatic function, which may also be exploited. A new generation of aptamer, BT200, was recently designed, which showed good subcutaneous bioavailability and a long half-life in non human primates.
Aims: This first-in human, randomised, placebo-controlled trial set out to test the hypothesis, that BT200 is well tolerated, safe and has favourable pharmacokinetic and pharmacodynamic effects.
Methods: Normal healthy volunteers received single ascending doses of the anti VWF aptamer BT200 ranging over 2.5 orders of magnitude from 0.18 mg to 48mg by subcutaneous injection or sc or iv. infusions. Blood samples were collected over 4 weeks after the last dose. This was followed repeated dosing in a multiple ascending dose part of the trial. Pharmacokinetics were characterised and the effects were measured by VWF parameters, FVIII, platelet function tests, viscoelastometry and thrombin generation.
Results: BT200 plasma concentrations increased dose-proportionally. Mean plasma peak of BT200 concentration ranged from 0.01 to 5.53 µg/mL. Mean plasma BT200 terminal elimination half-life (t½) ranged between 118 to 284 hours following subcutaneous injection. Bioavailability increased dose-dependently and reached 90% at the highest dose level. BT200 inhibited the A1 domains of VWF in a dose dependent fashion particularly at doses >=12mg. BT200 decreased VWF activity, ristocetin induced aggregation, and prolonged collagen adenosine diphosphate closure times. At maximal doses complete inhibition of VWF was achieved ($p<0.001$), with clinical signs of mild mucosal bleedings. However, BT200 also dose-dependently increased VWF:Antigen levels and Factor VIII clotting activity >4-fold ($p<0.001$). This resulted in increased thrombogenicity as measured by thrombin generation and enhanced clotting. In the absence of an increase in VWF propetide levels, this effect is considered due to decreased clearance of VWF. Interestingly a clinically meaning full increase in VWF/FVIII (2-fold increase) was already visible at doses <=6mg. Simulations indicate that BT200 will be able to achieve a 2-3 fold increase in endogenous VWF/FVIII levels in mild/moderate bleeding disorders, as well as a substantial half-life prolongation of all kind of substituted VWF/VIII products in severe hemophilia or type III VWD.
Summary/Conclusion: This trial identified a novel mechanism of action for BT200: it decreases the clearance of VWF/FVIII, which can be exploited for congenital bleeding disorders. This built a solid foundation for an ongoing basket trial in patients with von Willebrand disease or haemophilia A, which already confirms the expected effect sizes.

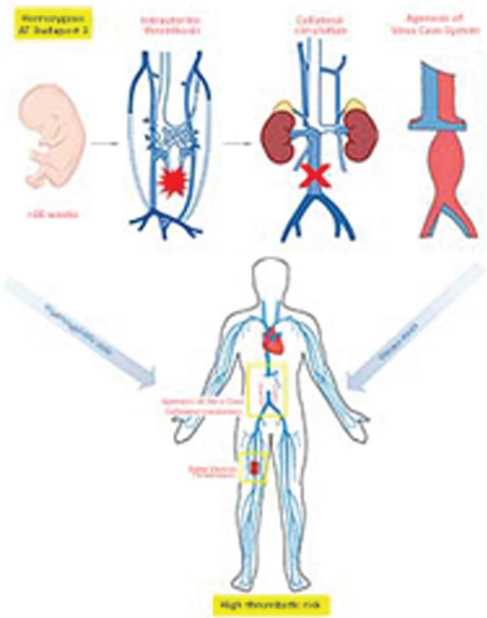
S303 SEVERE ANTITHROMBIN DEFICIENCY, HOMOZYGOUS ANTITHROMBIN BUDAPEST 3, CAUSES AGENESIS OF THE INFERIOR VENA CAVA SYSTEM.

M. E. De La Morena-Barrio [1,*], C. Bravo-Pérez [1], R. Gindele [2], P. Ilonczai [3], I. Zuazu [1], M. Speker [2], Z. Oláh [4], J. J. Rodríguez-Sevilla [5], L. Entrena [6], M. S. Infante [7], J. M. García [7], B. de la Morena-Barrio [8], A. Schlammadinger [9], A. Miñano [8], V. Vicente [8], J. Corral [10], Z. Bereczky [2]

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Background: Agenesis of inferior vena cava (IVC) is a rare congenital malformation with unknown etiology that might be associated with intrauterine IVC thrombosis. The identification of IVC agenesis in a case with early idiopathic venous thrombosis and antithrombin deficiency caused by the homozygous SERPINC1 c.391C>T variant (p.Leu131Phe; antithrombin Budapest 3), encouraged to evaluate the role of severe thrombophilia in this vascular abnormality.
Aims: To study the mechanisms and molecular base of inferior venca cava system.

Methods: Retrospective study of the worldwide largest series of patients homozygous for the Budapest 3 variant (N=60) selected from two cohorts of patients with congenital antithrombin deficiency (Spain, N=638 and Hungary, N=426). Image analysis included computed tomography and phlebography.
Results: IVC system agenesis was observed in 16 out 23 cases homozygous for antithrombin Budapest 3 with available computed tomography (69.6%), fifteen had agenesis of IVC and one atresia of the left iliac vein. All cases with vascular defects had compensatory mechanisms, azygos-hemiazygos continuation or double IVC, and five had other anatomic defects. Short Tandem Repeat analysis supported the specific association of the IVC system agenesis with SERPINC1.



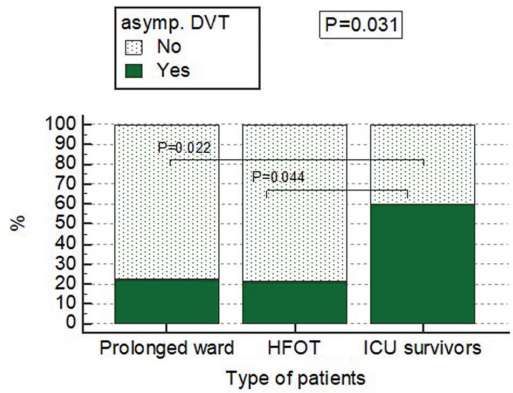
Summary/Conclusion: We show the first evidence of the role of a severe thrombophilia in IVC system agenesis. The impaired control of thrombin in carriers might facilitate intrauterine or perinatal thrombosis at this localization. Moreover, the underlying thrombophilia also explains the high risk of thrombosis described in patients with agenesis of IVC. Our results encourage the search for severe thrombophilic states in patients with agenesis of IVC and to consider the use of antithrombotic prophylaxis at risk situations with these vascular defects.

S304 ASYMPTOMATIC DEEP VENOUS THROMBOSES ARE HIGHLY PREVALENT AMONG PROLONGED HOSPITALIZED SEVERE COVID-19 PATIENTS DESPITE THROMBOPROPHYLAXIS

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Background: Patients with severe symptoms of COVID-19 often require prolonged hospitalization with reduced mobility due to both imposed restrictions and objective decline in functional status.
Aims: Prompted by literature reports of high asymptomatic VTE prevalence in COVID-19 patients and our own clinical experience, we aimed to assess a prevalence of DVT among prolonged hospitalized COVID-19 patients without deep venous thrombosis (DVT) clinical suspicion and to investigate its potential predictors.
Methods: During January 2021 we have prospectively undertaken bilateral lower extremity deep veins duplex ultrasound evaluation in 102 consecutive COVID-19 patients without clinical suspicion of DVT that were prolonged hospitalized in our institution. Eligible patients were adult (≥18 years) ward patients that required hospitalization for ≥7 days. Patients who developed clinical suspicion of DVT, unable to cooperate with the ultrasound procedure or were not sufficiently stable to undergo the ultrasound procedure were considered ineligible for the study. All patients received at least prophylactic doses of low molecular weight heparin.
Results: Median age was 71.5 years. A total of 54/102 (52.9%) patients were males, 96/102 (94.1%) required oxygen-supplementation therapy. Median length of hospitalization at the time of evaluation was 18 days and median time from the start of COVID-19 symptoms was 27 days. DVT was detected in 26/102 (25.5%) patients without clinical suspicion. Distal DVT was the most common [22 patients (84.6% of the DVT cohort; 21.6% of the overall cohort)]. Proximal DVT was present in four patients (16% of the DVT cohort; 3.9% of the overall cohort), among them three had popliteal thrombosis and one had femoral thrombosis. Pulmonary embolism (PE) was detected in 17/70 (24.3%) patients who were similarly distributed among patients with and without asymptomatic DVT [5/17 (29.4%) and 12/53 (22.6%); P=0.571]. Patients that were mechanically-ventilated ICU survivors presented with highest frequency of DVT [6/10 (60%)], whereas patients treated with high-flow oxygen therapy and prolonged-hospitalized patients had similar DVT frequency [7/33 (21.2%) and 13/59 (22%), respectively]; P=0.031, Figure. D-dimers at the time of hospital admission showed no significant association with the presence of DVT (P=0.280) but there was a statistically significant trend of higher frequency of asymptomatic DVT among patients with higher level of control D-dimers (P=0.034). Patients with and without DVT significantly differed in modified IMPROVE (median 3 and 2 points, respectively; P=0.021) and IMPROVEDD VTE risk-scores (median 4 and 3 points, respectively; P=0.029). Only 17/26 (65.4%) of patients with DVT would fulfill post-discharge thromboprophylaxis criteria (modified-IMPROVE score ≥2 and D-dimers 2x above normal or modified IMPROVE score ≥4 (COVID-19 Treatment Guidelines Panel 2021)). Other variables that were significantly associated with the presence of DVT were known thrombophilia (P=0.015) and higher body temperature on admission (P=0.001). Intensity of thromboprophylaxis, previous anticoagulation, CRP, age, sex, COVID-19 clinical prognostic-scores (MEWS, 4C-mortality score) and Padua VTE risk-score were not significantly associated with the occurrence of DVT (P>0.05 for all analyses).



Summary/Conclusion: Systematic ultrasound assessment of prolonged hospitalized severe COVID-19 patients prior to hospital discharge is probably needed, especially of ICU survivors, to timely recognize and appropriately treat patients with asymptomatic DVT.

Malignancies and thrombosis

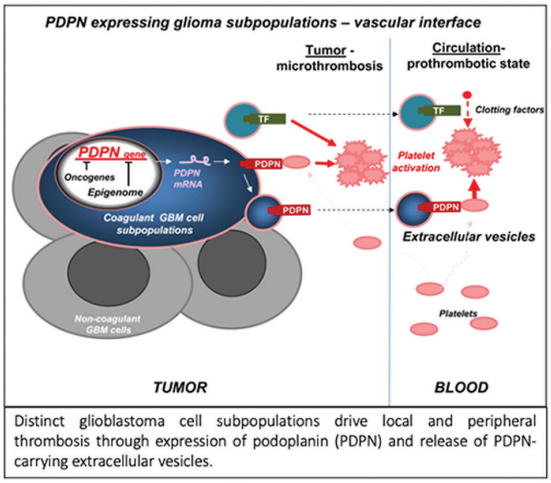
S305 GLIOBLASTOMA CELL POPULATIONS WITH DISTINCT ONCOGENIC PROGRAMS RELEASE PODOPLANIN AS PROCOAGULANT EXTRACELLULAR VESICLES

N. Tawil [1,*], R. Bassawon [2], B. Meehan [3], L. Montermini [3], A. Nehme [2], D. Choi [3], C. Spinelli [3], L. Adnani [3], S. Chennacrishnaiah [3], J. Rak [3]

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Background: Vascular anomalies, including thrombosis, are a hallmark of glioblastoma (GBM) and an aftermath of dysregulated cancer cell genome and epigenome. The upregulation of podoplanin (PDPN) by cancer cells has recently been linked to an increased risk of venous thrombo-embolism (VTE) in GBM patients. Thus, regulation of this platelet activating protein by transforming events and release from cancer cells is of considerable interest.
Aims: I. (a) Investigate the pattern of PDPN expression and characterize PDPN expressing populations. (b) Evaluate the contribution of oncogenic driver pathways to PDPN expression modulation in GBM models. (c) Explore the modes of PDPN expression modulation by implicated oncogenic drivers.

II. (a) Investigate the potential involvement of extracellular vesicles as route for systemic dissemination of GBM-associated PDPN. (b) Examine the role of GBM-associated and systemically disseminated PDPN in peripheral activation of platelets. (c) Assess the contribution of PDPN to intratumoral thrombosis and explore the possible cooperation with TF.
Methods: We used single cell and bulk transcriptome data mining, as well as cellular and xenograft models in mice to analyze the nature of cells expressing PDPN, their impact on activation of coagulation system, and platelets. We also took advantage of various analytical techniques including immunoblotting, immunofluorescence, electron microscopy, density gradient fractionation, Cytoflex, and ELISA.
Results: We report that PDPN is expressed by distinct (mesenchymal) GBM cell subpopulation and downregulated by oncogenic mutations of EGFR and IDH1 genes, via changes in chromatin modifications (EZH2) and DNA methylation, respectively. GBM cells exteriorize their PDPN and/or tissue factor (TF) as cargo of exosome-like extracellular vesicles (EVs) shed from cells in vitro and in vivo. Injection of glioma PDPN-EVs activates platelets, while TF-EVs weakly activate the clotting cascade. Similarly, increase of platelet activation (PF4) or coagulation markers (D-dimer) occurs in mice harboring the corresponding glioma xenografts expressing PDPN or TF, respectively. Co-expression of PDPN and TF by GBM cells cooperatively affects tumor microthrombosis.



Distinct glioblastoma cell subpopulations drive local and peripheral thrombosis through expression of podoplanin (PDPN) and release of PDPN-carrying extracellular vesicles.

Summary/Conclusion: In GBM distinct cellular subsets drive multiple facets of cancer-associated thrombosis and may represent targets for phenotype and cell type-based diagnosis and antithrombotic intervention. Accordingly, we suggest that the preponderance of PDPN expression as a risk factor in GBM and involvement of platelets in our GBM model may merit investigating antiplatelets for potential inclusion in VTE management strategies in GBM setting.

S306 THROMBOPHILIA AS RISK FACTOR FOR ASPARAGINASE RELATED VENOUS THROMBOEMBOLISM IN PEDIATRIC AND YOUNG ADULT PATIENTS AFFECTED BY ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Venous thromboembolism (VTE) is one serious complication in patients with acute lymphoblastic leukemia (ALL) with an incidence of 1-14% in thromboembolic symptomatic patients and up to 37% in the asymptomatic. In these patients, VTE is a multifactorial event: leukemia, central venous catheter (CVC), chemotherapy, in particular, asparaginase (ASP), and steroids. ASP is an effective chemotherapeutic agent that catalyzes the hydrolysis of asparagine. Treatment with ASP increases the risk for VTE. Among the causes that can determine an increased thromboembolic risk, the presence of congenital or acquired thrombophilia can play a crucial role.
Aims: The aim of our study was to evaluate the role of thrombophilia on VTE events in pediatric patients (age < 18 years) and in adolescents and young adults (AYA) < 40 years old with ALL during ASP chemotherapy regimens.
Methods: We defined ASP-associated thrombosis when the event occurred within 1 month from the drug administration. The types of drugs used were: the native form derived from E. Coli (Medac® and Kidrolase®); the form derived from Erwinia Chrysanthemi (Erwinase®); and the pegylated E. coli ASP (PEG-ASP -Oncaspar®). Patients were treated according to the following chemotherapy protocols: GIMEMA LAL 1913; GIMEMA LAL 1308; GIMEMA LAL 2000; NILG-LAL 10/07; GIMEMA LAL 0904; GIMEMA LAL 0496; ESPHALL; AIEOP-EURO-LB02; AIEOP-BFM LAL2009; AIEOP-BFM LAL2000. All patients performed the inherited and acquired thrombophilia assays at disease diagnosis before chemotherapy start. In patients with clinical signs of thrombotic occlusion, the diagnosis of VTE was made with Doppler ultrasonography examination of vessels; chest computerized tomography (CT) for pulmonary embolism; magnetic resonance imaging (MRI) in case of thrombosis of the cerebral circulation.
Results: We studied 96 ALL patients and their characteristics are summarized in table 1. Thrombotic complications occurred in 15/96 (15.6%) patients, including 12 deep vein thromboses (DVT) of upper limbs, 1 thrombosis of the central vein of retina, 1 thrombosis of the superior sagittal sinus, 1 DVT extended to both lower and upper limbs associated with pulmonary embolism. Overall, 6/15 (40%) patients with the thrombotic complication presented thrombophilia (p = 0.265). Of the 15 thrombotic events, 7/15 (47%) were associated with the use of ASP. Three/seven (43%) patients presented B-ALL and 4/7 (57%) T-ALL (p = 0.027). Five/7 were treated with PEG-ASP (Oncaspar®) and 2/7 with the native E.coli ASP (p = 0.511); notably, 5 were thrombophilic (p=0.008). In the multivariate analysis, among the predictive factors for ASP-related thrombosis considered (sex, age, thrombophilia, and T-ALL), the only significant factor for thrombotic events development was thrombophilia (p = 0.0029, IC 0.025-0.823; HR 0.143).

TABLE I. Patients' characteristics.

	Number Of patients	Percentage Of Population	Median value
Sex			
Male	53	56,3%	
Female	43	44,8%	
Type of ALL			
B-ALL	79	67,5%	
T-ALL	38	32,5%	
Age (Years)			13 (range 1.7 -47.5)
Plts (10^3/mmc)			103 (range 19-630)
WBC (10^3/mmc)			9.4(range 0,140-400)
Screening for thrombophilia			
Normal	60	55,2%	
Mutated	36	37,5%	
Thrombosis			
None	81	84,4%	
At least 1 event	15	15,2%	
ASP related thrombosis			
No	89	92,7%	
Yes	7	7,3%	

ALL= acute lymphoblastic leukemia; Plts= platelets; WBC= white blood count; ASP= asparaginase

Summary/Conclusion: Although thrombophilia is a well-known risk factor for VTE in ALL, our study focused on its link with ASP-related VTE. We suggests that screening for thrombophilia should be performed in ALL patients before ASP administration, since thrombophilic ALL patients may benefit from VTE prophylaxis.

S307 THROLY SCORE SUCCESSFULLY CLASSIFIES HODGKIN LYMPHOMA PATIENTS AT RISK OF THROMBOEMBOLIC COMPLICATION

D. Antic [1,2,*], V. Otasevic [2], S. Borchmann [3], H. Müller [3], V. Vukovic [2], V. Djurasinovic [2], K. Tomic [2], B. Mihaljevic [2], A. Engert [3], G. Gerotziafas [4], J. Fareed [5]

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Background: Thromboembolism (TE) in lymphoma patients is gathering substantial attention due to its impact on morbidity and mortality of those patients. The association between lymphoma and increased risk for TE development, especially venous thromboembolism (VTE), has lately been well established through numerous publications. Thrombosis Lymphoma (ThroLy) score has been initially developed as a simple risk assessment model for the risk of TE development in lymphoma patients. It has been both internally and externally validated in several studies, which dominantly included patients with non-Hodgkin lymphoma (NHL).

Aims: Therefore, the aim of our study is to analyse and validate ThroLy score in an extensive cohort of Hodgkin lymphoma (HL) patients.
Methods: A total of 5509 newly diagnosed HL patients, from the German Hodgkin Study Group (GHSG) HD13-15 trials, were included in this study. Data has been obtained for all venous and arterial TE events in HL patients from time of diagnosis to 3 months after the last cycle of therapy. TE was diagnosed objectively based on radiographic studies (duplex venous ultrasound, contrast-enhanced thoracic computed tomography scan, magnetic resonance imaging (MRI) - for central nervous system (CNS) thrombosis, or angiograms (for arterial thrombosis), clinical examination and laboratory evaluation. Based on ThroLy score, patients were divided in three risk categories: low (score 0-1), intermediate (score 2-3) and high risk (score >3). Patients with intermediate and high-risk score were classified at risk. The validation was conducted through Chi-square test, ROC analysis and logistic regression.
Results: The mean patients' age was 35.9 years (range, 18-75 years); 55.7% were males. The majority of patients had limited or intermediate stage of disease: Ann Arbor stage I 10.6%, and stage II 57.5%. 190 (3.4%) patients developed thromboembolic events, 173 patients with VTE (3.14%), and 17 with arterial TE (0.31%), respectively. Chi-square test showed statistically significant association between TE and ThroLy score, both in three risk groups (chi-square = 18.236, p≤0.001) and two risk groups: low and at risk (chi-square = 18.029, p≤0.001). The sensitivity, specificity, negative and positive predictive value were 49%, 65%, 95%, and 97%, respectively. Binary logistic regression of ThroLy score showed statistically significant performance in prediction of TE events in HL patients, with satisfactory validity indicators (Ombinus Test chi-square = 11.668, p=0.001; AIC=44.956, BIC = 97.869). Diagnostic accuracy of ThroLy score was calculated via ROC curve (area under curve (AUC)=0.57).
Summary/Conclusion: ThroLy score demonstrated its capability of risk prediction for TE events in HL patients. The limited statistical performance of the ThroLy score requires further research towards possible score enhancement.

S308 FREQUENCY AND RISK FACTORS FOR THROMBOSIS IN ACUTE MYELOID LEUKEMIA TREATED WITH INTENSIVE CHEMOTHERAPY: A TWO CENTERS OBSERVATIONAL STUDY

F. Martella [1], M. Cerrano [2,*], D. Di Cuonzo [3], C. Secreto [1,2], M. Olivi [1,2], S. D'Ardia [2], C. Frairia [2], V. Giai [2], G. Lanzarone [1], V. Apolito [1,2], I. Urbino [1,2], R. Freilone [2], L. Giaccone [4], A. Busca [4], C. Dellacasa [4], E. Audisio [2], D. Ferrero [1], E. Beggiato [1]

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Background: Thrombosis is one of the most frequent complication in cancer. Although recent studies suggest that patients with blood cancers may be at a similar or even higher thrombotic risk than those with solid tumors, the frequency of thrombosis in acute myeloid leukemia (AML) has been evaluated in a few reports only and no validated predictive model is currently available.
Aims: In this study we aimed to evaluate the frequency of thrombosis in AML patients treated with intensive chemotherapy and to assess the ability of genetic and clinical factors to predict the risk of thrombosis, including the Khorana risk score (KRS) or disseminated intravascular coagulation (DIC) score.
Methods: We performed a retrospective observational study including 222 newly diagnosed adult AML patients treated with intensive chemotherapy between January 2013 and February 2020, stratified by European Leukemia Net (ELN) 2010 genetic/cytogenetic risk assessment. The diagnosis of thrombosis was confirmed by imaging modalities including venous ultrasonography, computer tomography or magnetic resonance imaging and clinical, enzymatic and electrocardiographic criteria for myocardial infarction.
Results: 222 patients (52% males) were included, with a median age of 59.5 years (range 20-78), 20.5% in the ELN2010 adverse risk category. With a median follow-up of 43.5 months, we observed 50 thrombotic events and 90% were venous (VTE): twenty-eight patients (62.2% of VTE) had catheter-related thrombosis (CRT), 93% of which were peripherally inserted central catheter (PICC)-related; in 6 and 5 case VTE occurred in lower and upper extremity, respectively, while 3 patients experienced pulmonary embolism. Among arterial thrombosis, 2 myocardial infarctions and 3 cerebral vascular accidents occurred. The prevalence of thrombosis was 22.5% and 6-months, 1-year and 2-year cumulative incidence was 10%, 22% and 25%, respectively. The median time to thrombosis was 84 days and 52% of the events occurred within 100 days from AML diagnosis, during induction/consolidation chemotherapy or just before starting treatment. History of a thrombotic event (p=0.043), especially VTE (p=0.0053), and baseline platelet count higher than 100x10^9/L (p=0.036) significantly increased the risk of thrombosis while AML genetic profile did not affect its occurrence with statistical significance. A sub-analysis considering only early thromboses (i.e. occurring within day 100) confirmed these results. Conversely, if only no-CRT VTE were considered, ELN Intermediate-1 risk group was significantly associated with thromboses (p=0.039), especially FLT3-ITD/NPM1 mutated patients. KRS and DIC score failed to stratify patients according to their thrombotic risk, but DIC score at diagnosis was independently associated with reduced survival (p=0.004) by multivariate analysis. No impact of thrombosis on survival was observed.
Summary/Conclusion: Thromboses are a frequent complication in AML, especially during chemotherapy, and most of them are VTE. However, no impact on survival was observed. Previous VTE and baseline platelet count could predict thrombotic risk, while AML genetic profile did not significantly affect thrombosis occurrence. We confirmed that KRS is not a robust tool in this setting, and we could not validate the association of DIC score with thromboses, warranting further studies on the subject to better predict thrombosis occurrence, hopefully allowing to design therapeutic measures to prevent it.

S309 OUTCOME OF ELDERLY PATIENTS WITH VENOUS THROMBOEMBOLISM TREATED WITH DIRECT ORAL ANTICOAGULANTS - A RETROSPECTIVE COHORT STUDY

I. Ayalon Dangur [1,*], Y. Vega [2], M. R. Israel [1], A. Grossman [2,3], G. Spectre [2,4], T. Shochat [5], L. Leibovici [1,2], A. Gafter-Gvili [2,4,6]

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Background: Large randomized controlled trials that compared direct oral anticoagulants (DOACs) to vitamin K antagonists (VKA), for the treatment of venous thromboembolism (VTE), demonstrated both efficacy and safety of DOACs.
Aims: The aim of the current study was to compare DOACs to low molecular weight heparin (LMWH)/VKA in terms of efficacy and safety, for the treatment of VTE in the elderly, in a real-life setting
Methods: Retrospective cohort study performed in Rabin Medical Center encompassing a 7 –year period. We included all hospitalized patients > 65 years old, with a diagnosis of lower extremity deep vein thrombosis (DVT) and/or pulmonary emboli (PE) discharged with DOACs or LMWH/VKA. The primary outcome was a composite of all-cause mortality, major bleeding events, recurrent VTEs and hospitalizations throughout the follow up period of one year. Secondary outcomes included recurrent VTEs, major bleeding events and all-cause mortality in one year. Overall survival was assessed by the Kaplan Meier model, with the log-rank test. The Cox Proportional Hazards model was used to calculate hazard ratios (HR). Medication was included in the Cox model as a time dependent covariate. Propensity score matching was used to create a matched cohort
Results: Overall, 603 patients were identified and included in the final analysis. A total of 476 patients were treated with VKA/LMWH and 127 patients were treated with DOACs. The mean age was 79.9 ± 8.5 years) VKA/LMWH group(and 78.6 ± 8.1 years)DOAC group(, P=0.24. The primary unadjusted composite outcome of all-cause mortality, major bleeding events, recurrent VTEs and hospitalizations occurred in 355/476 patients (74.6%) in the VKA/LMWH group and in 72/ 127 (56.7%) patients in the DOACs group, hazard ratio (HR) of 0.59, 95% confidence interval (CI) 0.46 to 0.76, in favor of the DOAC group. HR for recurrent VTEs and major bleedings events was 0.58 (95% CI 0.26 to 1.29) and 1.15 (95% CI 0.50 to 2.65), respectively for the DOAC group. There was a significant reduction in mortality in the DOAC group - HR 0.30, 95% CI 0.20 to 0.44. In a multivariable analysis, treatment with DOACs, as well as age, elevated creatinine levels and malignancy were all significantly associated with the composite outcome of all-cause mortality, major bleeding, recurrent VTE and hospitalizations, HR of 0.64 (CI of 0.49-0.83) for the treatment with DOAC. In a matched cohort analysis, the results were the same as the original analysis, with a HR of 0.66 for the DOAC group for the composite outcome, 95% CI 0.51 to 0.87
Summary/Conclusion: In the elderly population, treatment of VTE with DOACs was associated with a lower rate of the composite outcome of all-cause mortality, major bleeding, recurrent VTE and hospitalizations in a follow up of one year. DOACs are safe and effective for elderly patients with VTE

Patient's voice and health outcomes in hematology

S310 INTEGRATION OF A MACHINE LEARNING-BASED MODEL INTO ROUTINE CYTOMORPHOLOGICAL DIAGNOSTICS: FIRST EXPERIENCES FROM THE BELUGA TRIAL

C. Pohlkamp [1,*], N. Nadarajah [1], A. Wahida [2], I. Heo [3], W. Wetton [3], R. Drescher [4], S. Hänselmann [4], T. Lörch [4], C. Haferlach [1], W. Kern [1], T. Haferlach [1]

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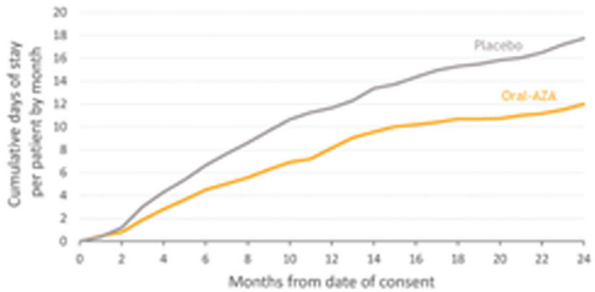
Background: Cytomorphology is essential to quickly assess hematological neoplasms. Experienced personnel and short TAT of <24 hours are mandatory. Machine learning (ML) has proven its power in image classification. Following our pilot study (ASH 2020, Blood 136, # 195) we report on our first experiences with an ML-based blood cell differentiation tool in daily routine.
Aims: To evaluate feasibility in a prospective blinded trial in parallel to daily routine workflow, we registered the BELUGA study (ClinicalTrials.gov Identifier: NCT04466059) which includes a head-to-head-comparison between human investigators and the ML-based classifier regarding accuracy over all malignant/non-malignant cell types in peripheral blood.
Methods: We established an automated routine workflow including the capture of 500 digital cell images per blood smear in 40x oil magnification after focusing on regions of interest (Metafer Scanning System, MetaSystems, Altlussheim; Zeiss Axio Imager.Z2 microscope). Cells are classified by the ML-based deep neural network (DNN). Resulting data are compared to the independent microscopic cell differentiation done by hem specialists. With regard to future use in routine, misclassifications can be corrected by humans. Corrected images can be manually flagged to join a dataset for continuous retraining of the DNN.
Results: Since Jan 1, 2021 the BELUGA trial included 1,586 blood samples. The most common malignant diagnoses were: CLL, MPN, mature B-cell neoplasm, MDS, MBL, CML, AML and CMML. In all cases human investigators reach out to count 100-200 cells according to WHO guidelines. The addressed cell classes were PMN, lymphocytes, monocytes, eosinophils, basophils, bands, metamyelocytes, myelocytes, promyelocytes, myeloblasts, atypical/bilobulated promyelocytes in APL/APLv, hairy cells, atypical lymphocytes (potentially neoplastic), plasma cells, normoblasts, smudge cells, plus one garbage class for damaged cells. 155,159 cells were differentiated by humans (12 individuals, median experience in the field: 8 years), 769,347 cells (median 500 per sample) by the DNN model as described (ASH 2020, Blood 136, # 195). While human analysis took 5-10 minutes per sample, the DNN processes ~500 cells/images within 15 seconds after automated scanning time of 7min. Probability of prediction was ≥0.95 for 46% of images, ≥0.90 was achieved for 55%. During the pilot study, we noticed misclassifications in cells representing neighbouring stages of maturation or in reactive vs. neoplastic lymphocytes. For refining the DNN, we reduced the number of images used for training, keeping only 10% (8,425 cells) of the original dataset. Our new version (V.2) tested now in the BELUGA study achieves an overall accuracy of 96.6% (vs. 89.6% in V.1) on this separate prospective test set. First evidence of clinical relevance could be seen in two cases with low count APL. The DNN (V.1) was able to detect atypical promyelocytes at a probability of ≥0.98.
Summary/Conclusion: We successfully integrated a fully automated process (cell scanning and classification by DNN) parallel to our diagnostic routine workflow without critical delay in TAT. The DNN outperformed human experts (investigation time, number of cells investigated) in a real-life setting and seems to also provide a higher sensitivity and specificity for critical cell types, thus being a helpful support for cytomorphologists. Such infrastructure being cloud-based and allowing access for uploading/classifying digital cell images could serve experts worldwide 24/7.

S311 ESTIMATED HOSPITALIZATION-RELATED COSTS WITH ORAL AZACITIDINE (ORAL-AZA) VS PLACEBO (PBO) FOR REMISSION MAINTENANCE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) IN SPAIN AND THE UNITED KINGDOM (UK)

C. Pocock [1], P. Montesinos [2], T. Braun [3], S. Kambhampati [4,5], A. Oriol [6], I. La Torre [7], B. Skikne [8,9], C. Beach [8], J. Zhong [8], C. Chen [8], S. Ranjan [10], R. Potluri [11], E. Natalie Oliva [12,*]

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Background: While ~50% of patients (pts) with AML aged >60 years attain complete remission (CR) with intensive chemotherapy (IC), up to 90% who do will eventually relapse. In the continuum of AML care, the highest costs are related to relapsed/refractory disease, and hospitalization is the largest component (~70%) of direct healthcare costs. In the randomized, phase 3 QUAZAR AML-001 trial, maintenance treatment (Tx) with Oral-AZA significantly prolonged overall and relapse-free survival vs. PBO for pts with AML in first remission after IC.
Aims: Determine rates of hospitalization and days (d) in hospital with Oral-AZA and PBO for all pts in QUAZAR AML-001, and estimate associated hospitalization costs in Spain from the Spanish National Health System (NHS) perspective, and in the UK from the UK NHS perspective.
Methods: Eligible pts were age ≥55 yrs, had intermediate- or poor-risk cytogenetics and ECOG PS ≤3, and were not candidates for transplant. Within 4 months (mo) of achieving CR or CR with incomplete blood count recovery (CRi) after induction ± consolidation, pts were randomized 1:1 to Oral-AZA 300-mg or PBO QD for 14d/28d cycle. Pts who received ≥1 study drug dose were followed for hospitalization from informed consent through 28d after last dose. The mean number of hospital days/mo (30d) was the total number of days in hospital divided by the number of ongoing pts each mo. Hospitalization rates and durations were adjusted for total drug exposure. Confidence intervals (CI) for relative risk (RR) estimates and related *P* values are based on asymptotic methods.
Unit cost of hospitalization in Spain was derived from literature (Arenaza et al. *Clinicoecon Outcomes Res*, 2019), and in the UK from NHS reference costs (https://improvement.nhs.uk/resources/reference-costs/#rc1718), as the average total AML-related hospitalization costs per day, adjusted for inflation to 2019 prices, using the medical component of the consumer price index for each country.
Results: 469 pts received Oral-AZA (n=236) or PBO (n=233); median time on Tx was 11.6 vs 5.7 mo, respectively, and total exposures were 363.8 pt-years (PY) and 234.9 PY. Similar proportions of patients were hospitalized during the study: Oral-AZA 46% (n=108), PBO 51% (n=118). Total number of hospitalization events was numerically higher in the Oral-AZA arm (173 vs 151 in the PBO arm), but the exposure-adjusted hospitalization rate was significantly lower with Oral-AZA: 0.48/PY vs. 0.64/PY (RR 0.740 [95%CI 0.595, 0.920]; *P*=0.0068). Total days hospitalized were 2,872 in the Oral-AZA arm and 3,139 in the PBO arm; the exposure-adjusted rate was also significantly lower with Oral-AZA (7.89 vs. 13.36 d/PY, respectively; RR 0.591 [95%CI 0.562, 0.621]; *P*<0.0001).
Mean hospitalization cost in Spain was €1,398/d. Using exposure-adjusted days-in-hospital, estimated mean costs of hospitalization in Spain were €11,030/PY with Oral-AZA and €18,676/PY with PBO. Cumulative cost savings with Oral-AZA vs. PBO ranged from €557 at mo 2 to €8,025 by mo 24 (**Figure**).
In the UK, mean hospitalization cost was £696/d, resulting in estimated exposure-adjusted mean costs of £5,490/PY with Oral-AZA and £9,296/PY with PBO. Cumulative cost savings with Oral-AZA in the UK ranged from £277 at mo 2 to £3,995 by mo 24 (**Figure**).



Month	2	4	6	8	10	12	14	16	18	20	22	24
Estimated cumulative hospitalization cost savings per patient with Oral-AZA vs placebo												
Cumulative cost savings in Spain*	€557	€2,101	€3,976	€4,250	€5,233	€4,900	€5,322	€5,795	€6,429	€7,104	€7,455	€8,025
Cumulative cost savings in the UK†	£277	£1,046	£1,481	£2,115	£2,605	£2,439	£2,649	£2,885	£3,200	£3,536	£3,711	£3,995

*Based on average cost per day in hospital in Spain (€1,398) (Arenaza et al. 2019).
†Based on average cost per day in hospital in the United Kingdom (£696) (from NHS Reference costs).

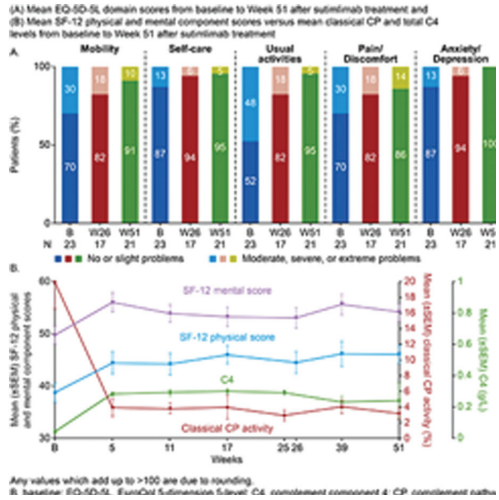
Summary/Conclusion: Compared with PBO, Oral-AZA was associated with significantly reduced exposure-adjusted rates of hospitalization and days in hospital, and considerable estimated cost savings in Spain and the UK. Delaying relapse with Oral-AZA may lead to substantial economic benefits due to lower hospitalization costs.

S312 SUSTAINED IMPROVEMENTS IN PATIENT-REPORTED OUTCOMES WITH SUTIMLIMAB IN PATIENTS WITH COLD AGGLUTININ DISEASE: 1-YEAR FOLLOW-UP INTERIM RESULTS FROM THE CARDINAL STUDY

A. Röth [1,*], C. M. Broome [2], W. Barcellini [3], T. H. A. Tvedt [4], Y. Miyakawa [5], D. J. Kuter [6], Q. A. Hill [7], J. Su [8], F. Joly [9], X. Jiang [10], P. Patel [10], F. Shafer [10], I. C. Weitz [11]

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Background: Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia characterized by classical complement pathway (CP)–mediated hemolysis. Apart from anemia, patients with CAD experience fatigue and poor quality of life (QOL). Before the CARDINAL study, QOL and patient-reported outcomes (PRO) such as Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue were not examined in CAD patients. Sutimlimab (formerly BIVV009), a humanized monoclonal antibody that selectively inhibits C1s of the C1 complex, prevents classical CP activation, while leaving alternative and lectin pathways intact. In CARDINAL Part A, sutimlimab treatment resulted in rapid, clinically meaningful improvement in all PRO measures (Röth et al. ASH 2020), in addition to halting hemolysis, improving hemoglobin (Hb) levels, and normalizing bilirubin levels, in patients with CAD (Röth et al. ASH 2019).
Aims: To report sutimlimab effect on PROs at 1-year, from the ongoing CARDINAL Part B extension (data cut: January 16, 2020).
Methods: CARDINAL is a Phase 3, open-label, single-arm, multicenter, two-part study. After informed consent and study enrollment, sutimlimab was administered on Days 0 and 7, followed by biweekly infusions, in both Parts A and B. Interim Part B efficacy endpoints included evaluation of Hb levels and other hemolytic markers over 1-year and QOL assessed by the FACIT-Fatigue Scale, to Week 51 (last scheduled visit within 1-year of treatment), in patients with CAD. Mean change from baseline for exploratory QOL endpoints such as EuroQol 5-dimension 5-level (EQ-5D-5L) scores, 12-Item Short Form Health Survey (SF-12), Patient Global Impression of Change (PGIC), and Patient Global Impression of (fatigue) Severity (PGIS) were also assessed at Week 51. Outcomes were reported using descriptive statistics.
Results: Of 24 enrolled patients, 22 patients completed Part A, and all entered Part B. At baseline, mean (standard deviation [SD]) FACIT-Fatigue score was 32.5 (10.6) points and mean (SD) EQ-5D-5L index and visual analog scale (VAS) scores were 0.70 (0.23) and 62.0 (14.7), respectively. Mean (SD) SF-12 physical and mental component scores were 38.7 (8.7) and 49.8 (8.2). One-third of patients (33%) had severe PGIS fatigue status at baseline. Upon sutimlimab treatment, mean (SD) FACIT-Fatigue scores improved within 1-week (n=22/24), with scores >40 from Week 3 (Part A) to Week 51. Overall, from baseline to Week 51, mean (SD) FACIT-Fatigue score (n=18/22) was improved by 11.4 (11.9) points. The mean (SD) change from baseline in EQ-5D-5L index and VAS scores (n=20/23) at Week 51 was 0.08 (0.19) and 14.50 (19.05). At Week 51, among 21 evaluable patients, none reported anxiety/depression; considerable improvements were seen in mobility, self-care, and usual activities domains of the EQ-5D-5L (**Figure A**). The mean (SD) increase in SF-12 physical and mental component scores (n=19/22) from baseline to Week 51 were 6.6 (9.7) and 3.6 (9.4). SF-12 score increases appear to coincide with reduction in classical CP activity and normalized total C4 levels (**Figure B**). At Week 51, among 21 evaluable patients, a majority (90.5%) indicated "improved" disease state on the PGIC scale; no patients reported severe fatigue on completing PGIS, compared with one-third at baseline (n=2/6).



Summary/Conclusion: One-year interim follow-up CARDINAL study results demonstrate that continuous classical CP inhibition with sutimlimab resulted in rapid, sustained improvements in all PRO measures evaluated, further demonstrating the meaningful impact of sutimlimab on patient QOL.

S313 PATIENT AND PHYSICIAN PREFERENCES FOR POST–HEMATOPOIETIC STEM CELL TRANSPLANTATION MAINTENANCE TREATMENT OF ACUTE MYELOID LEUKEMIA

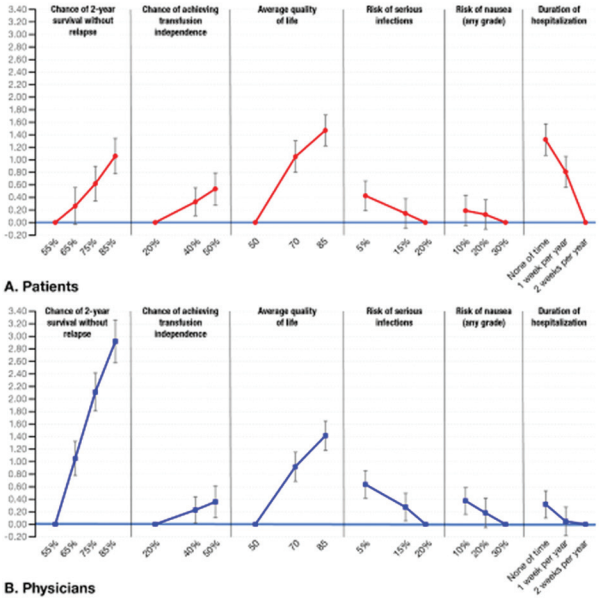
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Background: Patients with acute myeloid leukemia (AML) who have received a hematopoietic stem cell transplant (HSCT) may consider post-HSCT maintenance therapy to prolong remission. Since there are no universally accepted standard maintenance therapies, patients and physicians need to weigh the risks and benefits of each potential regimen when making treatment decisions. A better understanding of the differences in how patients and physicians each weigh the value of various treatment attributes, and whether either group's preferences affect the other's, would be of value in understanding why various treatments are selected.
Aims: To quantify patients' and physicians' preferences for post-HSCT AML maintenance treatment.
Methods: A targeted literature review and one-on-one patient (n=6) and physician (n=4) phone interviews informed the post-HSCT AML maintenance treatment attributes used in this discrete choice experiment (DCE). Attribute levels were selected to reflect the range of maintenance treatments available for post-HSCT patients. Patients with AML who had received HSCT and physicians who treat patients with AML in the US, UK, Canada, and Australia were recruited from physician panels to complete a web-based DCE. The DCE participants were presented choice cards each showing a pair of hypothetical treatment profiles with six attributes (chance of 2-year relapse-free survival [RFS], average quality of life [QoL], risk of serious infections, risk of nausea, chance of achieving transfusion independence, and duration of hospitalization per year) of varying levels and asked to choose a preferred treatment per card. This preliminary analysis used conditional logit regression models to estimate preference weights and analyze the impact of treatment attributes on participants' post-HSCT maintenance therapy treatment choices.
Results: A total of 78 patients with AML post-HSCT (US, n=46; UK, n=30; Canada, n=2) and 145 physicians who treat this population (US, n=48; UK, n=52; Canada, n=29; Australia, n=16) completed the DCE. For patients, average QoL was the most important treatment attribute for post-HSCT maintenance therapy based on preference weights, followed by duration of hospitalization and chance of 2-year RFS (**Figure A**). Post-HSCT patients were willing to accept a less effective treatment if it reduced hospital stay or improved QoL: the benefit of a 2-week reduction in hospitalization per year or an improvement of QoL by 35 on a 0-100 scale each compensated

for a 30% reduction in 2-year RFS. For physicians, chance of 2-year RFS was the most important treatment attribute, followed by average QoL and risk of serious infections (**Figure B**). Physicians valued duration of hospitalization and chance of achieving transfusion independence less when selecting treatments. Responses from physicians suggested that a 2-week reduction in hospitalization per year could compensate for having to bear an additional 5% risk of serious infection or 10% risk of nausea.

Figure. Preference Weights From DCE in the Post-HSCT Maintenance Therapy Setting



Abbreviations: DCE, discrete choice experiment; HSCT, hematopoietic stem cell transplantation.

Summary/Conclusion: Differences in treatment attribute importance for post-HSCT maintenance therapy were observed between patients and physicians. The DCE results highlight the value patients place on treatments that improve their QoL and reduce the duration of hospitalization. Physicians also valued patients' QoL when making treatment decisions, so informing physicians of patients' preferences may influence their choices regarding treatments that better meet patients' needs and improve patients' treatment satisfaction.

S314 THE BURDEN OF SICKLE CELL DISEASE (SCD) ON PATIENTS IN GHANA AND NIGERIA COMPARED WITH OTHER LOW-/MIDDLE-INCOME AND HIGH-INCOME COUNTRIES: RESULTS FROM THE SICKLE CELL WORLD ASSESSMENT SURVEY (SWAY)

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Background: SCD is a group of inherited blood disorders associated with a range of clinical complications mainly mediated by vaso-occlusion and hemolytic anemia. Vaso-occlusive crises (VOCs) are the hallmark of SCD, and the most common cause of hospitalization. SCD is a global public health problem, with African countries having the highest disease prevalence.
Aims: To use SWAY data to compare the negative impact of SCD (examining symptoms, complications and quality of life) on patients (pts) in Ghana/Nigeria vs pts in other low-/middle income (LMIC) and high-income countries (HIC). SCD impact stratified by primary care provider (specialist vs non-specialist HCP) was also assessed.
Methods: SWAY was a multicountry survey (Apr–Oct 2019) developed by international SCD experts, pt advocacy groups and Novartis. Pts with SCD ≥6 years old completed the survey (completion by proxy [parent/guardian/caregiver] was required for pts aged 6–11 years, optional for pts ≥12 years). The World Bank definition of an HI economy (gross national income/capita ≥US$12,536) was used to stratify countries into LMIC and HIC. VOCs (defined as 'severe pain crises'), symptoms (experienced in the month preceding survey completion [excluding VOCs]), complications (ever experienced) and genotype were all self-reported. Responses to questions on the impact of SCD were classified on a 1–7 Likert scale (1=not severe/strongly disagree, 7=worst imaginable/strongly agree; with 5–7 indicating high impact/agreement). Pt participants (N=2145) were grouped into Ghana/Nigeria (n=519), other LMIC (Brazil, India, Lebanon [n=422]) and HIC (Bahrain, Canada, France, Germany, Italy, Netherlands, Oman, Panama, Saudi Arabia, USA, UK [n=1204]).
Results: Pts in Ghana/Nigeria were younger than those in other LMIC/HIC, and the mean number of VOCs experienced in the year before survey completion was lower in Ghana/Nigeria (4.5) and other LMIC (4.2) vs HIC (6.0) (Table). The top 3 most commonly reported symptoms in the month preceding survey were headache (Ghana/Nigeria 58%; LMIC 39%; HIC 44%), fatigue (Ghana/Nigeria 34%; LMIC 69%; HIC 77%) and bone aches (Ghana/Nigeria 32%; LMIC 56%; HIC 58%). Of the top 10 most frequently reported complications, all (except blood clots and fever) were reported by a lower proportion of pts in Ghana/Nigeria vs pts in other LMIC/HIC (Table). In Ghana/Nigeria, pts treated by a non-specialist HCP generally reported greater symptom prevalence than those treated by a specialist HCP. In contrast, the proportion of pts in other LMIC reporting symptoms was higher in the specialist HCP-treated group for most symptoms assessed. Pts in Ghana/Nigeria reported a lower or similar use of analgesics compared with other LMIC/HIC, with 26% ever prescribed opioids (other LMIC 28%; HIC 73%) and 30% ever receiving OTC analgesics (LMIC 63%; HIC 64%). In Ghana/Nigeria, 52% of pts reported that SCD had a high negative impact on their emotional wellbeing vs 56% of pts in other LMIC and 64% in HIC.

Table. Baseline characteristics, VOC burden and SCD-related complications grouped by Ghana/Nigeria, other LMIC and HIC

	Ghana/Nigeria			Other LMIC			HIC		
	Overall (n=519)	Specialist HCP (n=217)	Non-specialist HCP (n=302)	Overall (n=422)	Specialist HCP (n=230)	Non-specialist HCP (n=192)	Overall (n=1204)	Specialist HCP (n=849)	Non-specialist HCP (n=355)
Age, years									
Mean (SD)	18.1 (9.4)	18.8 (10.9)	17.5 (8.1)	21.6 (12.7)	25.0 (12.7)	17.5 (11.5)	28.6 (13.1)	30.3 (12.6)	24.8 (13.7)
Median (IQR)	15 (11–23)	15 (11–23)	15 (11–22)	19 (11–30)	23 (15–32)	13 (9–25)	29 (18–37)	30 (22–38)	22 (14–35)
Sex, n (%)									
Male	296 (57)	109 (50)	187 (62)	197 (47)	90 (39)	107 (56)	529 (44)	338 (40)	191 (54)
Female	223 (43)	108 (50)	115 (38)	222 (53)	137 (60)	85 (44)	675 (56)	511 (60)	164 (46)
Self-reported genotype, n (%)									
HbSS	177 (34)	73 (34)	104 (34)	228 (54)	131 (57)	97 (51)	637 (53)	498 (59)	139 (39)
HbSC	150 (29)	71 (33)	79 (26)	67 (16)	42 (18)	25 (13)	229 (19)	151 (18)	78 (22)
HbSβ⁰ thalassemia	2 (<1)	2 (1)	-	9 (2)	6 (3)	3 (2)	43 (4)	26 (3)	17 (5)
HbSβ⁺ thalassemia	-	-	-	10 (2)	3 (1)	7 (4)	50 (4)	38 (4)	12 (3)
Other	10 (2)	6 (3)	4 (1)	6 (1)	3 (1)	3 (2)	14 (1)	10 (1)	4 (1)
Unknown	180 (35)	65 (30)	115 (38)	102 (24)	45 (20)	57 (30)	231 (19)	126 (15)	105 (30)
Number of VOCs*									
Mean (SD)	4.5 (4.0)	3.9 (3.8)	4.9 (4.1)	4.2 (5.2)	4.6 (5.44)	3.9 (4.8)	6.0 (8.0)	6.3 (9.1)	5.2 (4.8)
Median (IQR)	3 (2–6)	3 (1–5)	4 (2–6)	3 (1–5)	3 (1–6)	2 (1–5)	4 (2–7)	4 (2–7)	4 (2–7)
Proportion of patients with:									
0 VOCs* (%)	7	12	3	16	13	19	9	9	8
1–4 VOCs* (%)	56	56	56	54	52	55	50	50	49
≥5 VOCs* (%)	37	33	41	31	35	26	42	41	43
Patient-reported complications,† %									
Fever	64	67	61	75	74	77	60	61	57
Joint issues	29	33	27	62	67	56	65	68	59
Infections	37	42	33	66	69	63	58	60	53
Required blood transfusions	15	24	8	65	70	58	48	54	32
Tight chest pain	20	26	16	48	55	39	49	50	46
Swollen and/or painful fingers/toes	11	17	7	50	50	49	40	39	42
Gallbladder stones	5	3	6	30	42	16	28	33	18
Issues/damage of the spleen	6	4	8	28	31	25	25	26	23
Vision problems	9	7	11	23	27	18	24	26	21
Blood clots	14	8	18	11	15	7	18	20	14

*In the 12 months prior to survey completion; †Complications listed are the top 10 ever experienced across the entire patient population in SWAY.
HCP, healthcare professional; IQR, interquartile range; SD, standard deviation.

Summary/Conclusion: The reported overall burden of SCD appeared to be lower on pts in Ghana/Nigeria than for those in other LMIC/HIC. A possible explanation for this is the younger age of pts from Ghana/Nigeria, where a high infant mortality rate means many pts do not live long enough to develop chronic complications. Other explanations may include limited availability of resources to detect symptoms/complications, warmer climate, low usage of analgesics and poor education for both pts (and, potentially, non-specialist HCPs) in Ghana/Nigeria vs other countries participating in SWAY.

Acute lymphoblastic leukemia - Biology & Translational Research

EP316 BRANCHED CHAIN AMINO ACID TRANSAMINASE 1 IS OVER-EXPRESSED IN NOTCH1 ACTIVATED T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA CELLS AND MODULATES RESPONSE TO DNA DAMAGING AGENTS.

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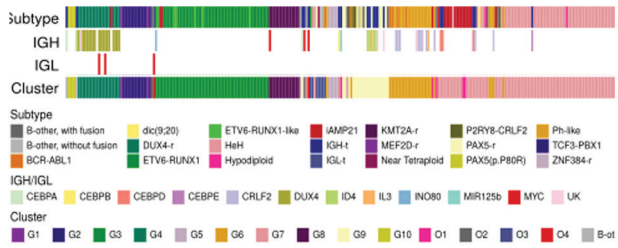
Background: T-cell acute lymphoblastic leukemia (T-ALL) is a biologically and clinically heterogeneous disease mostly associated with NOTCH1 mutations that characterize over 60% of cases. Therapy-resistant or refractory T-ALL remains a major clinical challenge. Recently, the metabolism of Branched Chain Amino Acids (BCAAs) has been associated with tumor growth and survival. In-fact, aberrant expression of BCAA Transaminase 1 (BCAT1), a cytosolic aminotransferase, involved in the first step of BCAAs metabolism, has been demonstrated in different tumor models, including leukemia. However, its biological role in T-ALL remains to be elucidated.
Aims: The purpose of this study was to evaluate the role of BCAT1 in T-ALL leukemogenesis, with particular emphasis on a putative link between BCAT1 and NOTCH1 in promoting T-ALL initiation and progression.
Methods: We evaluated BCAT1 expression using RNAseq data from 264 T-ALL samples (TARGET cohort enrolled on Children's Oncology Group ALL0434 protocol). BCAT1 transcript (qRT-PCR) and protein levels (western blot) were determined in T-ALL cell lines (n=13) and patient derived xenografts (n=12). Five T-ALL samples were treated with a g secretase inhibitor (DBZ) to dampen NOTCH signaling. BCAT1 promoter occupancy by NOTCH1 was determined in two T-ALL cell lines using Chromatin Immunoprecipitation (ChIP) coupled with qPCR. Tandem affinity purification (TAP) and mass spectrometry (MS) analysis were used to identify BCAT1 interacting proteins from CUTLL1 T-ALL cells. Further, BCAT1 knock-down experiments were performed to address its role on T-ALL cell growth, proliferation and drug sensitivity.
Results: We found variable BCAT1 expression levels amongst the different T-ALL molecular subgroups, with higher expression levels in TLX1 ($p<0.001$), HOXA-TLX3 ($p<0.05$) and NKX2-1 ($p<0.01$) subtypes. Considering recurrent genetic alterations, we found BCAT1 expression to be significantly higher ($p<0.01$) in NOTCH1 mutated cases compared to un-mutated samples. Further, BCAT1 was more highly expressed in the phenotypically mature cortical T-ALL subgroup. Analysis of T-ALL cell lines and PDX samples also evidenced heterogeneous BCAT1 expression levels, with a trend toward higher expression in these cells compared to their normal cellular counterparts (thymocytes). In agreement with our previous analysis, NOTCH1 mutated PDX samples showed higher BCAT1 expression compared to un-mutated cases. Inhibition of NOTCH1 signaling with DBZ decreased BCAT1 expression in numerous T-ALL models. In addition, ChIP analysis demonstrated binding of NOTCH1 on BCAT1 promoter in T-ALL cells, suggesting that NOTCH1 may directly regulate its expression. Functionally, we found BCAT1 knock-down T-ALL cells to have a compromised capacity to form tumors in vivo. Further, TAP followed by MS analysis of BCAT1 interacting proteins disclosed that BCAT1 may be implicated in non-metabolic processes such as DNA replication and repair. Indeed, we found BCAT1 KD cells to be particularly sensitive to topoisomerase inhibitors such as etoposide.
Summary/Conclusion: BCAT1 is highly expressed in a subgroup of T-ALL cases, particularly in NOTCH1 mutated T-ALL. NOTCH1 may directly regulate BCAT1 expression. Genetic depletion of BCAT1 slows tumor growth in vivo and renders cells particularly sensitive to topoisomerase inhibitors. Our results identify BCAT1 as a novel therapeutic target and suggest that a combination of BCAT1 inhibitor and topoisomerase inhibitor could be particularly useful in BCAT1 overexpressing T-ALL cases.

EP317 TRANSCRIPTOMIC CHARACTERISATION OF IGH-TRANSLOCATED B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKAEMIA: THE IMPACT OF IGH PARTNER GENES

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Background: Acquired genetic changes are essential diagnostic and prognostic markers in acute lymphoblastic leukaemia (ALL) used in the risk stratification of patients for treatment.
Chromosomal translocations result in either the formation of a fusion protein, or, in the case of translocations involving the *Immunoglobulin heavy chain* locus (*IGH*-t), they result in the activation of proto-oncogenes driven by strong regulatory elements.
IGH-t are observed in 5-10% of B-cell precursor ALL (BCP-ALL) and are associated with a poor prognosis in adults[1]. The *IGH* locus is highly promiscuous, rearranging with many different chromosomal partners. These observations led us to question the consequences of such rearrangements and their impact on gene expression signatures. Do all *IGH*-t lead to deregulation of the same signalling pathways or can we subdivide patients according to the function of the partner gene involved?
Aims: We hypothesise that the transcriptomic and clinical characteristics of *IGH*-t ALL are determined by the translocation partner gene. The aims of this study are (1) to characterise the transcriptome of *IGH*-t ALL; (2) to identify any potential druggable pathways to improve treatment options.
Methods: RNA sequencing data from 270 BCP-ALL cases (195 cases from Lund University (EGAS00001001795)[3] and 75 in-house cases), including 52 *IGH*-t cases, were processed for cluster analysis, with LASSO feature selection using label in Li et al.[4], followed by hierarchical cluster analysis. Gene set enrichment analysis (GSEA) was performed to identify enrichment in drug-related gene sets. The results were validated *in vitro* using patient derived xenograft cells (PDX). Drug experiments were conducted using an in-house high-throughput drug screening system.
Results: Cluster analysis revealed that *IGH-DUX4* plus *IGH-CRLF2* and *IGH-IL3* clustered together with *DUX4*-rearranged (G4) and *BCR-ABL1*(-like) (G6) cases, respectively (Fig. 1). One novel observation was that *IGH-ID4* cases, which were reported to associate with *PAX5* deletions[5], clustered with *PAX5*-rearranged (*PAX5*-r) and *P2RY8-CRLF2* (G9) cases (Fig. 1). GSEA indicated that *IGH-DUX4* ALL may have reduced sensitivity to asparaginase, characterised by higher expression of ribosome-related genes and GATA3. Asparaginase treatment of PDX samples revealed a higher IC50 for IGH-DUX4 (n=1) compared to non-IGH-DUX4 PDX (n=2) (logIC50: 0.4791 vs -2.896). Addition of dexamethasone (1nM), a GATA3 phorsphorylation inhibitor, enhanced the inhibition of *IGH-DUX4* PDX by asparaginase (logIC50: -2.761), suggesting potential synergism (Average ZIP score: 5.377).



Summary/Conclusion: *IGH*-t ALL comprises a heterogeneous subtype in which further subtyping may provide insight into novel therapeutic avenues. Patients with *IGH-DUX4* and *IGH-CRLF2* clustered with *DUX4*-r and *BCR-ABL1*-like cases, as expected.We report a novel observation that *IGH-ID4* patients cluster with *PAX5*-r ALL. Although *IGH-DUX4* ALL has been shown to confer a good prognosis, our study suggests these patients may have reduced sensitivity to asparaginase, a drug used in induction phase chemotherapy. Further investigation of their response to induction phase chemotherapy is required to understand its clinical implication.

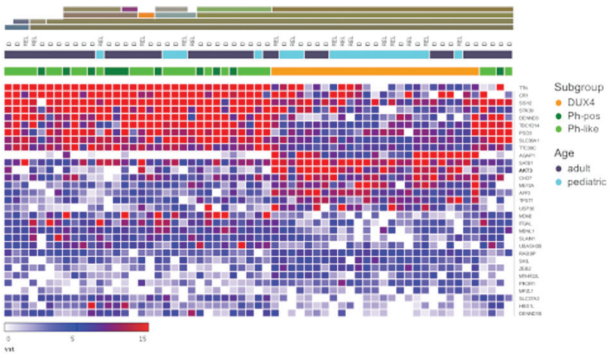
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EP318 CIRCRNA EXPRESSION DELINEATES MAJOR SUBGROUPS IN B CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: B cell precursor acute lymphoblastic leukemia (BCP-ALL) is a molecularly heterogenous disease, characterized by uncontrolled proliferation of early lymphoid progenitor cells. As fusion-driven disease, it is further characterized by limited therapeutic options at relapse in adults. In recent years, it has been shown that non-coding RNAs (ncRNAs) exhibit oncogenic properties. Especially, circular RNAs (circRNAs) are of increasing interest, as these are remarkably stable, covalently closed structures with tissue-specific expression and oncogenic potential.
Aims: Since their role in ALL remains largely uncharacterized, we investigated the expression pattern of circRNAs in BCP-ALL to identify and characterize new molecular markers for a deeper biological understanding.
Methods: We isolated ribosomal depleted RNA from a well-characterized cohort of 84 BCP-ALL samples from 63 patients (46 adults and 17 pediatric patients), consisting of 61 samples from initial diagnoses (ID) and 23 (21 paired) relapses (REL). RNA paired-end sequencing was performed on an Illumina HiSeq2500 with ~50 million reads per sample. Subgroup classification was based on mRNA expression and underlying driver fusion genes (FusionCatcher) in an established reference cohort of ~600 ALL samples. We used CIRCexplorer for circRNA detection and examined both individual circRNAs and circRNA variants condensed to their gene of origin. Differential expression analysis using DESeq2 was applied, and circRNA existence was confirmed by RT-PCR. All differentially expressed circRNAs were used for subsequent pathway analyses with ShinyGO.
Results: We identified a total of 79280 different circRNAs from 9400 genes in 84 analyzed samples. According to their mRNA expression, we defined molecular subgroups for all samples: DUX4 (ID n=15, REL n=10), Ph-pos (ID n=13), Ph-like (ID n=22, REL n=7) and others (ID n=11, REL n=6). To elucidate relapse specific circRNA expression, we compared paired samples from ID and REL in the subgroups of DUX4 and Ph-like, however found no significant change in circRNA expression. Due to minor difference in circRNA expression and the biological similarity of Ph-pos and Ph-like these samples were pooled and compared to DUX4 samples. Molecular BCP-ALL subgroups were classified by a unique circRNA expression pattern (Figure) with 259 differentially expressed circRNAs (FDR ≤ 0.05, log2 fold change ≥2) in DUX4 vs. Ph-pos/-like samples. We carried out pathway analyses and obtained over-represented pathways related to EGFR tyrosine kinase inhibitor resistance and cancer associated pathways involving known oncogenes like IGF1R, PIK3R1 and MDM2 (FDR ≤ 0.05). Of interest is the association to miRNAs in cancer, reflecting a potential sponge function of our identified circRNAs. Ph-pos/-like ALLs are characterized by deregulated JAK-STAT. In supervised analyses of circRNA expression of JAK-STAT members (DUX4 vs. Ph-pos/-like), we identified circAKT3 as potential target candidate (FDR ≤ 0.05, fold change 4.3).



Expression pattern of differentially expressed circRNAs in DUX4 vs Ph-pos/-like. Heatmap demonstrates supervised hierarchical clustering of 31 differentially expressed circRNAs (FDR ≤ 0.1). CircRNA variants were summed to their gene of origin. Upper bars demonstrate clustering of the samples (n=61). ID: initial diagnosis, REL: relapse.

Summary/Conclusion: We present a comprehensive analysis of circRNA expression in BCP-ALL in a well characterized cohort. Detected circRNA expression profiles discriminated BCP-ALL samples in molecular subgroups and remained stable between initial diagnosis and relapse. Moreover, we found differentially expressed circRNAs, corresponding to their gene of origin, enriched in different cancer pathways. Within JAK-STAT signaling, circAKT3 emerged as target candidate in BCP-ALL. These findings introduce circRNAs as new deregulated layer in BCP-ALL, warranting further exploration of potential therapeutic options.

EP319 COMBINING GENOMIC AND EXPRESSION PROFILES OF INTRACHROMOSOMAL AMPLIFICATION OF CHROMOSOME 21 B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA TO IDENTIFY POTENTIAL LEUKEMIC TARGETS

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Background: Intrachromosomal amplification of chromosome 21 (iAMP21) is a rare, but high-risk subtype of pediatric B-cell acute lymphoblastic leukemia (B-ALL). iAMP21 was discovered by routine screening for the *ETV6-RUNX1* fusion, resulting in the current definition of iAMP21 as three or more extra copies of *RUNX1* on a single abnormal chromosome 21. Using copy number profiling, iAMP21 can also be detected as regions of amplifications, deletions and inversions. It is currently unknown how the abnormal chromosome 21 contributes to development of leukemia.
Aims: We aimed to determine the common region of amplification in iAMP21 patients. In addition, by correlating the chromosome 21 copy number gain, and resulting gene expression change, to genome wide gene expression, we aimed to shed light on the potential leukemic target of the abnormal chromosome 21.
Methods: Copy number aberrations were determined in a population based pediatric B-ALL cohort using array Comparative Genomic Hybridization (aCGH). As an independent cohort, the supplementary SNP array data from Gu et al (Nature genetics, 2020) was used. Gene expression was evaluated using Affymetrix U133 Plus2 expression arrays. Differential gene expression was evaluated using Limma and Globaltest was used to evaluate genome wide gene expression correlations. As an independent cohort, publicly available RNA expression data from B-other and *BCR-ABL1*-like B-ALL patients from the PeCan database was used.
Results: Within our population based aCGH cohort, 12 out of 398 patients showed an aCGH profile suggestive of iAMP21 (median age = 8.5 years, range = 5-14; median white blood cell count = 7.6 x 10^9/L, range = 2-129). By scoring their chromosome 21 copy number gain per probe, we identified three regions of a total of 3.9 Mb that were commonly amplified (at least 2 copies gained). A similar strategy was applied to the supplementary SNP array data of 34 pediatric and young adult iAMP21 patients from Gu et al (Nature Genetics, 2019). Combined with the common region of amplification (CRA) determined by Rand et al (n = 18, Blood, 2011), it resulted in a narrowed down CRA of 1.5 Mb, containing 12 protein-coding genes. Interestingly, the CRA was located telomeric from *RUNX1*, but did not include this gene. Although gained in all patients, in 4 of our 12 iAMP21 patients the highest amplified region was located telomeric from *RUNX1*. In accordance, *RUNX1* expression did not correlate with copy number (p = 0.371, spearman correlation) and was only moderately overexpressed in iAMP21 cases, both in our samples (n = 155 of which 12 iAMP21, fold change (FC) = 1.6, adjusted p-value = 0.030), as well as in the independent PeCan dataset (n = 246 of which 17 iAMP21, FC = 1.4, p-value < 0.001). Only 7 of these 12 protein-coding genes were significantly upregulated (adjusted p-value < 0.01). *RIPPLY3* was the highest overexpressed gene (FC = 4.2) within the CRA, confirmed in the independent PeCan dataset (FC = 9.8). The expression of *RIPPLY3* was most correlated to the expression of the 1128 differentially expressed probesets in iAMP21 (R = 0.59).
Summary/Conclusion: We narrowed down the common region of amplification in iAMP21 B-ALL to 1.5 Mb which surprisingly did not include the *RUNX1* gene. Our data suggest that *RIPPLY3*, a negative regulator of the transcriptional activity of TBX1 and suggested to regulate STAT3 transcriptional activity, is the potential target of the iAMP21 transformation, making it an interesting gene for further functional studies.

EP320 METABOLIC ALTERATIONS TRIGGERED BY NPAT/JAK2, A NOVEL FUSION GENE ACTIVATING KINASE SIGNALING IN CHILDHOOD BCR/ABL1-LIKE ALL

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Background: The JAK2 kinase plays an essential role in mediating growth-promoting activities of various cytokines. Constitutive activation of this kinase, via chromosomal translocations, has been previously described in acute lymphoblastic leukemia (ALL), with PAX5, BCR and ETV6 being the most common partner genes. ALLs with JAK2 fusions usually have the BCR-ABL1-like phenotype associated with unfavorable outcome. The metabolic consequences potentially contributing to leukemogenesis in cells harboring JAK2 fusion genes have not been investigated so far.
Aims: We identified and studied in detail a novel JAK2 involving fusion gene, NPAT-JAK2, in a patient with high-risk B-cell precursor ALL.
Methods: Seahorse Metabolic Analysis
Results: The NPAT gene is located on chromosome 11 and encodes a nuclear protein acting as a co-activator of histone gene transcription. No functional domains in the N-terminal part of the NPAT protein involved in the NPAT/JAK2 chimera, have been described, but, importantly, the chimera involved the complete JAK2 kinase domain. We cloned the full-length coding sequence of NPAT/JAK2 and studied its biological properties in model cell lines. We found that the NPAT/JAK2 protein is localized both in the cytoplasm and in the nucleus of transfected cells and that it is autophosphorylated on Y1007/Y1008 in the activation loop of JAK2 whose phosphorylation is essential for JAK2 kinase function. Next, we tested the oncogenic potential of NPAT/JAK2 in the Ba/F3 cells dependent on interleukin 3 (IL3), in which the fusion induced cytokine independent growth. This effect was abolished by a mutation of the NPAT/JAK2 ATP-binding site, demonstrating its dependence on the JAK2 kinase activity. Western blot analysis of the transformed BAF3 cells showed increased phosphorylation of STAT1 and STAT5. Importantly, the phosphorylation and pro-proliferative effect was blocked by the JAK1/2 inhibitor Ruxolitinib.
The cell energy phenotype test revealed an overall enhanced metabolic state of the NPAT/JAK2 transformed BA/F3 cells grown without IL3, with elevations of both the mitochondrial and the glycolytic function. Differences were visible already under steady-state cultivation conditions, however the major divergence between the NPAT/JAK2 transformed cells and controls occurred after stress induction. Concomitantly, the ATP production was increased in NPAT/JAK2 transformed cells, together with the NAD+/NADH ratio when compared to the empty vector and NPAT/JAK2-positive BAF3 cells dependent on IL3 (in pre-transformation phase), as assessed by a luciferase assay. To validate our result, we used 2-deoxy-D-glucose (2DG), a competitor of glucose which is a main substrate utilized in bioenergetics pathways of cancer cells. The proliferation of NPAT/JAK2 transformed cells treated with 2DG was dramatically inhibited, compared to controls. Interestingly, metabolic differences were not observed in the case of the recurrent JAK2 kinase fusion PAX5-JAK2. Therefore we presume that the here described metabolic alterations most likely do not represent a general mechanism for all of the fusion genes involving the JAK2 kinase domain.
Summary/Conclusion: To conclude, we identified and characterized in detail a novel druggable JAK2 fusion gene, NPAT/JAK2, with a constitutively active chimeric tyrosine kinase. The oncogenic potential of cells harboring this fusion is likely driven by signaling pathway alterations and intensive metabolic changes with dependencies on sufficient energy substrate supply, a mechanism that could potentially be exploited in future therapeutical strategies.
Support: AZV NV18–07-00129

EP321 GENOMIC ANALYSES IN T-ALL PATIENTS IDENTIFY RECURRENT AND NOVEL ABNORMALITIES

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Background: 15% of pediatric and 40% of adult T-cell Acute Lymphoblastic Leukemia (T-ALL) patients fail conventional therapy highlighting the need for novel therapeutic strategies based on the genomic alterations of individuals.
Aims: We interrogated genomic alterations in Australian T-ALL patients for patterns of mutation and druggable targets. A subset of samples were used to establish patient-derived xenograft (PDX) models to evaluate novel therapies.
Methods: T-ALL patients' samples underwent transcriptomic analyses (148 total samples including diagnosis, refractory and relapse timepoints from 137 patients of all age groups). mRNA sequencing (mRNAseq) identified gene fusions and structural variants and assessed differential gene expression (n=120). Fusion calling relied on FusionCatcher, SOAPfuse, JAFFA; variant calling utilized GATK HaplotypeCaller. Possible germline alterations and common SNPs were filtered prior to manual curation. DNA copy number variations (CNVs) were detected via MLPA (MRC Holland, P202/P335/P383; n=80). Establishment of PDX models from patient material (bone marrow, peripheral blood) is ongoing.
Results: Genomic fusion genes were identified in 58/120 samples (48%) by mRNAseq; the most common was *STIL-TAL1* (n=9). Increased expression of *LCK* and/or *LAT* (encoded proteins are involved in T-cell receptor (TCR) signal transduction) was observed in patients harbouring *STIL-TAL1* indicating TCR signaling may be perturbed in this sub-group. Other common gene fusions were *MLLT10-DDX3X* (n=5) and *KMT2A-MLLT4/AFDN* (n=4). We also observed *SET-NUP214, KMT2A-MLLT1, PICALM-MLLT10, NUP214-ABL1*, several fusions involving TCR subunits as well as novel fusions involving *KMT2A*, *NOTCH1*, *SUZ12, CTCF*, *ZEB2*.
Nonsynonymous mutations were identified in 106/120 patients (88%) with mRNAseq data. Broadly, mutated genes encode proteins in the following categories: oncoproteins (*NRAS, KRAS*); tumour suppressors (*TP53, PTEN*); epigenetic regulators (*DNMT3A*, *EZH2*, *IDH1/2*, *PHF6*); regulators of NOTCH signalling (*NOTCH1/2*, *FBXW7*); transcription factors and regulators (*ETV6*, *IKZF1*, *LEF1*, *RUNX1*, *WT1*); kinase and cytokine signal regulators (*JAK1*, *JAK2, JAK3, TYK2*). Clinically relevant INDELS were identified in 67/120 patients (56%) including alterations to: *CDKN2A, FBXW7*, *IL7R*, *JAK3, LEF1*, *NOTCH1*, *PHF6*, *PTEN*, *WT1*.
The most common copy number alterations identified were *CDKN2A/B* deletions (37/80 patients, 46%), *PHF6* duplication (30/80 patients, 38%) and *MLLT3* deletion (14/80 patients, 18%). In patients with homozygous *CDKN2A/B* deletions and additional CNVs, *PHF6* duplication (n=9) and *MYB* duplication (n=4) were mutually exclusive. *MLLT3* deletion always co-occurred with *CDKN2A/B* deletions (19/19 patients with *MLLT3* deletion), but was rarely observed with *PTEN* deletion (1/11 patients with *PTEN* deletion). Patients with either *CDKN2A/B* deletions or *PHF6* duplications frequently harbored *NOTCH1* abnormalities: 24/36 patients (67%) and 15/26 patients (58%), respectively.
PDX primagrafts investigated the engraftment latency and peripheral organ infiltration. Primagrafts established from patients harboring gene fusions typically engrafted at a slower rate (n=4, 70-93 days) than primagrafts from patients harboring *CDKN2A/B* deletions (n=2, 32-53 days).

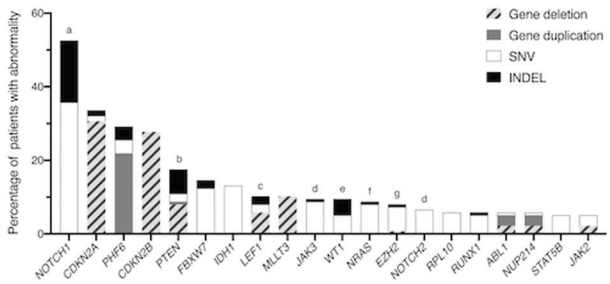


Figure 1: Top 20 genes with copy number variations and mutations in T-ALL patient cohort (n=137 patients). SNV=single nucleotide variant; INDEL=insertion or deletion

[a] 15 cases had either multiple SNVs/INDELs or an SNV+INDEL; [b] 4 cases had either multiple SNVs/INDELs or an SNV+INDEL; [c] 1 case had multiple SNVs and 1 case had multiple INDELs; [d] 4 cases had multiple SNVs; [e] 4 cases had SNV+INDEL; [f] 1 case had multiple INDELs; [g] 1 case had SNV+INDEL. In all instances, multiple mutations were counted as SNVs only

Summary/Conclusion: In our cohort the majority of cases harbor rearrangements, structural variations and duplication/deletion of genes associated with malignant transformation. We identified several co-occurring

lesions as well as mutually exclusive genomic abnormalities. Secondary PDX models investigating targeted treatment strategies are ongoing.

EP322 WHOLE GENOME SEQUENCING PROVIDES NOVEL INSIGHTS INTO GENOMIC LANDSCAPE OF PEDIATRIC T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: T-cell acute lymphoblastic leukemia (T-ALL) is a highly heterogeneous and aggressive hematological malignancy. Genomic landscape of T-ALL has been largely characterized by whole exome sequencing (WES) and RNA-seq. Whole genome sequencing (WGS) enables to extend beyond the coding sequence but also offers more uniform sequencing coverage as compared to WES. Here we focus on protein coding genes affected by mutations detected by WGS in pediatric T-ALL.
Aims: To provide novel insights into genomic landscape of pediatric T-ALL by WGS
Methods: We performed WGS in 64 T-ALL samples from diagnosis (Dg) and 24 matched remission samples (Rem). TruSeq Nano DNA library kit and Illumina HiSeq X-Ten were used to generate 150bp paired-end reads. WGS coverage was 60x for Dg and 30x for Rem samples. FastQC and FastQ Screen were used for sequencing data quality control. Reads were aligned to GRCh38 using BWA mem, achieving an average alignment rate of 99.6%. Mapped reads were de-duplicated using MarkDuplicates (Picard tools) and processed with BaseRecalibrator (GATK v4.1.0.0). Average read duplication rate was 10.3%, thus true mean coverage across the entire genome was 72x for Dg samples (54x-82x) and 36x for Rem (31x-45x). Somatic variants were identified with Mutect2 (v4.1.4.0) and annotated using VariantEffectPredictor (v97). Potential germline variants were removed based on AF>0.05 in the NFE population (non-Finnish Europeans) as reported in gnomAD database and POLGENOM database (126 whole genomes of healthy long living Polish individuals). We then focused on single nucleotide variants (SNVs) and indels affecting coding sequence with moderate and high impact. Variants and affected genes were analyzed for potential involvement in processes classified by cancer-related terms selected from KEGG, Gene Ontology and Reactome databases. Affected genes were checked for previous reports as genes mutated in T-ALL patients in WES, WGS and RNA-seq studies [1-5].
Results: We identified 5535 somatic SNVs and indels affecting 4117 protein coding genes. In total, we identified 3817 genes not previously reported as affected in T-ALL studies [1-5]. Out of these genes, 764 (20%) were mutated in ≥2 Dg samples (2/64; frequency >3%), 54 genes (1.4%) were mutated in ≥5 Dg samples (5/64; frequency >7%). Among 'novel' T-ALL-mutated genes with >10% frequency, we identified 5 members of *Neuroblastoma Breakpoint Family* (*NBPF*) of putative roles in several cancer types. By functional classification of all mutated genes, according to KEGG terms, we revealed several processes to be affected in T-ALL patients, including: signal transduction (in 100% of T-ALL samples), transport and catabolism (97%), cell growth and death (86%), signaling molecules and interaction (81%), immune system (80%), translation (70%), folding, sorting and degradation (61%), transcription (48%), replication and repair (47%), membrane transport (38%).
Summary/Conclusion: WGS with high coverage (>60x) performed in a relatively high number of T-ALL Dg samples, identified numerous genes recurrently mutated in T-ALL patients, not previously reported to be affected in T-ALL. These findings provide further insights into genomic landscape of this heterogeneous malignancy. Results of this study form the basis for investigation of the biological and clinical relevance of novel genes in T-ALL.
References 1/De Keersmaecker et al. Nat Genet. 2013; 2/ Li et al. PLoS Med. 2016; 3/Liu et al. Nat Genet. 2017; 4/Chen et al. Proc Natl Acad Sci USA 2018; 5/Kimura et al. Cancer Sci. 2019

EP323 ANTI-CD47 MONOCLONAL ANTIBODY THERAPY EFFECTIVELY ELIMINATES ADRIAMYCIN RESISTANCE IN ACUTE LYMPHOBLASTIC LEUKEMIA CELLS

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Background: Acute lymphoblastic leukemia (ALL) is a common hematological malignancy with poor survival, especially in adults. Adriamycin (ADM)-based chemotherapy is a standard regimen of human lymphoid malignancies, including ALL. However, chemo-resistance & relapse hindered the outcome of the chemotherapy in high risk ALL patients. Human CD47 is an integrin-associated protein and highly expressed in hematological malignancy cells. CD47 served as a ligand for signal regulatory protein-α (SIRP-α) which expressed on phagocytic cells and CD47 interaction with SIRP-α promotes to inhibit phagocytosis activity. Blocking anti-CD47 monoclonal antibody (mAb) can stimulate phagocytosis activity of macrophages. So far, anti-CD47 mAb and antibody combination with ADM therapy against drug resistance human ALL is not clearly investigated.
Aims: This study targeted to detect cell surface expression level of CD47 in ADM resistant ALL cells and investigate the efficacy treating potential of anti-CD47 mAb against ADM resistant ALL cells in preclinical mouse models.
Methods: Stably luciferase expressing parental Nalm-6-Luc-cells were subjected with ADM to establish ADM resistant cells. CD47 expression in ALL cells was analyzed using FACS. Anti-CD47 mediated phagocytosis in vitro assay was performed. NOD/SCID mouse in vivo preclinical model using anti-CD47 mAb, mAb combination with ADM, and ADM alone therapy against human ALL were established. Tumor volume and burden were monitored. Survival of the leukemic mice were observed in using different treatments.
Results: We successfully established potently ADM drug resistant human ALL cells Nalm-6-Luc-ADMR. We found that CD47 was highly expressed (over 98%) in the resistant Nalm-6-Luc-ADMR, Nalm-6-Luc (parental), Molt-4 and Jurkat ALL cells. High expression level of drug resistance genes and proteins in ADM resistant ALL cells were detected. Anti-CD47 mAb with the presence of macrophage enabled phagocytosis of drug resistant ALL cells in vitro assay. The anti-CD47 antibody enabled significant levels of phagocytosis with blast ALL cells using macrophage effector cells as compared to blank control and anti-CD45 antibody ($P = 0.0001$). In our preclinical mouse model, drug resistant ALL cells were significantly eliminated in ALL engrafted mice when treated with anti-CD47 mAb and mAb combination with ADM, whereas ADM alone and control mice remained at risk of leukemia burden. Moreover, with anti-CD47 antibody alone treatment, the highest (leukemia free) survival rate (over 5 months) without any relapse case was achieved.
Summary/Conclusion: Our current results indicated that targeting CD47 with anti-CD47 antibody therapy could effectively eliminate drug resistant ALL cells and provided a promising preclinical evidence for novel treatment in relapsed/refractory ALL.

EP324 B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA INDUCES AN INTERFERON-SIGNATURE IN MESENCHYMAL STROMAL CELLS

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Background: B-cell precursor acute lymphoblastic leukemia (BCP-ALL) cells that are present in the bone marrow microenvironment are able to hijack the normal hematopoietic stem cell niches to create a leukemic niche. The importance of this microenvironment for leukemic cells is demonstrated by the protection that the niche provides against chemotherapeutic agents. Patient derived mesenchymal stromal cells (MSCs) mimic this protective effect *in vitro*. Unraveling the mechanism of protection is important to provide potential novel therapeutics. Therefore, our research is focused on the interaction between ALL cells and MSCs.
Aims: We aimed to determine gene expression changes in ALL cells and MSCs after co-culture compared to mono-culture, and to investigate

which cyto/chemokines are differentially secreted upon contact between ALL cells and MSCs.
Methods: We performed mono- and co-cultures of primary MSCs and ALL cells for 40 hours to determine gene expression changes. Viable cells were sorted by FACS and RNA was isolated. Total-RNA sequencing data (Illumina) were analyzed using R. Supernatant was saved to determine cyto/chemokine profiles by Luminex technology, and to investigate the effect of these cyto/chemokines on the survival and migration of the leukemic cells. Migration experiments using transwells (3.0µm pores) were performed to determine the level of ALL migration towards chemokines of interest. Moreover, using lentivirus, knockdowns (KD) of genes of interest were performed in MSCs. KD efficiency was tested using Taqman qPCR. Subsequently, co-cultures of ALL cells and KD- or control-MSCs were performed to study the role these genes in ALL survival.
Results: RNA sequencing data from 15 independent co-culture experiments revealed that interferon (IFN)-related genes, such as *IFI6, MX1, IFI27, and OAS1,* were 2.5 to 3.1-fold upregulated in the MSCs after co-culture with ALL compared to MSC mono-culture. The type of upregulated pro-inflammatory genes and amount of upregulation varied between ALL patients. However, the observed changes were always similar when an ALL case was co-cultured with different MSC samples, suggesting that the changes are induced by the leukemic cells. Survival benefit (0.3 - 37.9%) was observed in ALL cells after co-culture with MSCs compared to ALL mono-culture. Co-cultures of KD-MSCs and ALL cells showed that ALL cell viability was affected upon KD of some IFN-related genes. The effect of the number of viable MSCs in these cultures is currently being addressed. Moreover, pro-inflammatory cytokines, and migration-related chemokines such as CCL2, CXCL8, and IP10 were upregulated after co-culture compared to the sum of the separate ALL and MSC mono-cultures. A gradient of IP10 in transwell experiments showed that this chemokine did not enhance primary ALL cell migration, suggesting that the ALL-induced secretion of IP10 serves a different role in BCP-ALL. The role of IP10 and other cyto/chemokines in immune regulation at the time of overt leukemia is part of ongoing studies.
Summary/Conclusion: Our data show that IFN-related genes, pro-inflammatory cytokines and migration-related chemokines become upregulated in bone marrow MSCs upon exposure to ALL. These induced changes may be important for ALL cell survival, affecting the mobility of other immune cells, and/or ensure that leukemic cells remain in close contact with MSCs. We postulate that interference with these affected genes and cyto/chemokines may disrupt the direct contact between leukemic cells and their niche and may provide an alternative way to eliminate leukemic cells more efficaciously.

EP325 OPTICAL GENOME MAPPING FOR THE ASSESSMENT OF STRATIFICATION-RELEVANT GENOMIC ABERRATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is the most prevalent type of pediatric cancer. Even though, 85-90% of patients with ALL can reach a long-term cure, ALL does reoccur in about 15-20% of all patients and can be cured in just 30-50% of the relapsed cases. ALL is molecularly characterized by an increasing number of structural genomic aberrations that strongly correlates with prognostic and clinical outcomes. Usually, a combination of cyto- and molecular genetic methods (karyotyping, array-CGH, FISH, RT-PCR, RNA-seq) is needed to identify all the underlying genomic aberrations present in ALL.
Aims: This research aims to investigate the feasibility of next-generation cytogenomics to detect structural variants in an all-in-one approach.
Methods: As proof of principle, twelve pediatric B-cell precursor ALL samples from ALL-BFM-2000 and AIEOP-BFM-ALL-2017 were analyzed by means of optical genome mapping (OGM), a DNA-based approach for structural variant detection, using the Saphyr system (Bionano Genomics). Intensive validation of the results was performed by comparing OGM data to existing data from routine diagnostic workflows.
Results: All structural alterations among translocations (e.g., t(1;19), dic(9;12)), aneuploidies (e.g., -7, -11, high hyperdiploidy), and copy number variations (e.g., *IKZF1*^{plus} profile) detected by established techniques were identified by OGM as well. Additionally, OGM revealed a more complex structure of a known translocation t(12;21) and detected further alterations, among those a small deletion in *SETD2* as well as a stratification relevant gene fusion of *JAK2/NPAT* in an archived sample.
Summary/Conclusion: In this pilot study of very well characterized pediatric ALL cases we show that all previously known genomic aberrations were detected by means of OGM as well and that OGM has the potential to detect stratification-relevant markers in an all-in-one approach.

EP326 CD16XCD33 BI-SPECIFIC KILLER CELL ENGAGER (BIKE) AS POTENTIAL IMMUNOTHERAPY IN PEDIATRIC PATIENTS WITH AML AND BIPHENOTYPIC ALL

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Background: Similar to pediatric acute myeloid leukemia (AML) the subgroup of biphenotypic acute lymphoblastic leukemia (ALL) is a rare complex entity with adverse outcome, characterized by the surface expression of CD33. Despite novel and promising anti-CD19 targeted immunotherapies such as chimeric antigen receptor T cells and bispecific anti-CD19/CD3 antibodies, relapse and resistance remain a major challenge in about 30% to 60% of patients.
Aims: Aim of this study was to investigate the potential role of the fully-humanized bi-specific antibody CD16×CD33 (BiKE) in children with CD33$^+$ acute leukemia.
Methods: For this purpose, we tested whether the reagent was able to boost NK cell effector functions against CD33$^+$ pediatric AML and biphenotypic CD33$^+$ pediatric ALL blasts.
Results: Stimulation of primary NK cells from healthy volunteers with 16x33 BiKE led to increased cytotoxicity, degranulation, and cytokine production against CD33$^+$ cell lines. Moroever, BiKE treatment significantly increased degranulation, IFN-γ, and TNF-α production against primary ALL and AML targets. Importantly, also NK cells from leukemic patients profited from restoration of effector functions by BiKE treatment, albeit to a lesser extent than NK cells from healthy donors. In particular those patients with low perforin and granzyme expression showed compromised cytotoxic function even in the presence of BiKE. In patients with intrinsic NK cell deficiency, combination therapy of CD16xCD33 BiKE and allogeneic NK cells might thus be a promising therapeutic approach.
Summary/Conclusion: Taken together, CD16xCD33 BiKE successfully increased NK cell effector functions against pediatric AML and biphenotypic ALL blasts and constitutes a promising new option for supporting maintenance therapy or "bridging" consolidation chemotherapy before hematopoietic stem cell transplantation.

EP327 DASATINIB AND NAVITOCLAX REVERSE GLUCOCORTICOID RESISTANCE IN PRE-T-CELL RECEPTOR ACTIVATED T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA

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Background: Outcomes in patients with T-cell Acute Lymphoblastic Leukaemia (T-ALL) have improved markedly over the recent decades, with intensive glucocorticoid-based chemotherapy accounting for 5-year event free survival (EFS) rates of over 80% in paediatric cases. [Patrick, et al, British Journal Haematology, 2014] Outcomes for patients refractory to or relapsing after treatment remain extremely poor. Overcoming glucocorticoid resistance is central to improving outcomes in these patients. Physiological T-lymphocyte development is directed by pre T Cell Receptor (pTCR) signalling and expression of pro-survival factors, such as BCL2 and BCL2L1. We have shown that pTCR signalling activity is

relevant in T-ALL. Dasatinib (DAS) effectively blocks the kinase LCK, which is an instrumental signalling molecule in the pTCR pathway. Combination of DAS with dexamethasone (DEX) impairs in vivo T-ALL expansion and results in cell death. [Shi, et al, Haematologica, 2020] Potent inhibitors of the BCL2 family have entered the clinical arena, and demonstrated single drug activity against T-ALL.
Aims: Establish efficacy of DEX+DAS and a BCL2 family inhibitor in T-ALL cell lines and patient-derived samples.
Methods: Cell viability assays combining DEX+DAS at a fixed ratio and BCL2 family inhibitors Venetoclax (ABT-199) or Navitoclax (ABT-263) were performed. Cell viability was determined by resazurin assay.
T-ALL PDX, in OP9-DL1 co-culture, were exposed to DEX+DAS and BCL2 inhibitors. Cell viability was assessed by resazurin assay, CytoQuant analysis and quantitative imaging.
Results: Both Venetoclax and Navitoclax act in an additive manner when combined with DEX+DAS in T-ALL cell lines and primary samples. In PDX samples sensitive to DAS, we observed superior cell kill with the addition of Navitoclax when compared to Venetoclax. Conversely, we observed that PDX samples resistant to dasatinib are more likely to respond to Venetoclax. The latter group is particularly enriched for Early T-cell Precursor ALLs, which rely on BCL2 for cell survival.
Summary/Conclusion: Based on these preliminary data, we suggest that T-ALL patients with activation of pTCR signalling, as exemplified by LCK status, benefit from DEX+DAS + Navitoclax treatment to overcome GC resistance. Other subgroups, including ETP ALL, may benefit from Venetoclax-based treatment. We will test this treatment recommendation in preclinical models to inform future patient management.

EP328 CHARACTERIZATION OF RNA-PROTEIN INTERACTION NETWORKS IN ACUTE LEUKEMIAS

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Background: Treatment of pediatric acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) remains challenging, in particular after relapse. In both pediatric ALL and especially AML, death from intensity-maximized conventional chemotherapies is still unacceptably high, and outcome re-mains poor in both AML and high-risk ALL. Thus, there is still an urgent need to identify new targetable structures and/or pathways. Transcriptional regulation in leukemias has been extensively studied and targeted therapies are under evaluation, however, the post-transcriptional layer of gene-regulation remains underexplored. Mutations and aberrant expression patterns of RNA-binding proteins (RBPs) has been detected in leukemia and implicated in leukemic transformation, with notable examples like IGF2BP3 (IGF2 mRNA binding protein 3) and MSI2 (Musashi 2). However, the oncogenic potential of most of the more than 1500 RBPs has not been studied in pediatric acute leukemias.
Aims: We aim to identify oncogenic RBPs that play a significant and targetable role in hard-to-cure subtypes of leukemias.
Methods: We performed pooled CRISPR-Cas9 dropout screenings followed by next generation sequencing using a pool of sgRNAs directed against 1500 RBPs. The screens were performed in four AML and five ALL cell lines (CMK, NOMO1, M-07e, SKNO1, NALM6, HAL-01, SEM, REH, KOPN8), representing either common leukemic subtypes or those associated with poor prognosis. SgRNA frequencies were quantified at the outset of the experiment and after 16 doublings using deep sequencing (Illumina HiSeq 4000). MAGeCK analysis was conducted for each cell line, with negative scores indicating depleting sgRNAs.
Results: We identified 191 putative oncogenes whose knockout led to a significant loss of cell fitness in at least one of the 9 screens. We further observed overlaps of depleting RBPs between the ALL cell lines and the AML cell lines. To differentiate between a general essential role of a given RBP in any cell (e.g. essential in RNA/cellular metabolism) and a putative necessary function in initiating or promoting leukemic growth, we integrated our data with cell line data collected in the framework of the project Achilles. We compared essentiality scores in leukemic cell lines to those cell lines of all origins to derive those RBPs, which display oncogenic properties (as opposed to just representing core essential factors).
One of 191 identified putative oncogenes is CAD, which pro-proliferative potential was verified experimentally in both, AML and ALL. In terms of clinical relevance, we found a tendency towards reduced overall survival (OS) in AML patients with high CAD protein expression. Since CAD protein is a multi-domain enzyme and plays a pivotal role in pyrimidine synthesis, we will dissect its independent function as an RBP.
Summary/Conclusion: Our CRISPR-Cas9 screening in combination with functional validation states the pro-proliferative potential of many RBPs including CAD in AML and ALL cell lines and highlights its utility for identifying novel targetable mechanisms in leukemia.

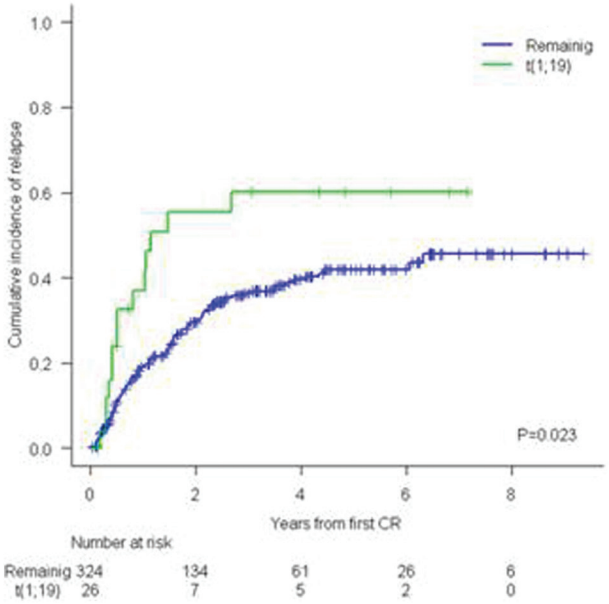
EP329 T(1;19)(Q23;P13) TCF3-PBX1 MAY NOT BE AN INTERMEDIATE-RISK SUBTYPE IN ADULT B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH MRD-ORIENTED PROTOCOLS FROM THE PETHEMA GROUP

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Background: Translocation t(1;19)(q23;p13) encoding the TCF3-PBX1 fusion gene is considered an intermediate-risk B-cell precursor acute lymphoblastic leukemia (BCP ALL) subtype. In adult BCP ALL there is a debate regarding the impact of this alteration. While German, English and American study groups have shown no prognostic significance, French and Italian groups have reported poor outcomes.
Aims: To analyze the frequency and clinical impact of t(1;19) in a series of adult BCP ALL patients (pts) treated with protocols from the PETHEMA Group.
Methods: A review of 513 adult BCP ALL pts (15 to 60 years) diagnosed between 2003 and 2017 and treated with MRD-oriented protocols of the PETHEMA Group was done. G-banding and FISH were performed on BM samples. Measurable residual disease (MRD) was centrally assessed by multi-parametric flow cytometry. Main outcome measures were complete response (CR), overall survival (OS) and cumulative incidence of relapse (CIR), assessed by competing risk analysis.
Results: A total of 26 pts with t(1;19)/TCF3-PBX1 were identified, representing 5% of all BCP ALL. 9/23 (39%) cases showed isolated t(1;19) while 14/23 (61%) had additional chromosomal aberrations (ACA) (in 3 cases the TCF3-PBX1 fusion was detected by FISH in the context of a normal karyotype). Pts with t(1;19) were more likely to be female (73% vs. 45%, p=0.006) and to have a pre-B phenotype (63% vs. 17%, p<0.001). Although TCF3-PBX1 pts showed higher WBC count than the remaining patients, the difference was not statistically significant (median 16.2 [0-199.5] vs. 12 [0.23-638] x10^9/L, p=0.144).
CR was achieved in 100% of t(1;19) vs. 90%, in the remaining BCP ALL pts (p=0.151). The proportion of pts with end induction MRD level <0.01% was similar (70% vs. 61%, p=0.417). No differences in OS were observed (5y-OS t(1:19) 41% [19%>63%] vs. 44% [38%>50%], p=0.562). Pts with t(1;19) experienced more deaths due to disease progression (77% vs. 59%) and less deaths due to treatment-related toxicity (15% vs. 38%). No differences were observed in OS among pts with isolated t(1;19) and those with t(1;19) with ACA (5y-OS 59% [23%>95%]

vs. 33% [1%>65%], p=0.645). A significantly higher CIR was observed for patients with t(1;19) compared with the remaining BCP ALL pts (5y-CIR 60% [36%>77%] vs. 42% [35%>48%], p=0.023)(Figure). The 5y-CIR of patients with isolated t(1;19) showed a trend to be lower to that of t(1;19) with ACA (28% [3%>63%] vs. 71% [36%>89%], p=0.119). All outcome parameters were also calculated for patients with balanced t(1;19) or unbalanced der(19)t(1;19) without statistical differences between them.



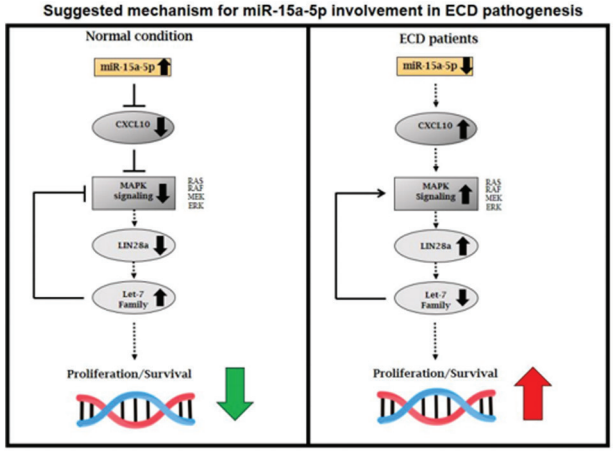
Summary/Conclusion: Although showing favorable initial treatment response, pts with t(1;19) experience a higher rate of relapse (especially those with ACA to t(1;19)) than the remaining BCP ALL pts, without differences in OS. A deeper genetic analysis may identify markers of poor outcome enabling a more precise risk stratification of t(1;19) pts.

EP330 MICRORNA-15A-5P ACTS AS A TUMOR SUPPRESSOR IN ERDHEIM-CHESTER DISEASE BY MEDIATING THE CXCL10-ERK-LIN28A-LET7 AXIS

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Background: Erdheim-Chester disease (ECD) belongs to a group of rare hematological diseases and is characterized histologically by proliferation of mature histiocytes on a background of inflammatory stroma. The disease is systemic, with clinical manifestations ranging from focal indolent bone lesions to a multi-systemic, life-threatening disease. We have recently reported an aberrant expression of microRNAs (miRNAs) in ECD patients (Weissman et al, *Cancers*, 2020). NanoString analysis revealed downregulation of 95% of differentially expressed miRNAs in ECD patients compared to healthy controls. Subsequent bioinformatics analysis suggested that lower expression of certain miRNAs in ECD results in upregulation of target genes that participate in cell survival signaling and inflammation. The most prominent and significant change detected between ECD and healthy controls was downregulation of miR-15a-5p. The miR-15/16 cluster represents the most frequently deregulated miRNAs reported in hematological malignancies, and has been associated with disease progression, prognosis, and drug resistance.
Aims: To study the biological role of miR-15a-5p in ECD pathogenesis.
Methods: Global miRNA expression was analyzed in plasma samples of untreated ECD patients (n=34) and healthy controls (n=15) using the NanoString nCounter miRNA assay. As several lines of evidence have suggested that ECD may originate from a myeloid progenitor, we used the human myeloid cell lines KG-1a and OCI-AML3 as a model to study the biological effects of miR-15a-5p. Cytokine-dependent murine pro-B Ba/F3 lymphoid cells that stably expressed the MIGII-BRAF^{V600E} vector were also used. The effects of aberrantly expressed miRNAs on potential molecular targets was analyzed using quantitative real-time polymerase chain reaction (qRT-PCR), luciferase assay, enzyme-linked immunosorbent assay (ELISA), Western analysis, proliferation assay, cell-cycle analysis and Annexin-propium iodide staining.
Results: Bioinformatics target predictor (TargetScan) identified a conserved target site for miRNA-15a-5p in the 3' UTR of the chemokine ligand 10 (CXCL10). A luciferase assay confirmed that CXCL10 is a target gene regulated by miRNA-15a-5p. Low levels of miR-15a-5p in ECD patients were associated with upregulation of CXCL10 in patients plasma samples. Increased expression of miR-15a-5p, by transfection of miR-15a-5p mimic, resulted in CXCL10 downregulation, followed by downregulation of the oncogene *LIN28a* and p-ERK signaling, leading to upregulation of the tumor suppressor let-7 family miRNAs. Furthermore, overexpression of miR-15a-5p in cell lines and in a primary culture, derived from an ECD patient, inhibited cell growth and induced apoptosis by decreased levels of Bcl-2 and Bcl-xl. Finally, analysis of sequential samples from 7 ECD patients treated with MAPK inhibitors (vemurafenib/cobimetinib) for 4 months resulted in upregulation of miR-15a-5p and downregulation of CXCL10.



Summary/Conclusion: Our findings strongly suggest that miR-15a-5p acts as a tumor suppressor in ECD patients through the CXCL10-ERK-LIN28a-let7 axis, highlighting an additional layer of post-transcriptional regulation in this disease. Upregulation of miR-15a-5p in ECD patients may have a potential therapeutic role.

EP331 IDENTIFICATION AND MOLECULAR CHARACTERIZATION OF BCR-ABL1-LIKE ACUTE LYMPHOBLASTIC LEUKEMIA IN INDIAN PATIENTS

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Background: A new provisional entity 'B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*-like' has been incorporated in the revised edition of WHO classification (2017). Authors across globe employ two approaches namely Microarray Gene Expression Profiling (GEP) or targeted Next-Generation Sequencing (NGS) and LDA (low-density array) card for its detection. In India, both these techniques are either not available or are prohibitively expensive. Therefore, we planned to perform identification and molecular characterisation of Indian *BCR-ABL1*-like ALL patients, using a different approach.

Aims: To identify *BCR-ABL1*-like ALL cases using two different platforms, followed by its molecular characterization.
Methods: Flowcytometric Immunophenotying (FCM-IP) and multiplex RT-PCR were performed on 611 B-lineage ALL cases to detect *BCR-ABL1* fusion transcripts. Further, microarray profiling of 12 *BCR-ABL1*-positive cases was performed using Affymetrix U133 Plus 2.0 array. A total of 96 B-ALL cases were subjected to a targeted panel of 50 genes using nCounter GEP. Furthermore, we performed a deep molecular analysis in various genetic subgroups of identified *BCR-ABL1*-like ALL cases using nCounter GEP, quantitative Real time (RQ)-PCR & digital droplet PCR (DD-PCR). Lastly, we performed quantification of chosen 8 best differentially expressed (DE) genes on 551 B-ALL cases, to make a logistic regression model for its rapid detection.
Results: Multiplex RT-PCR assay revealed *BCR-ABL1* transcripts in 17.67% (108/611) cases. Global transcriptome profiling of 12 *BCR-ABL1* RNA transcripts revealed a total of 1574 as DE genes. DE genes were further filtered through hierarchical clustering analysis and a total of 45 DE genes were identified. Based on previous literature and regression coefficient values, 15 best classifier genes were selected using penalized logistic regression. Out of 78 examined *BCR-ABL1*-negative cases, 33 (42.30%) cases were clustered together with 15 *BCR-ABL1*-positive cases and were categorised as *BCR-ABL1*-like ALL cases in principal component analysis. Further, we categorised *CRLF2* into two categories; high *CRLF2* cases 5/33 (15.15%) & low 28/33 (84.84%) among *BCR-ABL1*-like ALL cases. *JAK2* exon 16 was sequenced in 5 *CRLF2* high cases and we found 2 missense variants, R683S and P694L, by Sanger sequencing. The average log fold change of -1.105 & -4.574 was seen in *P2YR8* & *CSF2RA* respectively by RQ-PCR. In *CRLF2* low expressing cases, the average log fold change of 12 kinase genes showed -1.11 in *CENPC*, -0.77 *FOXP1*, -0.20 *NUP153*, 1.12 *RCSD1*, 0.76 *PAX5*, -0.19 *FLT3*, -4.41 *EPOR*, -4.01 *ILR2B*, -1.58 *CSFIR* -3.43 *PDGRFB*, -5.98 *NTRK3* and -1.99 *ZNF274*. The average log fold change of *IKZF1* in 78 *BCR-ABL1*-negative cases was found to be 10.93 in nCounter GEP and 1.07 in RQ-PCR. We found the CNV incidence of 8.33% (9/108) in *IKZF1* (4-7 deletion) gene and the ratio of *IKZF1* deletion ranged from 6.14 to 69.8% using DD-PCR. Further, 8 genes were selected and quantified in 511 *BCR-ABL1*-negative cases and we found 104/551 (18.87%) *BCR-ABL1*-like ALL cases using RQ-PCR. Further, we created a dynamic nomogram using logistic regression based classifier for its rapid detection.

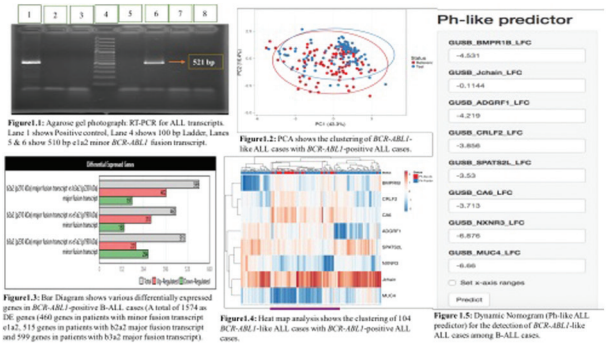


Figure1.1: Agarose gel photograph: RT-PCR for ALL transcripts. Lane 1 shows Positive control, Lane 4 shows 100 bp Ladder. Lanes 5 & 6 show 510 bp e1a2 minor *BCR-ABL1* fusion transcript.
Figure1.2: PCA shows the clustering of *BCR-ABL1*-like ALL cases with *BCR-ABL1*-positive ALL cases.
Figure1.3: Bar Diagram shows various differentially expressed genes in *BCR-ABL1*-positive B-ALL cases (A total of 1574 as DE genes (466 genes in patients with minor fusion transcript e1a2, 515 genes in patients with b2a2 major fusion transcript and 599 genes in patients with b3a2 major fusion transcript).
Figure1.4: Heat map analysis shows the clustering of 104 *BCR-ABL1*-like ALL cases with *BCR-ABL1*-positive ALL cases.
Figure 1.5: Dynamic Nomogram (Ph-like ALL predictor) for the detection of *BCR-ABL1*-like ALL cases among B-ALL cases.

Summary/Conclusion: We have reported the incidence and devised a logistic regression based simple, efficient, cost-effective classifier for the rapid detection of *BCR-ABL1* like ALL cases for the first time; which is likely to be suitable for developing countries. It is very important to detect *BCR-ABL1*-like ALL cases, so as to provide these patients the benefits of treatment stratification (including desirable TKI therapy) and prognostication.

EP332 PH+ ALL CELL LINE WITH PTPN11 MUTATIONS IS RESISTANT TO ALL TKIS AS WELL AS VENETOCLAX BUT SENSITIVE TO THE COMBINATION

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Background: Philadelphia positive acute lymphoblastic leukaemia (Ph+ ALL) is a high risk ALL subtype with an aggressive clinical course. While the incorporation of tyrosine kinase inhibitors (TKIs) into the chemotherapy regimen has improved upfront treatment, the development of resistance/relapse to TKIs is still a major problem. RAS pathway mutations (*PTPN11*, *NRAS* and *KRAS*) are prevalent in relapsed B-ALL and confer poor prognosis. Therefore, new targeted therapies to overcome the resistance induced by these mutations are needed.
Aims: To investigate targeted therapies to overcome the resistance induced by activating lesions in the RAS pathway in cell line models of Ph+ ALL.
Methods: Three Ph+ ALL SUP-B15 (p190 *BCR-ABL1*) resistant cell lines were generated by long term dose escalation of imatinib (to 5 µM, SUP-B15 IR), dasatinib (to 200 nM, DR) and ponatinib (to 200 nM, PR). Drug sensitivity was measured by Annexin V and viability stain 780. RNAseq and western blot analysis were performed to identify mechanisms of resistance. The combination index (CI) was calculated by Calcusyn software.
Results: In comparison to parental, the SUP-B15 IR, DR and PR cell lines were resistant to all TKIs (imatinib, nilotinib, dasatinib and ponatinib) and to asciminib. Interestingly, SUP-B15 IR showed primary resistance to venetoclax (VEN) (LD50 = 74.94 nM vs 2.1 nM in the parental, p=0.0054), while DR and PR cell lines were sensitive (LD50 = 8.36 nM and 5.98 nM respectively) (Figure 1A). RNAseq analysis identified *KRAS* p.G12S (VAF 37%) and *NRAS* p.G12S (VAF 100%) mutations in the DR and PR cell lines respectively. Two *PTPN11* (p.A461T, VAF 63.7% and p.P491H, VAF 40.2%) mutations were identified in the catalytic domain of tyrosine-protein phosphatase in SUP-B15 IR cells. Activating lesions in PTPN11 cause an oncogenic ERK signalling, which stabilises the anti-apoptotic protein Mcl-1 and is the likely cause of venetoclax resistance in acute myeloid leukaemia. We therefore investigated the activation of the MAPK/ERK pathway and Mcl-1 by western blot. SUPB15 IR^{PTPN11mut} had increased expression of pBCR-ABL (P=0.002), pERK1/2 (P<0.0001), Mcl-1 (P<0.0001) and similar levels of Bcl-2 in comparison to the sensitive cell lines. Because treatment with imatinib alone (0, 2, 5 and 10µM) led to a dose-dependent reduction of pBCR-ABL1 (Y177), pERK1/2 and Mcl-1 without affecting Bcl-2, we investigated whether co-targeting Mcl-1 and Bcl-2 could be an effective strategy for inducing cell death in SUPB15 IR$^{PTPN11\,mut}$ cell lines. Whilst these cell lines were resistant to the Mcl-1-selective inhibitor S63845 (LD50=290 nM vs 78.5 nM for parental), combination therapy with venetoclax was synergistic in overcoming resistance (CI=0.051 for 50 nM S63845 and 5 nM venetoclax). Interestingly, combination treatment with imatinib and venetoclax (CI = 0.075 for 2 µM IM and 5 nM VEN) (Figure 1B and 1C) or asciminib and venetoclax (CI=0.032 for 2 µM asciminib and 5 nM venetoclax) was also effective in inducing cell death. This combination therapy significantly reduced pERK1/2 (P<0.0001) and Mcl-1 expression (P<0.0001) and increased cleaved-PARP level (P=0.024).
The DR^{KRASmut} and PR^{NRASmut} lines instead showed overexpression of Bcl-2 (P=0.0079 and P=0.01 respectively), but not pBCR-ABL or Mcl-1, which could explain why venetoclax alone overcame resistance in these cell lines

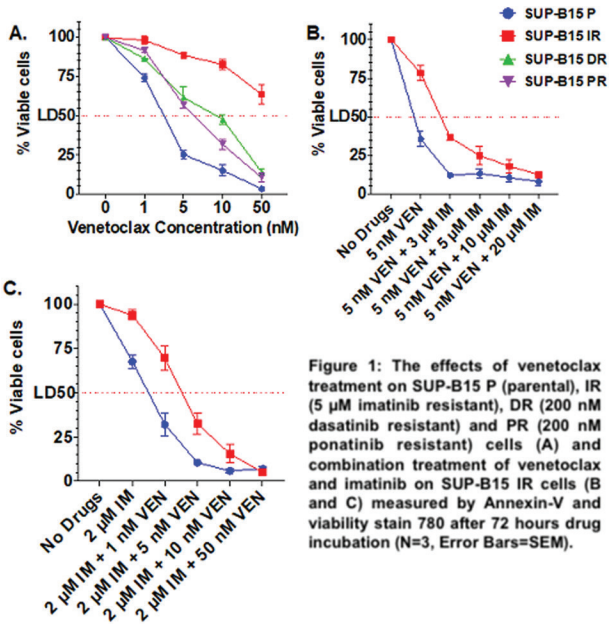


Figure 1: The effects of venetoclax treatment on SUP-B15 P (parental), IR (5 µM imatinib resistant), DR (200 nM dasatinib resistant) and PR (200 nM ponatinib resistant) cells (A) and combination treatment of venetoclax and imatinib on SUP-B15 IR cells (B and C) measured by Annexin-V and viability stain 780 after 72 hours drug incubation (N=3, Error Bars=SEM).

Summary/Conclusion: Combination therapy of TKIs and venetoclax could be promising for Ph+ ALL patients carrying *PTPN11* mutations and Mcl-1 overexpression. Studies are ongoing to determine the role of the mutations in *PTPN11* in the development of the resistance.

EP333 PARALLEL HIGH-THROUGHPUT PROFILING OF TRA, TRB, TRG, TRD, IGH, IGK, IGL REPERTOIRES USING ADVANCED UNBIASED MULTIPLEX PCR FOR CLONALITY ASSESSMENT IN ALL

A. Komkov [1,2,*], A. Miroshnichenkova [1,2], A. Smirnova [1], E. Volchkov [2], A. Popov [1,2], Y. Olshanskaya [1,2], Y. Lebedev [1], M. Maschan [2], D. Chudakov [1], I. Mamedov [1,2]

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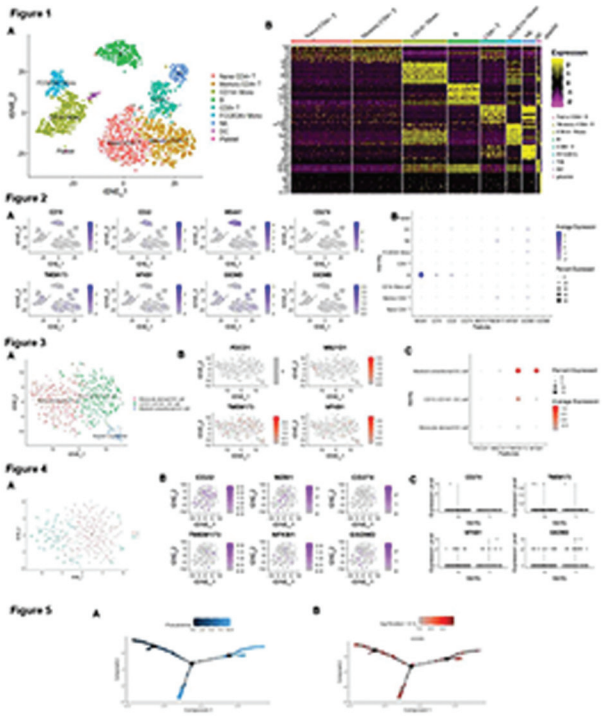
Background: Immune receptors (T-Cell Receptor, TCR and B-Cell Receptor, BCR) repertoire profiling is one of the key sources of basic and applied immunology insights. In clinical hematology, it is used for monitoring of immune system recovery after treatment, clonality assessment and minimal residual disease monitoring in lymphoid malignancies.
Aims: The most sensitive approach for TCR and BCR repertoire profiling in clinics is DNA-based multiplex PCR with subsequent high-throughput sequencing. The key drawbacks of existing protocols are quantitative bias, inability to receive the full repertoires in low input samples and absence of one of TCR genes – TRA. Here we resolve these issues, presenting the first method for simultaneous and unbiased profiling of all existing TCR and BCR genes named «7G».
Methods: 7G system includes primers for all V and J segments of all existing immune receptor genes, including TRA, TRB, TRG, TRD, IGH, IGK, IGL. The target multiplex PCR is performed in single tube using primer mix quantitatively calibrated with original iROAR software. The sequencing is performed on any Illumina platform. TCR and BCR rearrangements extraction from sequencing data is performed with modified MiXCR software allowing for the identification of incomplete D-J, D-D and Kde rearrangements in addition to complete ones. The remaining amplification bias is detected and removed with the use of iROAR (Immune Repertoire Over Amplification Removal) software. 20 genomic DNA samples from PBMC of healthy volunteers and 20 DNA samples from bone marrow of pediatric T-ALL or B-ALL patients were used for the method testing.
Results: The developed method was successfully tested on DNA samples from both healthy individuals and leukemia patients. We were able to reconstruct repertoires of all 7 immune receptor genes in all healthy individuals. The proportions of TCR and BCR repertoire size correlates with the phisiological B and T cell ratio in the blood. The repertoires containe 95% of all possible V-J segment combinations. V and J segment usages are in a range established for the European population in previous studies. The major clonal rearrangements (comprising 20-98% of total repertoire) were detected in all leukemia samples. In B-ALL patient BM samples we detected both BCR and TCR rearrangements. T-ALL patient samples are characterized by TCR rearrangements only. TRA gene rearrangement were detected in both T-ALL (50%) and B-ALL (5%) samples. Analysis of replicates showed high reproducibility of the method (R-square=0.98). Analysis of serial dilutions of DNA from both healthy donors and ALL patients showed that sensitivity of the method is sufficient for TCR and BCR profiling in small amount of DNA up to 10 genome equivalents.
Summary/Conclusion: The possibility to simultaneously analyze all TCR and BCR gene rearrangements makes the proposed method the most cost and labor effective among all analogous methods. The sensitivity of the method allow to analyze any small lymphoid cell populations, that makes it suitable for a wide spectrum of diagnostical tasks. This work was supported by RSF grant № 20-75-10091.

EP334 SINGLE-CELL TRANSCRIPTOME PROFILING REVEALS THE EXPRESSION PATTERN OF STING IN BONE MARROW CELLS OF B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: B-cell acute lymphoblastic leukemia (B-ALL) is an aggressive type of acute leukemia. Despite the high complete remission (CR) rate following first-line therapy, treatment refractoriness and frequent recurrence are remained to be solved. Immunotherapy and targeted therapy have been confirmed as the effective approach for refractory and relapse (r/r) B-ALL. Although immunotherapy has achieved higher complete remission rate, remission stage can be destroyed by genomic heterogeneity and instability. Mechanistically, the occurrence of r/r B-ALL not only relied on intrinsic properties of malignant leukemic cells, but also on extrinsic protective environment provided by the tumor microenvironment (TME), especially bone marrow (BM) TME.
Aims: To clarify the transcriptome patterns in BM cells of B-ALL, single cell RNA sequencing (scRNA-seq) data was performed to be analyzed.
Methods: ScRNA-seq data of BM cells from 3 B-ALL patients were obtained from the Gene Expression Omnibus (GEO, GSE130116). Raw data was firstly processed by Seurat package. After quality control and data normalization, variable genes were extracted for dimensionality reduction. Principal component analysis (PCA) and t-distributed stochastic neighbor embedding (t-SNE) were then executed to cluster cells, following with cell types' classification. To determine the features of cell subgroups, B cell and dendritic cell (DC) were isolated respectively and followed with gene expression analysis. Finally, pseudo-time analysis functioned by Monocle package was performed to display cell development trajectory and gene expression features over time.
Results: Based on cell clustering, 9 cell types were profiled in B-ALL BM, including naïve and memory $CD4^+$ T cell, $CD14^+$ monocyte, B cell, $CD8^+$ T cell, $FCGRA3^+$monocyte, nature killer (NK) cell, DC, and platelet (Fig.1A). Top 10 marker genes in each cell cluster were exhibited in heat map, demonstrating an effective cell classification (Fig.1B). Differential gene analysis further revealed that PD-L1 (CD274) was hardly expressed on BM cells while TMEM173 (STING), NFKB1 (NF-κB) were widespread, especially on immune cells (Fig.2A). In particular, elevation of STING and NF-κB indicated that BM cells were sensitive to the type I innate immune response rather than PD-1 mediated response (Fig.2B). Previous studies had revealed that immune cells activation and tumor cell pyroptosis could be induced by STING. To analyze the features of STING and its downstream molecules in B-ALL BM cells, DCs and B cells were isolated from total cells respectively. DCs were separated into 3 subtypes, including monocyte derived DC, CD1C-CD14-DC and myeloid conventional DC (Fig.3A). Gene expression analysis confirmed that the expression of cyclic GMP-AMP synthase (cGAS), STING and NF-κB were higher than PDCD1 (PD-1) in DCs (Fig.3B, 3C). Compared with DC, although STING and PD-L1 were hardly expressed in B cells, NF-κB and pyroptotic effector (GSDMD) were partially elevated (Fig.4). In other words, GSDMD might rescue the inefficiency of PD-L1 inhibitors by inducing cell pyroptosis. Furthermore, pseudo-time analysis of B cells profiled that the expression of GSDMD gradually decreased over time (Fig.5).



Summary/Conclusion: Our study firstly profiles the features of STING and its downstream molecules in BM cells of B-ALL at a single cell resolution. Activation of STING is expected to be an effective approach in the treatment of B-ALL in the future.

EP335 MULTICOLOR FLOW CYTOMETRY REVEALS IMMUNOPHENOTYPIC SUB-POPULATIONS IN T-ALL

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Background: Despite intensified treatment regimens, the outcome for T-ALL patients remains inferior to pre-B-ALL patients, especially for patients that are refractory to treatment or that relapse within 4 years after the start of therapy. An important prognostic factor for cancer relapse, in general, is tumor heterogeneity at the time of diagnosis. Yet, it remains unclear to what extend intra-tumor heterogeneity appears in pediatric T-ALL patients, and especially whether this reflects the heterogeneity in T-cell developmental arrest or heterogeneity in acquired mutations. T-ALL is initiated by the activation of specific oncogenic transcription factors due to chromosomal rearrangements. Activation of specific oncogenes has been linked to four different subtypes, namely: ETP-ALL/Immature, TLX, NKX2-1/TLX1, or TALLMO. The gene expression signatures and immunophenotypes of these four T-ALL entities reflect differences in developmental arrests comparable to the various developmental stages of healthy thymocytes. In the current study, we aim to decipher the immunophenotypic make-up and intra-tumor heterogeneity in T-ALL patients at diagnosis. Accessing T-ALL intra-tumor heterogeneity will further increase our insights on T-ALL disease onset and development that may drive therapy resistance and relapse.
Aims: To investigate the level of immunophenotypic heterogeneity in T-ALL patients.
Methods: We have designed and optimized a 20-parameter multi-color flow cytometry panel to identify all known thymocyte developmental stages using thymus samples of healthy donors. Thereafter this optimized panel was used to screen 28 bio-banked diagnostic T-ALL patient samples from all four T-ALL subtypes. Bioinformatic analysis using t-stochastic neighbor embedding (t-SNE) was used to visualize immunophenotypic heterogeneity in each T-ALL sample. Samples were also matched with normal thymocyte subpopulations to assess the stage of developmental arrest. Lastly, we use the FlowSOM package to differentially compare levels of heterogeneity in matched diagnostic and relapse patient samples and diagnostic PDX models.
Results: We show immunophenotypic heterogeneity in 26 of 28 diagnostic T-ALL patient samples. Within each patient, immunophenotypic subclones reflect differential sites of normal developmental arrest. Next, we observed that immunophenotypic heterogeneity is preserved in diagnostic and relapsed PDX samples, where relapse PDX samples grow out from minor subpopulations that are present already at diagnosis.
Summary/Conclusion: T-ALL patients show a high degree of immunophenotypic heterogeneity at diagnosis suggesting differential sites of developmental arrest at disease initiation. Moreover, the persistence of immunophenotypic subclones after PDX generation shows the competition of subclones under selective pressure while still maintaining heterogeneity. Our future efforts will focus on correlating the immunophenotypic heterogeneity with underlying mutations to improve our understanding of T-ALL intra-tumor heterogeneity at different multi-omic levels. Deciphering the different layers of T-ALL heterogeneity will greatly impact the current targeted treatment strategies that focus on specific mutations but may not acknowledge underlying heterogeneity.

EP336 RETROSPECTIVE ANALYSIS OF COPY NUMBER VARIATION OF IKZF1, CDKN2A/B, PAX5, EBF1, ETV6, BTG1, RB1 AND PAR1 GENES IN PEDIATRIC PATIENTS WITH B-ALL

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Background: Copy number variation (CNV) of *IKZF1*, *RB1*, *EBF1* genes and/or PAR1 region in childhood acute lymphoblastic leukemia B (B-ALL) confers a worse prognosis, with event-free survival (EFS) at 10 years of 68%. Recently, a new classification has been proposed to stratify pediatric patients with B-ALL according to cytogenetic alterations and CNV, defining four risk groups with prognostic impact.
Aims: The aim of this study has been to determine if CNV can change the prognosis determined by cytogenetic alterations in a series of pediatric patients with B-ALL.
Methods: We perform a retrospective analysis of CNV in 106 patients diagnosed with B-ALL in our hospital between January-2014 and January-2021, included in the ALL/SEHOP-PETHEMA 2013 therapeutic recommendation guidelines. We use SALSA MLPA P335 kit (MRC Holland), which includes probes for *IKZF1*, *CDKN2A/B, PAX5, EBF1, ETV6, BTG1, RB1* and PAR1 (*CRLF2* and *P2RY8*).
Results: Of the 106 cases, 55 were included in the study as they fulfilled the criteria to perform the MLPA (≥30% blasts in bone marrow and high-quality DNA). The clinical-biological characteristics are detailed in Table 1. The genes that were deleted with the highest prevalence were: *ETV6* (43%), *PAX5* (27%), *CDKN2A/B* (27%) and *IKZF1* (18%). CNV was not observed in 24% of the cases, while 26%, 16% and 34% showed 1, 2 or ≥3 CNV, respectively.
Good risk CNV profile (CNV-GR) was presented in 53% of the cases, 25 had good risk cytogenetics (CYT-GR) (45%), four intermediate risk cytogenetics (CYT-IR) (7%) and any patient showed poor risk cytogenetics (CYT-PR). Poor risk CNV (CNV-PR) was observed in 31% of the cases, of them, six patients had CYT-GR (11%), ten had CYT-IR (18%) and one had CYT-PR (2%). Age ≥10 years, phenotype, intermediate and poor cytogenetic risk, not achieving complete remission, relapse and lower EFS occurred more frequently in the CNV-PR group, with significant differences (Table 1). The 4-years EFS was 100% for CNV-GR, 80% for CNV-IR and 38% for CNV-PR.
Of the 55 patients, six relapsed, all of them within the good or intermediate cytogenetic group; five with CNV-PR and one with CNV-IR. Three cases had *CRLF2* rearrangements and a CNV profile with *IKZF1*, *CDKN2A* and *CDKN2B* deletions, among others. One case had a complex karyotype with *PAX5* rearrangement and a CNV-IR profile with *CDKN2A/B* biallelic deletion and *PAX5* deletion. Another patient had high hyperdiplod karyotype and an isolated *IKZF1* deletion. Finally, the last case had a complex karyotype with t(1;19) and a CNV-PR profile with deletion of *PAX5* and *RB1*. All of them were treated according to the ALL/SEHOP-PETHEMA 2013 protocol, five within the high-risk group and one in the good risk group.

Table 1. Clinical-biological characteristics according to the CNV risk group.

	CNV risk group*			
	CNV-GR	CNV-IR	CNV-PR	p
Patients	29	9	17	
Sex				
Female	14	1	9	ns.
Male	15	8	8	
Age				
0-9 years	27	6	7	
10-15 years	2	2	9	0,003
≥16 years	0	1	1	
B-ALL phenotype type				
Pro-B	0	1	1	
Common-B	29	7	11	0,025
Pre-B	0	0	3	
Cytogenetic risk group[Δ]				
CYT-GR	25	4	6	
CYT-IR	4	4	10	0,005
CYT-PR	0	1	1	
Complete remission				
Yes	29	9	14	0,029
No	0	0	3	
Relapse				
Yes	0	1	5	0,006
No	29	8	11	
Death				
Yes	1	0	2	ns.
No	28	9	15	
Median overall survival (months)	30	31	17	ns.
4-years EFS	100 %	80 %	38 %	0,001

*CNV risk group: CNV of good risk (CNV-GR: no deletion of the genes studied; isolated deletions of *ETV6*, *PAX5* or *BTG1* and cases with deletions of *ETV6* accompanied by an additional isolated deletion of *BTG1*, *PAX5* or *CDKN2A/B*), poor risk CNV (CNV-PR: deletion in *IKZF1*, *PAR1*, *EBF1* or *RB1*) and CNV of intermediate risk (CNV-IR: any other pattern not mentioned above) (Hamadeh et al. 2019).
Δ Cytogenetic risk group: good (CYT-GR; *ETV6-RUNX1*, high hyperdiploidy), poor (CYT-PR; *BCR-ABL1*, *KMT2A* rearrangements, near haploidy, low hypodiploidy, iAMP21 or t(17; 19)) and intermediate (CYT-IR; all other cases with altered or normal cytogenetics).
It has been considered significant when p <0.05

Summary/Conclusion: Despite it is a small cohort, the results confirm that the combination of conventional cytogenetic risk and CNV analysis

allows a better classification of the biological risk of the disease. We can identify a group with a very good prognosis (CYT-GR and CNV-GR) with 4-years EFS of 100% and a group with higher probability of relapse (CYT-GR/IR and CNV-PR) with 4-years EFS of 38%.

EP337 GENOME-SCALE SCREENING WITH CRISPR/CAS9 FOR PROLIFERATION RELATED GENES IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Abnormal proliferation of leukemia cells is one of the characteristics of acute lymphoblastic leukemia (ALL). But at present, we don't fully understand the molecular mechanism of ALL cell proliferation, and there is no research about ALL proliferation-related genes from the whole genome level.
Aims: Here, CRISPR/Cas9-mediated genome-wide knockout negative screening method was used to screen ALL proliferation-related genes on genome-wide level.
Methods: After Genome-scale CRISPR-Cas9 knockout (GeCKO) v2 library plasmid amplification, lentivirus packaging, virus infection, Jurkat and Nalm6 cells at day 0 and day 14 were collected for high-throughput sequencing, and two biological replicates were performed. Then gene ontology (GO) and pathway enrichment analysis were conducted by DAVID database to analyze the proliferation-related genes obtained from the screening. And one of the genes was selected as a candidate gene. After knockout of candidate gene using CRISPR/Cas9 technology, MTS method was performed to detect cell proliferation, and flow cytometry was used to detect cell cycle. Using the database to explore the expression of candidate gene and the relationship with the prognosis of ALL.
Results: After successful establishment of the screening model, Jurkat and Nalm6 cells of two screening time point were collected for high-throughput sequencing, and the data met the quality control standards. A total of 155 proliferation-related genes were screened. The GO analysis showed that proliferation-related genes were mainly related to translation and post-transcriptional modification, while pathway enrichment analysis was closely related to metabolic pathways. PTPTM1, which was closely related to metabolism, was selected for further verification. The cell proliferation ability of Jurkat and Nalm6 cells were significantly reduced, and the cell cycle G1 phase was blocked after PTPMT1 being knocked out. Through database analysis, it is found that PTPMT1 was generally highly expressed in tumor cell lines. Comparing with normal people, PTPMT1 had higher expression levels in ALL. In children with B-ALL, those with high PTPMT1 expression have a worse prognosis.
Summary/Conclusion: In this study, CRISPR/Cas9-mediated genome-wide screening system was used to screen out 155 proliferation-related genes of Jurkat and Nalm6 cells. PTPMT1, one of the candidate genes, can inhibit the cell proliferation and block G1 phase of Jurkat and Nalm6 cells, and its expression level associated with the prognosis in children ALL.

EP338 DOXORUBICIN/NUCLEOPHOSMIN BINDING PROTEIN-CONJUGATED

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NANOPARTICLE (DOX-PMS-NPMBP) ENHANCES ANTI-LEUKEMIA ACTIVITY IN ACUTE LYMPHOBLASTIC LEUKEMIA CELLS IN VITRO AND IN VIVO
Background: Acute lymphoblastic leukemia (ALL) is an aggressive malignancy. Adults with ALL have more than 50% relapse rates. We have previously validated that overexpression of nucleophosmin (NPM) is involved in the multidrug resistance (MDR) development during ALL; and a synthetically engineered recombinant NPM binding protein (NPMBP) has been developed in our group; NPMBP and doxorubicin (DOX) can be conjugated in a nanoparticle-based drug delivery system named DOX-PMs-NPMBP to counteract MDR during ALL.
Aims: Here, we evaluated the antileukemia potential of DOX-PMs-NPMBP in resistant ALL cells. This study demonstrates that DOX-PMs-NPMBP significantly enhances chemosensitivity to DOX in ALL cells. Despite at variable concentrations, both resistant and primary ALL cells from relapsed patients were sensitive to DOX-PMs-NPMBP.
Methods: In detail, the half maximal inhibitory concentration (IC50) values of DOX-PMs-NPMBP were between 1.6- and 7.0-fold lower than those of DOX in cell lines and primary ALL cells, respectively; and apoptotic cells ratio was over 2-fold higher in DOX-PMs-NPMBP than DOX. Mechanistically, p53-driven apoptosis induction and cell cycle arrest seem central in DOX-PMs-NPMBP-induced anti-leukemia effects. Moreover, DOX-PMs-NPMBP significantly inhibited tumor growth and prolonged mouse survival of ALL xenograft models; and no systemic toxicity occurrence was observed after treatment during follow-up.
Results: In conclusion, these data indicate that DOX-PMs-NPMBP may significantly exert growth inhibition and apoptosis induction, and markedly improve DOX antileukemia activity in resistant ALL cells. This novel drug delivery system may be valuable to develop as a new therapeutic strategy against multidrug resistant ALL.
Summary/Conclusion: Acute lymphoblastic leukemia (ALL) is an aggressive malignancy. Adults with ALL have more than 50% relapse rates. We have previously validated that overexpression of nucleophosmin (NPM) is involved in the multidrug resistance (MDR) development during ALL; and a synthetically engineered recombinant NPM binding protein (NPMBP) has been developed in our group; NPMBP and doxorubicin (DOX) can be conjugated in a nanoparticle-based drug delivery system named DOX-PMs-NPMBP to counteract MDR during ALL. Here, we evaluated the antileukemia potential of DOX-PMs-NPMBP in resistant ALL cells. This study demonstrates that DOX-PMs-NPMBP significantly enhances chemosensitivity to DOX in ALL cells. Despite at variable concentrations, both resistant and primary ALL cells from relapsed patients were sensitive to DOX-PMs-NPMBP. In detail, the half maximal inhibitory concentration (IC50) values of DOX-PMs-NPMBP were between 1.6- and 7.0-fold lower than those of DOX in cell lines and primary ALL cells, respectively; and apoptotic cells ratio was over 2-fold higher in DOX-PMs-NPMBP than DOX. Mechanistically, p53-driven apoptosis induction and cell cycle arrest seem central in DOX-PMs-NPMBP-induced anti-leukemia effects. Moreover, DOX-PMs-NPMBP significantly inhibited tumor growth and prolonged mouse survival of ALL xenograft models; and no systemic toxicity occurrence was observed after treatment during follow-up. In conclusion, these data indicate that DOX-PMs-NPMBP may significantly exert growth inhibition and apoptosis induction, and markedly improve DOX antileukemia activity in resistant ALL cells. This novel drug delivery system may be valuable to develop as a new therapeutic strategy against multidrug resistant ALL.

EP339 THE LABORATORY EXAMINATION CHARACTERISTICS AND CLINICAL OUTCOMES OF T(12;17)(P13;Q21)/TAF15-ZNF384 POSITIVE ACUTE LEUKEMIA

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Background: TAF15-ZNF384 is a recurrent but rare fusion gene in leukemia and lacks relevant reports.
Aims: To investigate the laboratory characteristics and clinical outcomes of acute leukemia (AL) with t(12;17)(p13;q21)/TAF15-ZNF384.
Methods: Laboratory examination results and clinical records of t(12;17)(p13;q21)/TAF15-ZNF384 positive cases admitted to Hebei Yanda Ludaopei Hospital from Feb.1, 2009 to Nov. 30, 2020 were retrieved and analyzed, including G-banding karyotyping, flow cytometry, fluorescence in situ hybridization (FISH, ZNF384 separation probe), RNA sequencing (RNA-seq), PCR, gene panel mutation screening, as well as routine inspections.
Results: A total of 12 positive cases were enrolled in this cohort, including 8 males and 4 females, with a median age of 25.5 (3-49) years. Eight cases had complete blood count records at the time of disease onset, and the white blood cell count ranged 1.58-38×10^9/L. Immunophenotyping showed that 11 cases were acute B lymphocytic leukemia (B-ALL) with myeloid antigen expression, and 1 was mixed-phenotype AL with B/myeloid lineage markers. All cases expressed CD19, CD34, CD13 and/or CD33, 10 cases expressed CD22, 7 cases expressed or partially expressed CD10, and only 1 case weakly expressed CD20. Nine cases

were positive for t(12;17)(p13;q21) at the disease onset or relapse, and 7 of them with additional chromosomal abnormalities (CAs). Among the 3 cases with t(12;17)(p13;q21) negative, 1 was normal karyotype, 1 was complex karyotype (CK) with t(11;17)(q21;q21) and ectopic 12p12, and 1 was t(5;17))(p12;p11.2) with additional CAs. All of them were tested positive for TAF15-ZNF384 transcript by RNA-seq and PCR. FISH detection showed 9 cases with typical ZNF384 separation signals, 1 case lost 1 ZNF384 signal, 1 CK case lost partial of one ZNF384 signal, and 1 normal karyotype case also showed a normal FISH signal. RNA-seq and PCR analysis identified TAF15 exon6-ZNF384 exon3 transcript in these 3 cases who manifested atypical FISH signal. TAF15-ZNF384 transcripts were analyzed by RNA-seq and PCR in 7 cases, there were 4 TAF15 exon6-ZNF384 exon3, 2 TAF15 exon9-ZNF384 exon3, and 1 TAF15 exon11-ZNF384 exon3 (Fig.1 A). Ten cases underwent 86 gene panel mutation analyses, 8 of them carried FLT3-PTPN11-CBL-NRAS/KRAS-NF1 pathway mutations, and other mutation genes included ETV6, TET2, and KMT2D. Induction and consolidation chemotherapy mainly include VDCLP/CVDP/CAM/VDLP/asparaginase and methotrexate (Fig.1 B). The overall response to induction chemotherapy was favorable, except for one case, which failed to achieve complete remission (CR). However, 9 cases relapsed during consolidation chemotherapy, and 5 of them relapsed within 8 months after diagnosis. Four cases underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). Two cases who underwent salvage HSCT relapsed 3 months and 6 months after transplantation, respectively; the other 2 cases had been followed up after HSCT and survived without relapse for 63 months and 13 months, respectively.

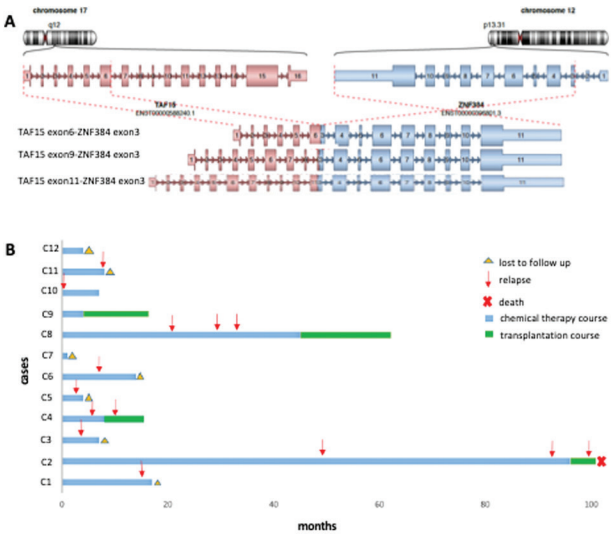


Fig. 1 Transcript isoforms (A) and clinical course (B) of acute leukemia cases with t(12;17)(p13;q21)/TAF15-ZNF384 positive.

Summary/Conclusion: AL cases with (12;17)(p13;q21)/TAF15-ZNF384 have unique genetic and immunophenotypic characteristics. They are often accompanied by FLT3-PTPN11-CBL-NRAS/KRAS-NF1 pathway mutations. There is a significant t(12;17)(p13;q21) negative rate, which may be attributed to CK and cryptic ectopic; RNA-seq and PCR analysis can help to ensure the detection rate. The immunophenotype is mostly B-ALL with myeloid antigen expression. The general response to conventional chemotherapy is favorable, but prone to relapse. Cases of this sub-entity may benefit from allo-HSCT at the first CR.

EP340 GENOMIC HETEROGENEITY CONTRIBUTED TO THE DIFFERENT PROGNOSIS OF ADULT AND PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Prognosis of acute lymphoblastic leukemia (ALL) in adults is inferior than children. Hence, ALL is still a challenging disease to be cured in adult population. Aberrant genetic alterations has been observed previously in ALL, while the patterns of differential gene alteration have not much been comprehensively determined in the adult and pediatric ALL on a genome-wide scale.

Aims: This study attempted to investigate the biological differences in genomic profiling between the adults and children with ALL, and the relationship between the genomic heterogeneity and prognosis.

Methods: 39 adults and 54 children patients with ALL in our institution were studied. All patients were de novo and treated with standard chemotherapy regimens. Clinical data were collected on all patients. Exome sequencing and anaiysis was performed. The genomic mutation was calculated. The driver genes of the mutated genes were selected from the COSMIC platform. The overlapped gene was subjected to Gene ontology and pathway enrichment analyses and mapped the PPI network.

Results: The results showed the similar common mutation types but the increased prevalence of genetic alterations in adult ALL. The median number of detected gene mutations was 19 (range: 1–53) per sample in adult ALL and 4.5 (range: 1–19) in pediatric ALL(P<0.001). A significant correlation between the increased number of gene mutations and age was found (R^2 = 0.3096, P<0.001). 67 and 53 driver genes were identified in adult and pediatric ALL samples, respectively. The SETD2 and TTN mutations were significantly enriched in adult ALL. While the KRAS, ARID1A and CREBBP mutations were significantly enriched in pediatric ALL. (P<0.05). 67 and 53 driver genes were identified in adult and pediatric ALL samples, respectively. Using integrated genomic analysis, we identified 4 functional pathways recurrently mutated in adult ALL: transcriptional regulation, VEGF signaling pathway, T cell receptor signaling pathway, and Fc epsilon RI signaling pathway(P<0.05), 5 in pediatric ALL: Transcriptional regulation, PI3K-AKT-mTOR signaling, JAK-STAT signaling, NOTCH1 signaling, FoxO signaling pathway(P<0.05). Using cytoHubba analysis, among the 53 nodes, NRAS, IDH1, WT1, FLT3, NF1, DNMT3A, CEBPA, PTPN11, TP53, ASXL1, the ten central node genes with degree >10, were considered as hub driver genes in the PPI network of adult ALL. While as to the pediatric ALL, MYC, EZH2, CDKN2A, CREBBP, SMARCA4, ATRX, NF1, EP300, NOTCH1, BRCA1, the ten central node genes with degree >10, were considered as hub driver genes in the PPI network.The incidence of relapse was 33.3% and 7.7% in the adult and pediatric ALL, respectively(P=0.003). The overall survival(OS) and relapse free survival (RFS) of adult ALL were poorer than pediatric ALL(P=0.003, P<0.001, respectively).

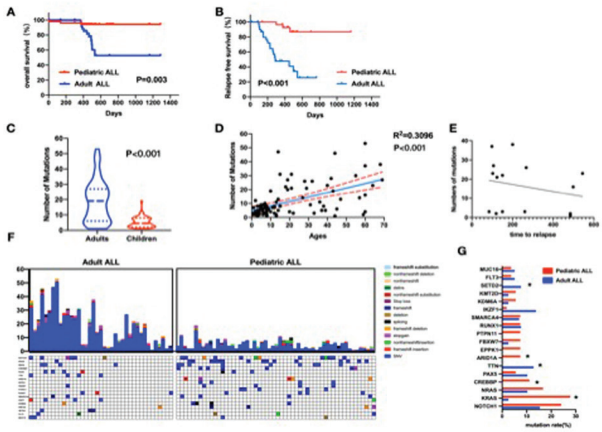


Figure. The genomic heterogeneity and survival of adult and pediatric ALL. (A, B) Survival of adult and pediatric ALL. The OS and RFS of adult ALL were poorer than pediatric ALL (P=0.003, P<001). (C) Violin plot of mutation counts in adult and children (P=0.001). The median number of detected gene mutations was 19 (range: 1–53) per sample in adult ALL and 4.5(range: 1–19) in pediatric ALL. (D)Correlation between mutation counts and age of ALL patients. A significant correlation between the number of gene mutations and age was found (R2 = 0.3096, P<0.001). (E)Correlation between mutation counts and times to relapse of ALL patients.(F)The genomic landscape of adult and pediatric ALL. The mutational heatmap indicated the most recurrently altered genes in the 93 ALL samples. Color coded by the genetic alteration types. (G) The percent of mutated genes in adult and pediatric ALL. The mutation rate was different in the adult and pediatric ALL.

Summary/Conclusion: This genomic landscape enhanced the understanding of the biological differences of ALL between the two populations and provided a clue for novel therapeutic approaches.

Acute lymphoblastic leukemia - Clinical

EP341 ZUMA-4 PHASE 1 LONG-TERM RESULTS: KTE-X19 CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN PEDIATRIC/ADOLESCENT PATIENTS WITH RELAPSED/ REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: We present long-term Phase 1 results of ZUMA-4, a study of KTE-X19 autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in pediatric/adolescent patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL).
Aims: To evaluate the long-term safety and efficacy of KTE-X19 in pediatric/adolescent patients with R/R B-ALL.
Methods: Patients (aged 2–21 years) with R/R B-ALL (Philadelphia chromosome-positive allowed) and >5% bone marrow blasts received 2×10^6 or 1×10^6 CAR T cells/kg after conditioning chemotherapy. The primary endpoint was incidence of dose-limiting toxicities. KTE-X19 formulation was optimized in a second 1×10^6-dose group using a lower infusion volume (40-mL vs 68-mL).
Results: As of 9/9/2020, the median follow-up was 36.1 months (range, 24.0–53.9), with 24 patients (median age, 14 years [range, 3–20]) of 31 enrolled receiving KTE-X19. The median time from leukapheresis to KTE-X19 product release was 14 days. Four patients received 2×10^6 cells/kg, with no dose-limiting toxicities in evaluable patients (n=3). Additionally, the 1×10^6 cells/kg dose level was explored (68-mL, n=11; 40-mL, n=9). Overall, Grade ≥3 adverse events occurred in 100% of patients, most commonly hypotension (50%) and anemia (42%). Rates of Grade ≥3 neurologic events/cytokine release syndrome were 25%/75% (2×10^6), 27%/27% (1×10^6 [68-mL]), and 11%/22% (1×10^6 [40-mL]). All 4 Grade 5 events (B-ALL, n=2; disseminated mucormycosis, n=1; *Escherichia* sepsis, n=1) were considered unrelated to KTE-X19. Overall complete remission rates (complete remission plus complete remission with incomplete hematologic recovery) were 75%, 64%, and 67% in the 2×10^6, 1×10^6 (68-mL), and 1×10^6 (40-mL) groups, respectively. Of responding patients, 100% had undetectable minimal residual disease. Sixteen patients (2×10^6, n=2; 1×10^6 [68-mL], n=8; 1×10^6 [40-mL], n=6) underwent subsequent allogeneic stem cell transplantation (median, 2.3 months post–KTE-X19). In the 2×10^6, 1×10^6 (68-mL), and 1×10^6 (40-mL) groups, the medians for duration of response (months) were 4.14, 10.68, and not reached, respectively. The median overall survival was not reached for the 1×10^6 groups (24-month rate: 68-mL, 73%; 40-mL, 88%) and was 8 months for the 2×10^6 group. In the 1×10^6 40-mL group (selected as Phase 2 dose), the median peak (range) of CAR gene copies per microgram of DNA in blood was 2.5×10^4 (0–2.5×10^5); among responders in this group, CAR T cells were undetectable by 3 months post-infusion.
Summary/Conclusion: Treatment with KTE-X19 at the recommended Phase 2 dose led to high complete remission rates, with the median overall survival not yet reached and a manageable safety profile. Phase 2 of ZUMA-4 is enrolling pediatric patients with R/R B-ALL or non-Hodgkin lymphoma, including patients with minimal residual disease-positive disease and early relapse (<18 months) after first-line therapy.

EP342 ANTIBODIES TO PEGYLATED E. COLI ASPARAGINASE PREDICT THE OCCURRENCE OF HYPERSENSITIVITY REACTIONS IN HIGH-RISK PATIENTS UNDERGOING THE CONSOLIDATION PHASE OF THE AIEOP-BFM ALL 2009 PROTOCOL.

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Background: In the AIEOP-BFM ALL 2009 study, hypersensitivity reactions (HSR) to pegylated E.coli asparaginase (PEG-ASNase) were most commonly reported in high-risk (HR) patients.[1] After induction with 2 doses of PEG-ASNase 2 weeks apart, HR patients - in contrast to standard and intermediate-risk patients - received 3 doses of PEG-ASNase, one in each of the three HR blocks (HR1-3), followed by three additional doses, one in each of the three subsequent PIII blocks (PIII 1-3).
Aims: We analyzed antibodies to native E.coli ASNase (anti-E.coli ASNase IgG/IgM), PEG-ASNase (anti-PEG-ASNase IgG/IgM) and polyethylenglycol (PEG) (anti-PEG IgG and anti-PEG IgM) in serum prior to administration of PEG-ASNase in the HR and PIII blocks and assessed the predictive value for HSR of the antibodies to PEG-ASNase.
Methods: A total of 563 samples from 202 patients were analyzed. 46 patients developed HSR (CTCAE grade ≥1) to PEG-ASNase (14 patients in HR1, 27 patients in HR2, 5 patients in HR3 and none in PIII).
Results: In each HR block pre-existing anti-PEG-IgG, anti-PEG-IgM, anti-PEG-ASNase-IgG/IgM or anti-E.coli-ASNase-IgG/IgM significantly increased the risk of HSR to PEG-ASNase ($p<0.05$, Fisher test). No HSRs were observed in the PIII blocks, which coincided with an overall low prevalence of pre-existing antibodies (1-4.5%) compared to the HR blocks where the prevalence was 13-26%.
The areas under the receiver operating characteristic (ROC) curve regarding the predictive accuracy of pre-existing antibodies for subsequent HSR to PEG-ASNase (Table 1) showed high predictivity of pre-existing antibodies for HSR in HR2. Among the four antibodies, pre-existing anti-PEG IgG predicted HRS with the highest sensitivity (true positive rate: 80 % for HR1 and HR3 and 100 % for HR2) and specificity (true negative rate: of 94 %, 96 % and 98 % for HR1, HR2 and HR3, respectively).
Table 1: Areas under the receiver operating characteristic (ROC) curves for pre-existing antibodies and HSR in HR blocks. The closer the AUC is to 1, the higher the predictive accuracy of a test.

	HSR to PEG-ASNase in		
pre-existing antibody	**HR1**	**HR2**	**HR3**
anti-E.coli ASNase IgG/IgM	0.63	0.78	0.89
anti-PEG-ASNase IgG/IgM	0.63	0.92	0.80
anti-PEG IgG	0.87	0.98	0.89
anti-PEG IgM	0.82	0.97	0.78

Summary/Conclusion: In the AIEOP-BFM ALL 2009 study, we observed a highly accurate predictivity of anti-PEG IgG antibodies for HSR in HR patients. This finding might be useful for future clinical decisions.
[1]*Rizzari C, Moericke A; Conter V, Valsecchi MG, Zimmermann M, Silvestri D et al. Incidence of Hypersensitivity Reactions (HSR) Reactions (HSR) to Peg-Asparaginase (PEG-ASP) in 6136 Patients*

Treated in the AIEOP-BFM ALL 2009 Study Protocol. Blood 2019; 134 (Supplement_1):2589.

EP343 OUTCOMES OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS DIAGNOSED BETWEEN 2011 AND 2017: RESULTS OF THE PROSPECTIVE COHORT STUDY EORTC 58081

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Background: EORTC-CLG 58081 was designed as a translational-observational study for the identification of prognostic factors in children ≥1 year with Ph-negative ALL. Treatment recommendations were built on the best arms of the randomized phase 3 trial EORTC-CLG 58951: prednisolone (PRED) 60 mg/m^2 in induction for all risk groups but for average risk (AR) T-ALL (dexamethasone (DEX) 10 mg/m^2) and AR2 B cell precursor (BCP)-ALL (DEX 6mg/m^2). The AR2 group comprised patients (pts) with BCP-ALL (≥100x10^9/L WBC or CNS or extramedullary involvement at diagnosis) and pts with T-ALL (no CNS involvement or VHR features). Very low risk (VLR) pts had high-hyperdiploïdy, WBC<10x10^9/l, age <10 years, and no very high risk (VHR) features (D8 blood blasts≥1x10^9/l, adverse genetic features, no CR or MRD≥10^{-2} at end of induction (EOI)). The risk stratification was left unchanged, except that MRD≥10^{-3} at the end of consolidation was added to VHR criterion in the 58081 study.
Aims: To evaluate event-free survival (EFS), (1) overall and according to each risk group in the 58081 as compared with the 58951 study (reference arm with PRED), and (2) from CR according to the EOI MRD level.
Methods: Between 2011 and 2017, 833 pts were enrolled in the 58081 study. The median follow-up was 5.5 yrs. Primary endpoint was EFS from date of first CR until relapse or death in CR; lack of CR achievement was an EFS event at T0.
Results: Results are presented in the Table. The 5-yr EFS rate were similar in the 2 studies, overall and in the BCP ALL subgroup, but in the T-ALL pts it was significantly higher in the 58081 study than in the 58951 study. Comparable EFS were obtained in both studies for AR1 and VHR pts (76.5% of the total). The EFS of VLR group was shorter in the 58081 study. In contrast, the EFS of AR2 pts significantly increased in the 58081 study, overall, and similarly in both subgroups, as same as the overall survival of AR2 patients which was 95.4% for the 58081 *vs* 88.3% for the 58951 (HR: 0.35; 95%CI 0.09-1.27, *P*=0.02). The 5-yr EFS for pts who reached CR was shorter for those with MRD≥10^{-2} at EOI (68.4%, HR=3.23) and those with 10^{-3}≤MRD<10^{-2} (55.2%, HR=5.63) as compared to pts with MRD<10^{-3} (89.8%).
Table
*: 95% CI

	58081		58951		
	n	5-yr EFS, % (95% CI)	n	5-yr EFS, % (95% CI)	HR (58081 vs 58951) (99% CI)
Overall	833	84.8 (82.0-87.2)	951	83.6 (81.1-85.9)	0.96 (0.76-1.21)*
Immuno-phenotyping					
BCP-ALL	693	84.3 (81.2-86.9)	803	84.9 (82.2-87.3)	1.07 (0.76-1.50)
T-ALL	140	87.3 (80.3-92.0)	148	76.6 (68.9-82.7)	0.58 (0.28-1.22)
EORTC Risk Group					
VLR	75	86.0 (74.7-92.5)	120	94.0 (87.7-97.1)	2.47 (0.75-8.19)
AR1	510	85.6 (82.0-88.5)	583	85.1 (81.8-87.8)	0.99 (0.65-1.48)
AR2	120	93.0 (86.5-96.5)	150	78.2 (70.6-84.1)	0.33 (0.13-0.88)
BCP-ALL	47	91.3 (78.5-96.7)	56	72.2 (57.9-82.3)	0.30 (0.07-1.26)
T-ALL	73	94.1 (85.0-97.8)	94	81.7 (72.2-88.2)	0.37 (0.10-1.38)
Initial VHR	128	73.5 (64.8-80.4)	97	71.7 (61.4-79.6)	0.96 (0.50-1.87)

Summary/Conclusion: The poor EFS of patients with intermediate MRD at EOI confirm the value of this early timepoint to distinguish patients with high relapse risk. The disappointing results obtained for patients in the VLR group despite unchanged therapy and a more stringent definition of risk (age 1-9 yrs) are difficult to interpret but should prompt caution about therapeutic de-escalation. The improved EFS in the AR2 group is most likely due to the use of DXM, in induction for all pts and in VCR-DEX pulses in pts with BCP-ALL, together with improved MRD-based stratification. This allowed a dramatic EFS improvement in T-ALL subgroup, which for the first time and although using a risk stratification based solely on response to treatment outperforms that of BCP-ALL.

EP344 CD22-TAGETED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY FOR ADULTS WITH REFRACTORY OR RELAPSED B ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Although CD19-specific chimeric antigen receptor (CAR) T-cell therapy has achieved high complete remission rates in relapsed/refractory B-cell lymphoblastic leukemia (r/r B-ALL), some patients relapse after CAR-T. This has become an urgent problem to be solved. CD22 isalso expressed in most cases of B-ALL. We conducted a CD22 CAR T-cell therapy in 19 relapsed orrefractory (r/r) B-ALL adult patients, including 18 patients who failed from previous CD19 CAR T-cell therapy and 1 patient without CD19 CAR T-cell therapy because of lossing CD19 antigen.
Aims: To evaluate the treatment efficacy of CD22 CAR T-cell for adults with refractory or relapsed B acute lymphoblastic leukemia.
Methods: From July 2017 to October 2020, a total of 19 treated adult r/r B-ALL patients were enrolled. The patients were hematological relapse. Eighteen patients had accepted prior CD19 CAR-T therapy, and relapsed with CD22 antigen expression identified by flow cytometer (FCM), 1 case had not a history of CD19 CAR-T therapy because of lossing CD19 antigen. CAR-T cells were produced by lentiviral vectors encoding second generation CARs composed of CD3ζ and 4-1BB. All patients accepted fludarabine and/or cyclophosphamide before infusion. The treatment effect was evaluated on day 30 after cell infusion, MRD was quantified by FCM and PCR for fusion gene. The last follow-up was as of October 24, 2020.
Results: The median age of 19 patients was 30 (range, 18-63) years, including 7 underwent allogeneic transplantation. All patients received ≥1×105 /kg CD22-CAR T cells.Complete remission (CR) or CR with incomplete count recovery (CRi) was achieved in 15 of 19 patients (78.9%) that could be evaluated on day 30 after infusion.Cytokine release syndrome (CRS) occurred in all patients,But most patients only experienced mild cytokine-release syndrome and neurotoxicity.In 15 CR and CRi patients, 8 patients followed by allogeneic hematopoietic cell transplantation after CD22 CAR-T, These patients remained in remission at 4 to 39.7 months after transplantation, another 7 patients did not undergo HCT, 1 relapsed at 1 months,6 of them remained in remission at 4 to 26.5 months after infusion. Among 4 NR patients, 3 died of disease progression, and 1 accepted salvage transplantation who had survived for 4.6 months.
Summary/Conclusion: CD22 CAR T-cells was highly effective in inducing remission in adult r/r B-ALL patients,transplantation followed-by CD22-CART allowed CR patients to obtain a remission of 4-39.7months.

EP345 EXTRAMEDULLARY RELAPSE AND DISEASE PROGRESSION AFTER BLINATUMOMAB THERAPY FOR TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

I. Aldoss [1,*], S. Otoukesh [1], J. Zhang [2], S. Mokhtari [3], M. Al Malki [1], A. Salhotra [1], H. Ali [1], A. Aribi [1], K. Sandhu [1], S. Arslan [1], F. Stewart [1], P. Curtin [1], A. Artz [1], R. Nakamura [1], G. Marcucci [1], S. Forman [1], A. Stein [1], V. Pullarkat [1]

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Background: Blinatumomab (BLINA) administration induces high response rates for treatment of relapsed/refractory (R/R) and persistent minimal residual disease (MRD+) acute lymphoblastic leukemia (ALL). A few reports have addressed the unique pattern of BLINA-failure during ALL therapy, manifesting either as extramedullary (EM) progression/relapse (P/R) or loss of CD19 antigen expression. However, EM P/R ALL phenomena during BLINA therapy remains largely underrecognized and is not fully understood.

Aims: We perform this study to identify the prevalence and factors influencing EM R/P in ALL following BLINA therapy.
Methods: We retrospectively reviewed outcomes of adults with B-cell ALL who were treated with BLINA at City of Hope between 2013 and 2021, and analyzed potential factors impacting response and EM P/R following BLINA therapy.
Results: We identified 132 patients treated with BLINA for either R/R (n= 103; 78%) or MRD+ (n= 29; 22%) B cell ALL. Median age at the time of BLINA treatment was 39 years (range:18-88). Higher response rate to BLINA was associated with treatment in the MRD+ ALL setting (p=0.008), lower bone marrow (BM) blast burden in R/R setting (p=0.029), no history of prior EM disease (p=0.001), and fewer lines of pre-BLINA therapies (p=0.048). In multivariable analysis, only lower pre-BLINA BM blast burden (p=0.049) and the lack of EM disease history (p=0.019) remained significantly associated with higher response to BLINA. BLINA failure (defined as initial progression in non-responders or post BLINA relapse in responders) was noted in 89 patients. At the time of BLINA failure, 38 (43%) patients P/R EM, including 24 patients as isolated EM disease without BM involvement. 17 (36%) patients of those were refractory to BLINA and 21 (50%) responders to BLINA who relapsed subsequently progressed EM. History of EM involvement (53% vs. 24%, p= 0.005) and P/R with CD19+ ALL (97% vs. 74%, p= 0.012) were associated with higher risk for EM P/R at the time of BLINA failure. Factors did not impact EM P/R include; response to BLINA, pre-BLINA stem cell transplant, disease setting (MRD vs. R/R), or pre-BLINA BM blast burden. EM P/R involving the central nervous system (CNS) occurred in 15 (39%) patients, and more frequently encountered in responders at the time of relapse (n= 12; 57%) compared to refractory patients at the time of progression (n= 3; 18%).

Table 1. Factors impacted ALL EMD relapse/progression post BLINA

	EMD R/P	No EMD R/P	P-value
Number	38	51	
Median age (range)	40 (18-74)	39 (19-88)	0.478
Sex			0.517
Male	22 (58)	26 (51)	
Female	16 (42)	25 (49)	
Response to blina			0.188
YES	21 (55)	21 (41)	
NO	17 (45)	30 (59)	
Prior alloHCT			0.432
YES	6 (16)	12 (24)	
NO	32 (84)	39 (76)	
History of EMD			0.005
YES	20 (53)	12 (24)	
NO	18 (47)	39 (76)	
Disease setting			0.547
MRD	7 (18)	7 (14)	
R/R	31 (82)	44 (86)	
Median blast% pre BLINA	70 (0.01-100)	70 (0.01-95)	0.803
N of prior lines of therapies	2 (1-5)	2 (1-5)	0.935
CD19 expression at P/R			
N of evaluable			
Positive	29	46	
Negative	28 (97)	34 (74)	0.012
	1 (3)	12 (26)	

Summary/Conclusion: In conclusion, EM P/R is common during BLINA therapy in ALL, especially in responders; since half of them relapsed EM (+/-BM). History of EM disease during ALL course predicted inferior response to BLINA and higher risk for P/R EM. CNS P/R is frequently observed at the time of BLINA failure, and the majority of extramedullary P/R cases retained CD19 expression. Therefore, BLINA therapy should be cautiously used in patients with history of EM disease and patients should be closely monitored for EM progression during treatment.

EP346 THE SALVAGE TREATMENT OF HUMANIZED-CD19 CAR-T CELLS FOR RELAPSED B-ALL AFTER PRIOR MURINIZED-CD19 CAR-T CELL THERAPY

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Background: Although CD19-specific chimeric antigen receptor (CAR) T-cell therapy has achieved high complete remission rates in relapsed/refractory B-cell lymphoblastic leukemia (r/r B-ALL), some patients relapse after CAR-T. For CD19-positive relapsed B-ALL, reinfusion of CD19-CART cells is a salvage treatment option. At present, most of CD19 CART cell products are murinized (mCD19-CART), reinfusion of mCD19-CART may not be effective owing to anti-mouse scFv antibody caused by mCD19-CAR. In this study, we used humanized CD19-CART (hCD19-CART) cells to treat relapsed B-ALL patients who had previously accepted mCD19-CART cells.
Aims: To evaluate the treatment efficacy of hCD19-CART cells for B-ALL patients relapsing after mCD19-CART therapy.
Methods: From January 2019 to October 2020, a total of 18 heavily treated adult and pediatric r/r B-ALL patients were enrolled. Seventeen patients were hematological relapse or with extramedullary diseases (EMD, n=6), 1 was minimal residual disease (MRD) relapse. All patients had accepted prior murinized-CD19 CAR-T therapy (once, n=15; twice, n=3), and relapsed with CD19 antigen expression identified by flow cytometer (FCM), 11 cases had a history of CD22 CAR-T therapy. CAR-T cells were produced by lentiviral vectors encoding second generation CARs composed of CD3ζ and 4-1BB. All patients accepted fludarabine and/or cyclophosphamide before cell infusion. The treatment effect was evaluated on day 30 after cell infusion, MRD was quantified by FCM and PCR for fusion gene, EMDs were evaluated by PET-CT/CT/ultrasound. The last follow-up was as of December 31, 2020. The informed consents were obtained in accordance with the Declaration of Helsinki.
Results: The median age of 18 patients was 19 (range, 4-49) years, including 10 adults and 8 children younger than 18 years old, 2 with BCR-ABL fusion gene and 2 with TP53 gene mutation, 10 underwent allogeneic transplantation. The median dose of infused CAR-T cells was 5.0 x 10^5/kg (range, 1.0-18.0 x 10^5/kg). Cytokine release syndrome (CRS) occurred in all patients, including 14 with grade 1, 3 with grade 2 and 1 with grade 4 CRS. Except for supportive care, 9 patients were administered steroids, 3 were given additional plasmapheresis. There were no neurotoxicity and treatment-related death.
On day 30 after T-cell infusion, 12 (67%) cases achieved complete remission (CR, 11 MRD-negative CR) and 6 had no response (NR). In 12 CR patients, 10 followed by allogeneic hematopoietic cell transplantation (allo-HCT, 3 were second HCT) in 1.3-2.3 months after CAR-T, 9 (9/10, 90%) patients remained in CR with a median remission period of 6.7 months (2.4-22 months), only 1 relapsed at 3 months after HCT. Another 2 CR patients did not undergo HCT, 1 relapsed at 9.9 months and 1 remained in CR for 8.9 months. Among 6 NR patients, 3 died of disease progression, and 3 accepted salvage transplantation (all were second HCT), of them, 2 relapsed at 4 and 8.5 months after HCT, and 1 had survived for 9.2 months.
Summary/Conclusion: The salvage treatment of humanized CD19-CART cells resulted in a 67% CR in CD19-positive relapsed B-ALL patients who had a prior murinized CD19-CART therapy, and transplantation followed-by hCD19-CART allowed 90% CR patients to obtain a remission of 2.4-22 months. The prognosis of NR patients was still poor.

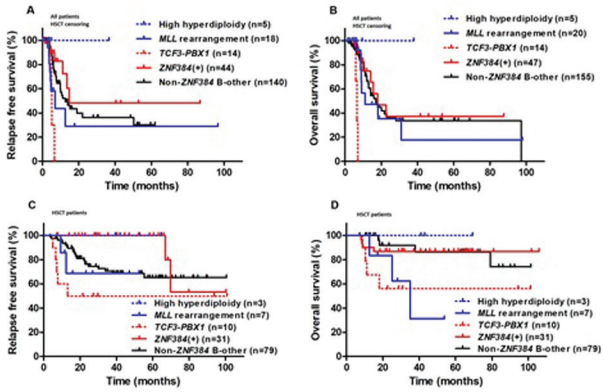
EP347 THE PROGNOSTIC SIGNIFICANCE OF ZNF384 FUSIONS IN ADULT PH-NEGATIVE B CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Novel recurrent fusion gene types such as zinc finger protein 384 (*ZNF384*) fusions have been identified in B-cell precursor acute lymphoblastic leukemia (BCP-ALL) with the application of next-generation sequencing technologies. However, the comprehensive large-scale clinical cohort study for clarifying their prognostic significance remains scarce to date.
Aims: To comprehensively evaluate the prognostic role of *ZNF384* fusions in adult BCP-ALL.
Methods: A total of 242 consecutive adult Ph-negative BCP-ALL patients treated in our institute were retrospectively screened *ZNF384* fusions at diagnosis by multiplex real time quantitative PCR.
Results: *ZNF384* fusions were identified in 47 patients (19.4%), 38 had *EP300-ZNF384*, 5 had *CREBBP-ZNF384*, 2 had *TCF3-ZNF384*, 1 had *TAF15-ZNF384* and 1 had *EWSR1-ZNF384*. All patients with *ZNF384* fusions belonged to B-other ALL (having no high hyperdiploid karyotype, *BCR-ABL1*, *TCF3-PBX1*, *ETV6-RUNX1* or *MLL* rearrangement).

In the whole cohort, patients with *ZNF384* fusions had significantly higher 3-year relapse-free-survival (RFS) and tended to have a higher 3-year overall survival (OS) than those with no *ZNF384* fusions (80.1% vs 52.5%, *P* = 0.011; 67.6% vs 54.0%, *P* = 0.10). For both patients receiving chemotherapy alone and when patients who received allo-HSCT were censored at the time of transplantation (Figure A, B), patients with *ZNF384* fusions had both similar RFS rate and similar OS rate to B-other ALL patients with no *ZNF384* fusions (RFS: P =0.94 and 0.30; OS: P =0.94 and 0.51). Furthermore, for patients receiving chemotherapy alone, patients with *ZNF384* fusions had both similar RFS and similar OS to those with *MLL* rearrangement and *TCF3-PBX1* fusion transcript, respectively (RFS: *P* = 0.45 and 0.13; OS: *P* = 0.80 and 0.45). When patients who received allo-HSCT were censored at the time of transplantation, patients with *ZNF384* fusions had significantly higher 3-year RFS and OS than those with *TCF3-PBX1* fusion transcript (P=0.0093 and 0.0009), and significantly higher 3-year RFS than and similar 3-year OS to those with *MLL* rearrangement (P=0.036 and 0.80). For patients receiving transplantation (Figure C, D), those with *ZNF384* fusions had significantly higher 3-year RFS than B-other ALL patients with no *ZNF384* fusions and their OS were similar (P = 0.022 and 0.24). Furthermore, patients with *ZNF384* fusions had significantly higher 3-year RFS and tended to have significant high OS than those with *MLL* rearrangement and *TCF3-PBX1* fusion transcript, respectively (RFS: *P* = 0.0026 and 0.0038; OS: *P* = 0.062 and 0.065). In addition, *ZNF384* fusion was not an independent prognostic factor for both RFS and OS in both adult Ph-negative BCP-ALL and B-other patients.



Summary/Conclusion: *ZNF384* fusion is common in adult BCP-ALL, which may define a new group from BCP-ALL containing no classical fusion transcript with better prognosis through receiving allo-HSCT.

EP348 ACUTE NEUROLOGICAL ADVERSE EVENTS DURING THE TREATMENT FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

S. Spadini [1,*], A. Di Paola [2], V. Conter [3], C. Rizzari [3], A. Colombini [3], F. Canonico [4], D. Silvestri [5], D. Onofrillo [6], R. Parasole [7], P. Stellato [7], R. Mura [8], E. Barisone [9], S. Cesaro [10], O. Ziino [11], A. Biffi [1], R. Manara [12], M. C. Putti [1]

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Background: In pediatric acute leukemias, balance of treatment results and toxic events has been addressed by the Ponte di Legno Toxicity Working Group (PdLTWG), stressing the need of correct reporting. Acute neurological adverse events (ANAE) on the central nervous system during chemotherapy for Acute Lymphoblastic Leukemia (ALL) are frequent (5,4%), but definitions of clinical and radiological criteria are challenging.
Aims: We collected the ANAE recorded during chemotherapy treatment in children enrolled in ALL AIEOP (Associazione Italiana di Emato-Oncologia Pediatrica) protocols to evaluate their incidence, clinical and radiological characteristics and severity.
Methods: Among patients enrolled in ALL AIEOP protocols, 115 ANAE were reported by 27 Centres from 2009 to 2018. Demographic, hematological and treatment data were obtained from the AIEOP Web database. These CNS ANAE were analyzed: seizures, Posterior Reversible leukoEncephalopathy Syndrome (PRES), Methotrexate Stroke-Like-Syndrome (MTX SLS), depressed level of consciousness (DLC). Vascular, infectious and peripheral ANAE were excluded. When available, MRI performed within 7 days from the NAE and follow-up images were evaluated centrally by two pediatric neuroradiologists blinded to clinical data.
Results: One hundred fifteen ANAE were reported in 113 children. The clinical diagnosis was decided by the reporting center and confirmed centrally, based on reporting details.
The most frequently reported event was PRES (42 patients), which occurred mostly (one third) in high risk leukemia patients and mostly during induction and delayed intensification. Seizures were reported in 25 patients, mostly during induction phase. MTX-SLS occurred in 14 patients, predominantly older ones (median 11 y); almost all these events occurred during consolidation or delayed intensification. ANAE were severe (CTCAE ≥3) in 64% of patients but long-term outcomes were rarely reported (9%). One patient died (0.8%). Stopping or reducing chemotherapy occurred in 36% of patients.
MRI images from 67 events were available for centralized analysis. MRI was unremarkable in 22 cases, mostly patients presenting with seizures (n=17). Abnormal MRI (n=37) outlined three main radiological patterns: PRES (32%); MTX-SLS (22%); non-specific leukopathy (9%). Central evaluation confirmed PRES in 18/19 cases, 1 case was considered MTX-SLS; diagnosis changed from DLC to PRES in 1 case. MTX-SLS were confirmed in 9/13 cases; 4 more cases of MTX-SLS were found, changing the diagnosis from PRES (1 case) and seizure (3 cases). Leukopathy was identified in patients with seizures (n=2), DLC (n=2) and MTX-SLS (n=1). On follow-up scans, 43% of the patients displayed radiological sequelae: cortico-subcortical atrophic changes, leukopathy and in one case hippocampal sclerosis. Sequelae were statistically related (p<0,05) with holo-hemispheric watershed pattern in PRES and with FLAIR hyperintensity in MTX-SLS; their clinical meaning requires further observation.
Summary/Conclusion: This study confirms the need for accurate reporting and centralized clinical and radiological review of ANAE, to allow modulations of chemotherapy on evidence criteria.

EP349 THE EPIDEMIOLOGY, TREATMENT PATTERNS AND SURVIVAL OF ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) IN TAIWAN, 2002-2017

H.-H. Huang [1,*], M.-Y. Lu [2], C.-M. Chen [3], M.-T. Chen [3], H.-M. Chen [4], B.-S. Ko [1,5], F.-Y. Hsiao [3,6,7]

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Background: The clinical features, treatments, and survivals of adult ALL patients are very different from the paediatric ALL patients. In the past decades, tyrosine kinase inhibitors (TKI) demonstrate clinical benefits in *Philadelphia* chromosome-positive ALL patients. Nevertheless, data on the epidemiology, treatment patterns, and survivals of adult ALL patients in the era of TKI are very limited, particularly in the Asia Pacific region.
Aims: The aim of this study was to investigate the incidence, treatment patterns, and survivals of adult ALL patients in Taiwan.
Methods: We conducted a population-based retrospective cohort study and used data from the Taiwan Cancer Registry Database (TCRD), the National Health Insurance Research Database, and the National Death Registry. From the TCRD, we identified patients older than 18 years with newly diagnosed ALL from January 2002 to December 2017. The crude

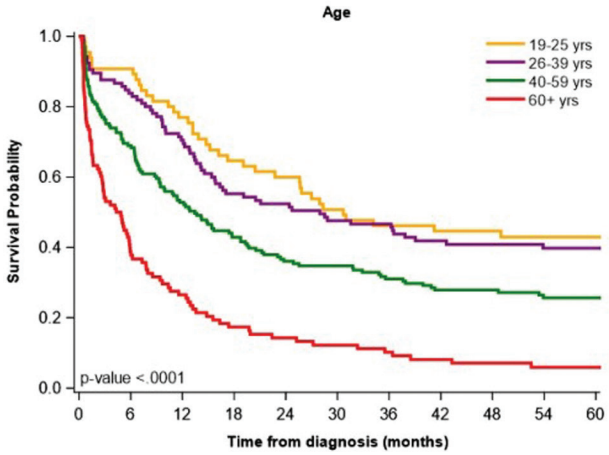
and adjusted annual incident rates of adult ALL were reported. Among all identified adult ALL patients, we further included the patients with newly diagnosed B-ALL from 2009 to 2015 for further analysis of treatment patterns and survivals. We stratified the newly diagnosed B-ALL patients by the use of TKI (TKI-containing treatments or TKI-free treatments). The clinical features, treatment patterns, and clinical outcomes including complete remission rate, refractory rate, and survival of the two groups were reported.

Results: We identified 1800 adult ALL patients between 2002 and 2016. The incidence of adult ALL was 0.69 cases per 100,000 person-years with male predominance. The median age at diagnosis was 44 years old. The incidence rates of adult ALL was highest in the age group of 19-25 and 60+ with 0.8 and 0.88 cases per 100,000 person-years, respectively.

Among 765 adult patients with newly diagnosed B-cell ALL during 2009 and 2015, 429(56.1%) patients received TKI-free treatments, 223(29.2%) patients received TKI-containing treatments, and others did not receive standard chemotherapies. The median age of patients receiving TKI-free treatments and TKI-containing treatments was 46 and 48 years old, respectively. Age is an important prognostic factor in adult B-ALL patients. The median overall survival (mOS) was 37.51, 32.36, 17.59, and 3.56 months in the age groups of 19-25 years, 26-39 years, 40-59 years and 60+ years respectively.

In the TKI-free treatment group, the median time to induction treatment was 7 days. 217 (50.6%) patients achieved complete remission, 40(9.3%) encountered refractory disease, and 172 (40.1%) died within 9 months after the initiation of induction chemotherapy. The median followed up duration was 30.2 months with a cumulative mortality of 74.8%, and 128(29.8%) patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). The mOS was 13.67(95% CI: 11.87-16.33) months in the TKI-free treatment group.

In the TKI-containing treatment group, the median time to induction treatment was 16 days. 210(94.2%) patients received imatinib and 13(5.8%) patients received dasatinib as the first line TKI. The median followed up duration was 36.2 months with a cumulative mortality of 64.6%. 90(40.4%) patients underwent allo-HSCT. The mOS was 26.89 (95% CI: 19.51-33.97) months in the TKI treatment group.



Summary/Conclusion: This study is the first population-based study conducted in Asia providing comprehensive evidence of epidemiology, treatment patterns and survival of adult ALL. Compared with patients receiving TKI-free treatments, patients receiving TKI-containing treatments had better survival and higher proportion of them underwent allo-HSCT.

EP350 CHARACTERISTICS AND OUTCOME OF ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND COVID 19 INFECTION IN THE FIRST VS. SECOND EPIDEMIC WAVE IN SPAIN: A STUDY FROM THE PETHEMA AND GETH GROUPS

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Background: SARS-CoV-2 infection has bimodal distribution in Europe with a 1st wave in March-June 2020 and a 2nd in September 2020-February 2021. In cancer patients (pts) the lethality of COVID-19 infection was 25%>35% in the 1st wave. Comparison on impact of COVID-19 infection in the 1st vs. 2nd waves have not been performed in ALL.

Aims: We compared the frequency, clinical characteristics and outcome of adults with ALL and COVID-19 infection in the 1st vs. 2nd waves in Spain.

Methods: Between March 1, 2020-May 31, 2020, and between September 12, 2020- January 12, 2021 (date of vaccination onset in Spain), a registry from the PETHEMA (Programa Español de Tratamientos en Hematologia) and GETH (Grupo Español de Trasplante Hematopoyético y Terapia Celular) groups prospectively recruited adult ALL pts with COVID-19 infection confirmed by PCR. Demographic and clinical characteristics of ALL and COVID-19 infection, comorbidities, treatment and outcome were collected and compared in the two periods. In addition, prognostic factors for survival were analyzed.

Results: Fifty-six patients were collected in 82 centers contacted, 4 of them being excluded (COVID infection >3 yr. after end of ALL therapy [n=3] and Burkitt lymphoma [n=1]). Twenty-eight pts were collected in the 1st wave and 24 in the 2nd. Median age was 46 (range 20-83), (34 pts [65%] >40 yr). Comorbidities were present in 18 pts (35%). ALL was of B-cell precursors in 38 pts (74%) (Ph+ in 8, 15%). Thirty-one pts (60%) were under frontline treatment, 16 (31%) in rescue, 1 (2%) palliative and 4 (7%) had recently finished the therapy. Eight pts had received allogeneic HSCT (5 of them at COVID-19 infection diagnosis), CAR T (n=1, 2 yr prior to COVID-19 infection) or received immunotherapy (inotuzumab, n=6, 2 at COVID-19 infection, and blinatumomab, n=1, prior to COVID-19 infection). Eleven pts were receiving immunosuppressive drugs at COVID infection (fludarabine in 6, among others).

No significant differences were observed in ALL characteristics in the two COVID-19 waves, except for a significantly higher number of patients on first line therapy in the second wave, and a higher frequency of severe neutropenia and lymphocytopenia in the first wave. COVID19 therapy was different in the two periods, with significantly higher use of hydroxychloroquine, remdesivir and lopinavir-ritonavir in the first wave and corticosteroids in the second wave. No significant differences were observed in need of oxygen support (12 vs. 8 pts), ICU requirement (7 vs. 4 pts), days in ICU (medians 16 vs. 21) and time to COVID infection recovery (medians 17 vs. 13 days). Seventeen patients (33%) died (11 vs. 6), being death attributed to COVID infection in 15 (29%), without significant differences in the 100-day survival probabilities (Figure 1). By multivariable analysis only comorbidities at COVID-19 infection had a negative impact on survival (HR: 5.358 [95% CI: 1.875; 15.313]).

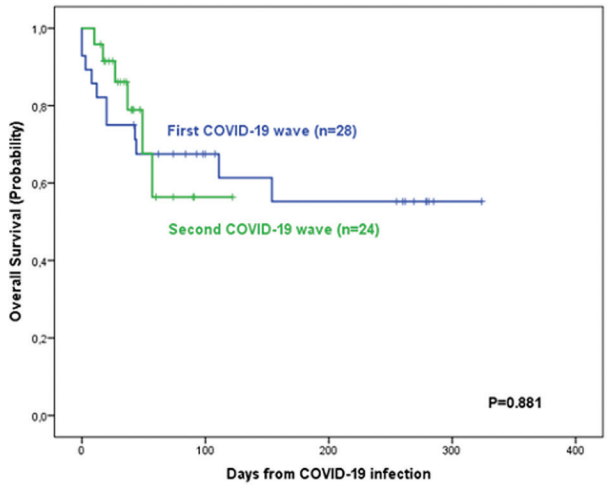


Figure 1. Survival probability of COVID-19 infection according to the period studied.

Summary/Conclusion: COVID-19 infection was frequent in ALL pts, especially in those with advanced age and under ALL frontline or rescue therapy. The frequency of severe COVID-19 infection and mortality were high, with negative impact of comorbidities on survival. No significant differences were observed in ALL characteristics, response to therapy and outcome in the two waves of COVID infection. The poor outcome of COVID infection makes vaccination a priority for ALL patients in this pandemic period.

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EP351 FAVORABLE OUTCOMES AFTER NOVEL THERAPIES FOR RELAPSE/REFRACTORY PHILADELPHIA-LIKE ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Philadelphia-like (Ph-like) acute lymphoblastic leukemia (ALL) is a high-risk disease associated with high rates of persistent minimal residual disease (MRD+) and relapse rate when treated with conventional chemotherapy. Several novel therapies such as blinatumomab (BLINA), inotuzumab (INO), CAR T cell therapy (CAR), and venetoclax-based regimens have shown promising activity in treatment of relapsed/refractory (r/b) B-cell ALL regardless of prior chemo-refractoriness or high-risk genetics; but the impact of Ph-like genotype on response to novel therapies in r/r ALL remains largely unknown.

Aims: Here, we retrospectively analyzed CR/CRi rates in adults with Ph-like ALL who were treated at City of Hope with novel agents from 2013 to 2021.

Methods: To identify the Ph-like status, we utilized our Anchored Multiplex PCR™-based multi-gene NGS assay designed to detect known and novel fusions, and elevated gene expression levels using a proprietary algorithm in ALL.

Results: We identified 67 adult patients with Ph-like ALL treated with 84 novel therapies. The median age was 33 years (range: 18-71) and the majority were males (n=45; 67%) and Hispanics (n=57; 85%). CRLF2r was detected in 49 (73%) patients. BLINA was administered to 43 (64%) and 6 (9%) patients for overt relapsed/refractory (r/r) or persistent MRD+ ALL, respectively. Eighteen patients (27%) received INO, 13 (19%) received CD19CAR and 4 (6%) were treated with venetoclax-navitoclax. Median number of prior lines of therapies were 2, 3, and 4 for patients treated with BLINA, INO, and CAR, respectively. Only one patient who was treated with BLINA received prior INO, while 72% and 6% of patients treated with INO had BLINA and CAR before, and 85% and 38% of patients treated with CAR had BLINA and INO before, respectively.

Complete remission/complete remission with incomplete hematologic recovery (CR/Cri) rates were 64%, 89% and 85% in patients treated with BLINA, INO and CAR, respectively. MRD- rate was 93%, 70%, and 100% in responders who received BLINA, INO, and Car, respectively. Once in CR, 57%, 56% and 55% of responders to BLINA, INO and CAR underwent allogeneic hematopoietic cell transplantation (HCT) consolidation. 12-month relapse-free survival for responders from the time of BLINA, INO and CAR response were 67%, 41% and 75% (p=0.54), respectively. All 6 patients with Ph-like ALL treated with BLINA in MRD setting achieved MRD, of whom 5 received consolidation with HCT; and 3 out of 4 patients treated with venetoclax-navitoclax achieved CR/CRi and only one received HCT afterward.

	Blinatumomab (r/r)	Blinatumomab (MRD)	Inotuzumab	CAR T cell	Venetoclax-Navitoclax
Number	43	6	18	13	4
Median age (range)	36 (18-71)	35 (23-49)	32 (22-71)	25 (19-52)	36 (24-48)
Ph-like subtype					
CRLF2r	29 (67)	4 (67)	14 (78)	10 (77)	4 (100)
Non-CRLF2r	14 (33)	2 (33)	4 (22)	3 (23)	0
Prior alloHCT					
Yes	9 (21)	0	5 (28)	7 (54)	2 (50)
No	34 (79)	6 (100)	13 (72)	6 (46)	2 (50)
Median lines of therapies (range)	2 (0-5)	1 (1-2)	3 (1-6)	4 (2-7)	5 (4-5)
Median BM blast% (range)	69 (5-95)	0.2 (0.01-0.5)	82.5 (15-95)	60 (0.5-85)	50 (0.2-99)
Prior Novel therapy					
Blinatumomab	NA	NA	13 (72)	11 (85)	4 (100)
Inotuzumab	1 (2)	0	NA	5 (38)	4 (100)
CAR T cell	0	0	1 (6)	NA	1 (25)
Venetoclax	0	0	0	2 (15)	NA
CR/CRi; N (%)	28 (65)	6 (100)	16 (89)	11 (85)	3 (75)
MRD-negative response	13/14 (93)	6/6 (100)	7/10 (70)	9/9 (100)	2/3 (67)
Post response alloHCT	16/28 (57)	5/6 (83)	9/16 (56)	6/11 (55)	1/3 (33)

Summary/Conclusion: In conclusion, treatment of r/r Ph-like ALL with novel therapies resulted in excellent CR/CRi and MRD- response rates and successfully transitioned over half of patients to HCT. Response rates to INO and CAR were high despite most patients in these treatment groups had prior treatment with BLINA. Integrating these novel therapies in the frontline setting could improve outcomes of Ph-like ALL and overcome their refractoriness to conventional chemotherapy.

EP352 OUTCOME OF ADULTS WITH REFRACTORY OR RELAPSED (R/R) T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL) INCLUDED IN MINIMAL RESIDUAL DISEASE (MRD)-ORIENTED TRIALS

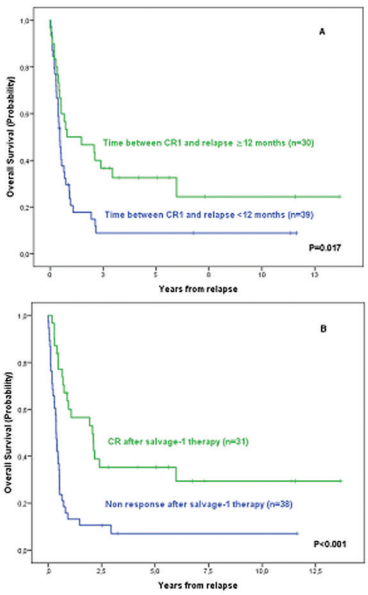
J. M. Ribera [1,*], E.-C. Chapchap [2], M. Morgades [1], E. Genescà [1], P. Montesinos [3], E. Acuña-Cruz [3], C. Gil [4], I. García-Cadenas [5], P. Barba [6], J. González-Campos [7], M.-P. Queipo de Llano [8], A. Torrent [1], T. Bernal [9], M. Díaz-Beyá [10], M.-L. Amigo [11], R. Coll [12], M. Tormo [13], F. Vall-llovera [14], I. Gómez-Centurión [15], J. Ribera [1], M.-J. Sánchez-Sánchez [16], B. Soria [17], A. Cladera [18], M.-T. Artola [19], A. Garcia-Guiñon [20], A. Giménez-Conca [21], M.-L. Amador [22], P. Martínez-Sánchez [23], J.-L. Algarra [24], M.-J. Vidal [25], N. Alonso [26], L. Llorente [27], R. García-Boyero [28], J. Ciudad [29], A. Orfao [29]

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Background: Despite a high complete remission (CR) rate is obtained with frontline therapy, relapses are a frequent event in T-ALL, with limited salvage options to date. Studies on outcome of patients (pts) with R/R T-ALL treated with MRD-oriented therapies are scarce.
Aims: We analyzed the outcome of pts with R/R T-ALL included in two successive MRD-oriented trials (ALL-AR-03 and ALL-HR-11) from the Spanish PETHEMA Group.
Methods: Retrospective study of R/R T-ALL adults diagnosed between 2003 and 2019 and included in the ALL-AR-03 (NCT00853008) and ALL-HR-11 (NCT01540812) protocols. The clinical characteristics at baseline and at relapse, the salvage therapies and outcomes (CR and OS) were analyzed, and a study of prognostic factors for response to rescue regimens and OS was performed.
Results: Seventy-four pts were identified (ALL-HR03 [n=36], ALL HR-11 [n=38], refractory [n=5], and relapsed [n=69]). Median age (range) at diagnosis was 31 (16-58) yrs., 57 were males (77%), with CNS involvement in 9 (12%), mediastinal mass 32 (43%), PB blast count 30.6 x10^9/L (0-284), early T-cell precursor (ETP) 17 (25%), pre-T 11 (16%), cortical 27 (40%), mature 13 (19%), T-unspecified 5. Post-induction-1 MRD level ≥0.1% was found in 13/56 pts (23%), and ≥0.01%: in 20/53 (38%). Fourteen pts (19%) received 2nd induction therapy (resistant disease after induction-1 [n=9], MRD≥0.1% after induction-1 [n=5]). Allogeneic-HSCT was performed in CR1 to 11/69 pts (16%). Interval CR1-relapse: 9.4 (0.1-36.7) months.
Relapse was located in BM (n=29, 42%), BM+extramedullary (n=20, 29%) and extramedullary (n=20, 29%). CNS involvement at relapse was found in 23 pts (33%, isolated in 11 cases). Median number of salvage lineages was 2 (range: 1-5). The most frequent salvage-1 schedules were FLAG-Ida (n=41, 56%), HyperCVAD (n=9, 12%) and nelarabine (n=6, 8%) (other schedules: 18 pts). Second CR was attained in 33/74 pts (44%), being higher for patients treated with FLAG-Ida vs. the remaining regimens (23/41 (56%) vs 10/33 (30%), p=0.026). The CR rate and outcome were not significantly different on comparison of ETP vs. the remaining T-ALL subtypes. Good morphologic and/or MRD response after Induction-1 in first line therapy and salvage treatment with FLAG-IDA were independently associated with CR after salvage therapy (OR: 5.077 [95%CI 1.275-20.218] and 2.879 [95%CI 1.052-7.876], respectively). Allogeneic-HSCT was performed to 35 pts (29 in CR2). Sixty pts died (progression: 34, toxicity of rescue regimens: 15, TRM: 11). Median OS (95%CI) was 6.2 (3.9-8.6) months, with a 5yr OS probability of 18% (9%>27%). By multivariable analysis, only the interval between CR1 and relapse >12 months and CR after salvage-1 therapy emerged as favorable prognostic factors for OS (HR 2.071, 95%CI: 1.185-3.622 and HR 3.227, 95% CI: 1.859-5.780, respectively) (Figure 1 A-B).

Figure 1. Overall survival according to first CR duration (A) and to response to salvage-1 therapy (B).



Summary/Conclusion: This study shows poor outcome of adults with R/R T-ALL, with CR to first salvage therapy of 44% and median OS of 6 months. Good cytological or MRD response to first line therapy and FLAG-Ida rescue therapy were associated with better response to salvage-1 treatment, whereas late relapse and response to salvage-1 regimen were associated with better OS. This study highlights the unmet need for novel effective therapies for T-ALL.
Supported in part by grant 2017 SGR288 (GRC) Generalitat de Catalunya and "La Caixa" Foundation and ISCIII (PI19/01828).

EP353 A REGISTRY-BASED, OBSERVATIONAL SAFETY STUDY OF INOTUZUMAB OZOGAMICIN (INO) IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PROCEEDING TO HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

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Background: InO is a CD22-directed antibody-drug conjugate indicated for treatment of relapsed/refractory (R/R) ALL. InO has been associated with hepatotoxicity and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), particularly post-HSCT.
Aims: To assess toxicity in patients (pts) with ALL who received InO prior to HSCT, utilizing registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR).
Methods: CIBMTR patient data are being collected for a 5-year period after US approval of InO (Aug 2017 – Aug 2022). Data from US pts age ≥18 y treated with InO who proceeded to allogeneic HSCT were included. Using interim data at 3 y, we evaluated post-HSCT outcomes, including clinical status, overall survival, transplant-related (non-relapse) mortality (NRM), relapse, death after relapse (time from HSCT to death after the first 28 d from any cause with prior relapse/progression post-HSCT), and investigator-defined adverse events, including hepatic VOD/SOS. All statistical analyses are descriptive.
Results: Data accrued from 18 Aug 2017 to 17 Aug 2020 for 131 adult pts (median age 40 y) who proceeded to first allogeneic HSCT: 31% in first complete remission (CR1), 46% in CR2, 13% in ≥CR3, 5% in 1st relapse, 2% in ≥3rd relapse, and 3% in primary induction failure. A majority (70%) had transplants from peripheral blood stem cells, and 47% involved an HLA-identical sibling or other related donor. Nearly half received myeloablative conditioning regimens. Before HSCT, 36% of pts received 1 cycle of InO, 46% had 2 cycles, and 17% had ≥3 cycles. Half (48%) received InO as a single agent. Median time from last dose of InO to HSCT was 2.0 mos (range: 0.4–26.2). At the time of data lock (11 Nov 2020), post-transplant data were available for 131 pts. Outcomes for these pts are shown in the Table. Among a subgroup of adults with active R/R ALL (n=91) at the time of HSCT (median of 4 lines of prior therapy), VOD/SOS incidence within 100 d of HSCT was 18%.

	Adults (n=131)
VOD/SOS within 100 d post-HSCT, n (%)	17 (13)
Post-HSCT continued complete remission (CR)*, n (%)	117 (89)
Post-HSCT overall survival, 12 mo, % (95% CI)	55 (45–65)
HSCT-related mortality (NRM), 12 mo, % (95% CI)	21 (14–29)
Post relapse mortality, 12 mo, % (95% CI)	25 (17–33)
Post-HSCT relapse, 12 mo, % (95% CI)	36 (27–45)

*Continued CR is defined as a patient who underwent HSCT during CR, and the CR is sustained post-HSCT

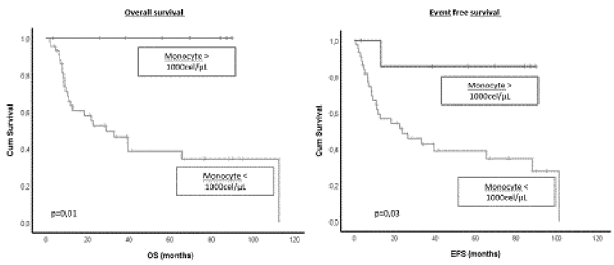
Summary/Conclusion: Incidence of VOD/SOS after first HSCT in InO-treated pts with R/R ALL in this study was similar to the 18-19% reported in pooled analyses of 2 clinical trials among InO-treated pts with R/R ALL (Marks et al, *Biol Blood Marrow Transplant* 2019) and in the INOVATE study (Kantarjian et al, *Lancet Haematol* 2017). The NRM at 1 y of 21% (23% R/R ALL) is lower than the NRM at 1 y of 38% reported in the pooled analyses of R/R ALL InO recipients.

EP354 POST INDUCTION MONOCYTOSIS IS ASSOCIATED WITH HIGHER PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA/ LYMPHOBLASTIC LYMPHOMA PATIENTS

A. Vagos Mata [1,*], J. Medeiros [1], E. Espada [1,2], H. Martins [1], C. Lopes [1], M. J. Costa [1], G. Esteves [1], J. Forjaz Lacerda [1,2,3], J. Raposo [1]

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Background: Unlike paediatric patients, adult ALL/LL patients face lower cure rates of about 40-50%.[1] Certain cytogenetic abnormalities and advanced age are well accepted prognostic factors, as well as the presence of minimal residual disease.[2] However, little is known about ALL/LL microenvironment and its impact on response to treatment and incidence of relapse. Monocytes are cells of the innate immune system that play an important role in cancer development. Different subsets of monocytes have been linked both to pro and anti-tumoral immunity.[3] Recent work showed that a high monocyte count at diagnosis was associated with higher mortality and relapse rate on B ALL patients, suggesting a protective role on tumour cell survival.[4] On the other hand, a normal monocyte count at first relapse have showed a benefit on overall survival (OS).[5]There is still uncertainty about the significance of monocytes on other time points of the disease course and what role they play on tumour cell survival at each moment.
Aims: To evaluate the prognostic significance of post induction monocyte count in ALL/LL adult patients.
Methods: Single centre, retrospective study of ALL/LL patients diagnosed between 2011-2020. Blood monocyte count at the time of response to induction assessment was correlated with OS and event free survival (EFS). Kaplan-Meier curves and log-rank test were used for comparison of OS and EFS. Univariate and multivariate Cox proportional hazard models were used for investigating factors associated with OS.
Results: Sixty-eight patients were included, 61.8% were male, median age of 46 years (IQR 24-64). Most patients (58) were diagnosed with ALL, 79.3% of B lineage and CD20+ in 26.9%. LL was diagnosed in 10 patients, 8 of T lineage. 21 patients had t(9;22), hyperdiploid karyotype was present in 6 patients, 2 patients had t(1;19) and 1 had complex karyotype. 7% of patients had CNS disease at diagnosis.
Most patients (70.6%) were treated with high intensity protocols, either HyperCVAD or DFCI-11001. The remaining patients were unfit for this approach and were treated with age-adjusted protocols. Response to induction was assessed in 52 patients, 85.5% of which were in complete response after induction.
OS and EFS were analysed according to monocyte count >1000cel/µL after induction. No significant differences on patient and disease characteristics were found between the two groups. At median follow up (FU) (10.5 months), OS and EFS were significantly higher in patients with >1000 monocytes/µL after induction: OS of 100% vs 68.5%, p=0.01; EFS of 85.7% vs 67%, p=0.03. In univariate analysis, blood monocyte count as a continuous variable had impact on OS (HR 0.99, 95% CI 0.997-1.00, p=0.018). This impact persisted in multivariate analysis against covariates hyperleukocytosis at diagnosis and age (HR 0.998, 95% CI 0.997-0.999, p=0.014). Of note, none of the patients with >1000 monocytes/µL after induction died so far and only one relapsed, with a median FU of 63 months in this subgroup.



Summary/Conclusion: Higher monocyte counts after induction were associated with higher OS and EFS. Interestingly, of all patients who had monocytosis after induction, only one relapsed, and all remain alive. These findings may represent a shift to an anti-tumoral monocyte phenotype and may be surrogate markers for bone marrow recovery and better disease control. To address these specific questions, prospective and translational studies are needed. Nevertheless, to the best of our knowledge, this is the first study on the impact of monocyte recovery after induction therapy concerning patients with B an T phenotype ALL/LL.

EP355 VORICONAZOLE PROPHYLAXIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Despite improvements in diagnosis and management, invasive fungal infections (IFIs) remain a major cause of morbidity and mortality in children receiving chemotherapy. Therefore, primary antifungal prophylaxis (PAP) has been recommended for patients treated in centers with a high incidence of IFI.
Aims: The aims of this study were to determine the effects of PAP on incidence, morbidity and mortality in children with acute lymphoblastic leukemia (ALL) and to compare those results with the historical study.
Methods: Children with ALL who were diagnosed before 31th January 2013, did not receive any primary antifungal prophylaxis (NoP Group), the patients who were diagnosed ALL between 1st February 2013 and 31st Jan 2020 received voriconazole (VCZ) as PAP(AFP Group).
PAP was started following the first occurrence of neutropenia after the diagnosis of ALL. VCZ was given 2x 9 mg/kg/ day per orally. If the patients had febrile neutropenia VCZ was switched to intravenous route. Because of the interaction of the drugs, during induction and reinduction phases of chemotherapy protocol patients did not receive VCZ on the days when they were given vincristine (7th, 15th, 22nd and 29th days of induction and reinduction phases). Additionally, patients who were stratified in the high risk group didn't receive VCZ during HR Blocks for the same reason. They were given liposomal amphotericin B at the dose of 3 mg/ kg/ day during HR block therapies.
The medical records of the children with ALL who were diagnosed after February 2013, were retrospectively reviewed. The chart review of the patients who underwent PAP and developed a proven or probable IFI according to EORTC (as in historical study) was completed.
Results: During the study period 166 children were diagnosed ALL and received PAP together with chemotherapy. Twenty-three patients (13.9%) with a mean age of 98.6 months (6.8- 206.0) were determined and male to female ratio was 9/14. The proven and probable IFI incidence was (13.9%) which was less than previous study (24%). Seventeen (73.9%) of 23 episodes were defined as proven IFI and 6 (26.1%) episodes were defined as probable IFI. The proven IFI incidence was similar to previous study (10.2% *vs.* 14.6%). However, there was a decline in probable IFI incidence (3.6% *vs*.10.4%). The majority of proven IFIs were candidemia (15/17;88.2%), one episode was caused by *Rhizopus* spp. (1/17;5.8%) as previous report and one episode was caused by *Fusarium* spp. (1/17;5.8%). Seventeen patients (73.9%) were neutropenic (<500/ mm^3) at the time of IFI diagnosis. None of the children developed major adverse events due to voriconazole that could lead discontinuation of voriconazole. Attributable mortality and crude mortality was 4.3%.
Summary/Conclusion: Primary prophylaxis has been recommended for centers with a high incidence of IFI. This study showed dramatically decline in probable IFI episodes those were commonly caused by a mold. In our study, the majority of proven IFI episode were due to Candida spp. one of the proven IFI episode was casued by *Rhizopus* and the other one was caused by *Fusarium* spp. Breakthrough Mucor infections under voriconazole prophylaxis had been well described. However, there was no increase in the incidence of *Mucorales* spp. caused infections. In conclusion, voriconazole was well tolerated and had effects on the incidence of mold infections. However, significant effect was not observed in the incidence of yeast infections.

EP356 HAPLOIDENTICAL TRANSPLANT HAS SUPERIOR GRAFT-VERSUS-LEUKEMIA EFFECT THAN HLA-MATCHED SIBLING TRANSPLANT FOR PH- HIGH-RISK B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

M. Fan [1,*], Y. Wang [2], R. Lin [1], T. Lin [1], F. Huang [1], Z. Fan [1], Y. Xu [3], T. Yang [4], N. Xu [1], P. Shi [1], D. Nie [5], D. Lin [6], Z. Jiang [7], S. Wang [8], J. Sun [1], X. Huang [2], Q. Liu [1], L. Xuan [1]

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Background: Compared with HLA-matched sibling donor (MSD) transplantation, whether haploidentical donor (HID) transplantation has superior graft-versus-leukemia (GVL) effect for Philadelphia-negative (Ph-) high-risk B-cell acute lymphoblastic leukemia (B-ALL) remains unclear.
Aims: This study aimed to compare the GVL effect between HID and MSD for Ph- high-risk B-ALL.
Methods: This study population came from two prospective multicenter trials (NCT01883180, NCT02673008). Immunosuppressant withdrawal, prophylactic or preemptive donor lymphocyte infusion (DLI) was administered in patients without active graft-versus-host disease (GVHD) for preventing relapse. All patients with measurable residual disease positive post-transplantation (post-MRD+) or non-remission pre-transplantation received prophylactic/ preemptive interventions. The primary endpoint was the incidence of post-MRD+.
Results: A total of 335 patients with Ph- high-risk B-ALL were enrolled, including 145 in HID and 190 in MSD group. The 3-year cumulative incidence of post-MRD+ was 27.2% (95% CI: 20.2-34.7%) and 42.6% (35.5-49.6%) in the HID and MSD groups (P=0.003). A total of 156 patients received DLI, including 60 (41.4%) in HID and 96 (50.5%) in MSD group (P=0.096). The 3-year relapse rate was 18.6% (95% CI: 12.7-25.4%) and 25.9% (19.9-32.3%; P=0.116) in the two groups. The 3-year overall survival was 67.4% (95% CI: 59.1-74.4%) and 61.6% (54.2-68.1%; P=0.382), leukemia-free survival was 63.4% (95% CI: 55.0-70.7%) and 58.2% (50.8-64.9%; P=0.429), and GVHD-free/ relapse-free survival was 51.7% (95% CI: 43.3-59.5%) and 37.8% (30.9-44.6%; P=0.041), respectively, in the HID and MSD groups.
Summary/Conclusion: HID transplantation has lower incidence of post-MRD+ than MSD transplantation, suggesting HID might have superior GVL effect than MSD for Ph- high-risk B-ALL patients.

EP357 VENETOCLAX PLUS DECITABINE IN THE TREATMENT OF MRD-PERSISTENT AND RELAPSED/REFRACTORY T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: The outcome of relapsed/refractory T-cell acute lymphoblastic leukemia (ALL) is dismal. The only evaluable effective, though quite toxic, therapeutic option is Nelarabine combinations followed by allogeneic HSCT (allo-HSCT). Recent preclinical studies and few case reports suggested that inhibition of antiapoptotic protein BCL-2 could be effective in T-cell ALL and this effect could be potentiated by hypomethylating agents.
Aims: We have conducted a small pilot study aiming to evaluate the efficacy of venetoclax with decitabine in the treatment of MRD persistent and relapsed/refractory T-cell ALL patients (pts) included in the RALL-2016 study (NCT01193933).
Methods: Since February 2019 till January 2021 seven T-ALL pts were included: 5 m, 2 f, median age 32 (range 19-39) yy. Two pts (ETP-TI-ALL and T-III ALL) had persisting MRD at day +133/+190 of the study, 3 had overt relapses (1 ETP-ALL, 1 T-I/II ALL, 1 T-II ALL), two – refractory (1 TII-ALL, 1 T/B ALL). Three pts (42%) had a complex karyotype, one (14%) – deletion in chromosome 17p [del(17p)]. All pts were monitored for MRD by MFC. Decitabine 20 mg/m2 was infused i.v. for 5 days, Venetoclax was used 400 mg by mouth daily in 28 day cycles. Two pts (29%) had second relapse after previous Nelarabine exposure followed by allo-HSCT.
Results: All of the 5 pts with relapse/primary refractory T-cell ALL achieved complete remission, 4 (80%) of them reached MRD-negativity. Both pts with MRD persistence achieved MRD negativity. The median time to remission was 0.9 month (range 0.7 – 2.1 months). Six pts (86%) underwent subsequent allo-HSCT, for one of them it was the second allo-HSCT. One patient is awaiting for allo-HSCT. The median follow-up since the start of venetoclax was 9,5 months (range 1,6 – 18,8). Three pts are alive (43%), 4 died (57%), and the 1-year OS in the whole cohort was 20% (Figure 1a). In total, 3 of the 7 pts had relapsed, and the median DFS was 7.3 months (0,6 – 15,14). The 1-year DFS was 27,8% (Figure 2b).

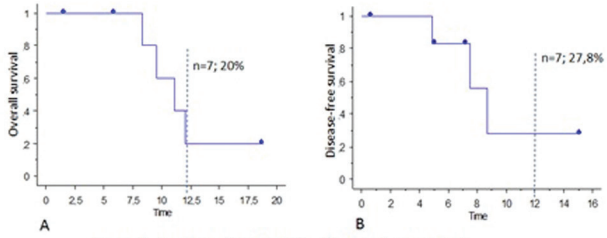


Figure 1. A – Overall survival, B – Disease-free survival

Summary/Conclusion: Though very small our study has demonstrated high efficacy (six out of seven deep responses) with low toxicity in the extremely poor prognostic group of pts. Though the responses are short and relapses occurred even after allo-HSCT. It could be supposed that the pts need after allo-transplant treatment with the same Ven+Dac combination.

EP358 PROGNOSTIC FACTORS IN INFANTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND 11Q23/KMT2A REARRANGEMENTS ENROLLED IN MLL-BABY TRIAL

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Background: Many attempts have been made worldwide to improve a prognosis of infants, with 11q23/*KMT2A*-rearranged acute lymphoblastic leukemia (*KMT2A*-r ALL). However, currently treatment outcome in infants with ALL is worse in comparison to older children.
Aims: To evaluate various prognostic factors (excluding MRD) in infant *KMT2A*-r B-cell precursor ALL enrolled in Russian-Belarus multicenter trial MLL-Baby
Methods: The study cohort comprised 100 consecutive infants aged 0–365 days with newly diagnosed *KMT2A*-r ALL enrolled between September 2003 and April 2016 (follow-up updated in January 2021). Among them there were 36 (36%) boys and 64 (64%) girls. Infants with translocation t(4;11)(q21;q23) were allocated to the high-risk (HR) arm, while all other *KMTA2*-r ALL patients who achieved complete remission (CR) by the end of induction (EOI) were treated by Intermediate-risk (ImR) arm. Only 2 of 100 patients were transplanted. EFS was estimated according to the Kaplan–Meier method [with Greenwood standard error (SE)], and differences between groups were compared using the log-rank test. The cumulative incidence of relapse (CIR) was estimated after adjusting for competing risks of other events and compared with the Gray test. Analysis of the prognostic relevance of various clinical and laboratory parameters was performed using the Cox model on the cause-specific hazard of event and the Wald test. Informed consent was obtained in all cases.
Results: EFS in the ImR group (n=50) of MLL-Baby trial was 35.1±6.9%, in the HR group (n=50) 38.3±7.1% (p=0.941). Patients older than 6 months (n=38) had better, but not statistically significant outcome (EFS 45.5±8,4%, CIR 43.3±8,7%) compared to younger than 6 mo infants (n=62) (EFS 31.2±6,0%, CIR 54.9±6,8%) (p=0.132 and p=0.245, correspondingly). Among various *KMT2A* rearrangements the most unfavorable prognosis had infants with translocation t(9;11)/ *KMT2A-MLLT3*: EFS 18.8±9.8%, CIR 75.0±9.7%. Intermediate results were obtained in patients

with translocations t(4;11)/*KMT2A–AFF1* and t(11;19)/*KMT2A-MLLT1:* EFS 36.9±7,2% and 32,7±10.4%, respectively; CIR 46.3±7.8% and 50.9±12.3%. The most favorable treatment outcome was achieved in infants carrying translocation t(10;11)(p12;q23)/*KMT2A-MLLT10:* EFS 83.3±15.2%, CIR 0,0%. CD10-negative immunophenotype (n=72) neither influenced on outcome (p=0.897) nor on relapse risk (p=0.350). Initial CNS involvement led to lower EFS (p=0.007) and higher CIR (p=0.001) in comparison to patients without CNS leukemia. Dexamethasone good response on day 8 (n=82) was not associated with better treatment outcome (p=0.060 for EFS and p=0.332 for CIR). Alternatively, M1 status of BM on day 15 (n=72) improved both EFS (p=0.016) and CIR (p=0.002). So CR achievement on day 36 (n=97) did (p=0.001 for EFS). Multivariate analysis of hazard on unfavorable event showed that unfavorable outcome of *KMT2A*-rearranged infant ALL was associated with initial CNS involvement (n=44) (p=0.020), initial white blood cell count higher than 300×10^9/L (n=26) (p=0.028), M2/M3 bone marrow status on day 15 (p=0.012) and presence of translocation t(11;19)/*KMT2A-MLLT1* (p=0.012). EOI CR achievement (n=97) had borderline significance (p=0.051).

Summary/Conclusion: Our data revealed several prognostic factors that led to unfavorable outcome in infants with *KMT2A*-r ALL enrolled in MLL-Baby trial. We did not include MRD in this analysis as we previously showed its prognostic value (G. Tsaur et al doi.org/10.1111/bjh.17304).

EP359 IMPROVED LONG-TERM SURVIVAL AFTER ALLOGENEIC TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS: A DANISH POPULATION-BASED STUDY

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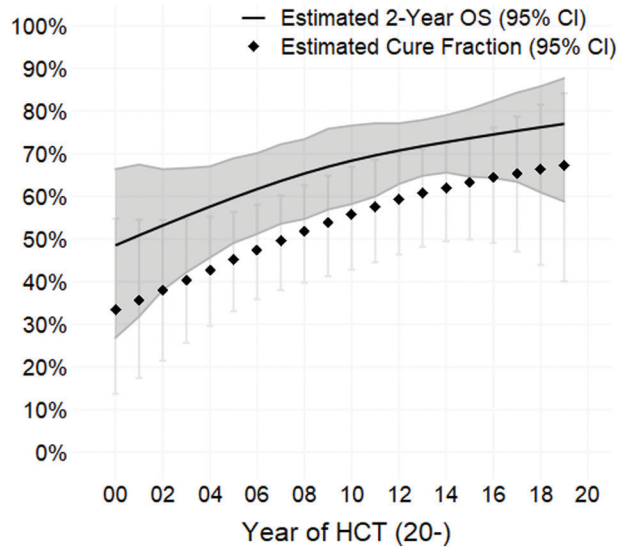
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Background: Survival after allogeneic hematopoietic cell transplantation (HCT) of high-risk acute lymphoblastic leukemia (ALL) is challenged by high risk of relapse and non-relapse mortality (NRM) due to conditioning toxicity or graft-versus-host disease (GvHD).

Aims: We aimed to investigate temporal trends of survival in a nationwide population-based cohort study of adults (≥18 years) who received HCT for ALL in Denmark between 2000–2019.

Methods: Indications for HCT comprised high-risk ALL (including Philadelphia chromosome positive [Ph+] ALL) or ALL in >1st complete remission (CR). From 2011, non-myeloablative HCT was perfomed for patients >50 years or with comorbidities, and from 2012, Ph+ patients received a tyrosine kinase inhibitor one year post-HCT. Temporal trends in overall survival (OS) were examined in a Royston–Parmar survival model. A non-mixture cure model was used to estimate temporal trends in short- and long-term survival, respectively (long-term survival estimated as the cure fraction, i.e. the fraction of patients who experienced no excess mortality compared to the Danish general population matched on calendar year, age and sex). Hazard ratios (HR) of relapse and NRM were estimated in cause-specific Cox models. Cumulative incidences of HCT outcomes were calculated by the Aalen-Johansen method and compared between patients transplanted in the earliest vs. latest quartile (years 2000–2005 vs. 2016–2019).

Results: From 2000 to 2019, 181 adults were transplanted for ALL in Denmark; 83% with B-cell, 17% with T-cell and 31% with Ph+ ALL. Median (min–max) age at transplant was 36 (18–74) years. Most patients (72%) were transplanted in CR1, and the median time from diagnosis to transplant was 7 months. The most common regimen was myeloablative (84%) transplant (Eto- or CyTBI) with a matched unrelated donor (56%). In later time periods, more patients were transplanted in CR1 and with non-myeloablative conditioning, while the proportion of patients with Ph+ ALL was constant. At a median follow-up of 8.1 years, 77 (43%) patients had died. The 2- and 5-year Kaplan–Meier OS (95% CI) were 69% (63%, 76%) and 62% (55%, 70%) in the entire cohort. OS increased with year of HCT (p = 0.03) with an estimated 2-year OS (95% CI) of 49% (27%, 66%) in patients transplanted in year 2000 vs. 77% (59%, 88%) in 2019 (Figure). The estimated cure fraction increased over time (odds ratio for cure per calendar year increase: 1.08; 95% CI: 1.01, 1.15; p = 0.03), whereas the short-term excess hazard of dying did not change significantly (HR per calendar year: 1.00; 95% CI: 0.93, 1.07; p = 0.97). This was reflected in the decreased risk of relapse over time (HR 0.92 per calendar year; 95% CI: 0.87, 0.98, p = 0.01; 2-year cumulative incidence in years 2000–2005: 26% [95% CI: 12%, 39%] vs. 12% [95% CI: 3%, 21%] in years 2016–2019), and the stable risk of NRM (HR 0.98 per calendar year; 95% CI: 0.93, 1.04, p = 0.49; 2-year cumulative incidence in years 2000–2005: 21% [95% CI: 9%, 33%] vs. 16% [95% CI: 6%, 26%] in years 2016–2019). The incidence of GvHD did not change markedly over time (grade II–IV acute GvHD: 35% [95% CI: 20%, 49%] in years 2000–2005 vs. 37% [95% CI: 24%, 51%] in years 2016–2019; chronic GvHD at 2 years: 40% [95% CI: 25%, 54%] in years 2000–2005 vs. 51% [95% CI: 37%, 65%] in years 2016–2019).



Summary/Conclusion: In a nationwide cohort study of HCT-treated ALL-patients, we found an improved long-term survival from 2000 to 2019, likely because of decreased relapse rates over time as NRM and short-term survival remained stable.

EP360 TWO CONSECUTIVE MULTICENTER RUSSIAN ACUTE LYMPHOBLASTIC LEUKEMIA (RALL) STUDIES IN PH-NEGATIVE ADULT ALL: SUCCESSES AND PITFALLS

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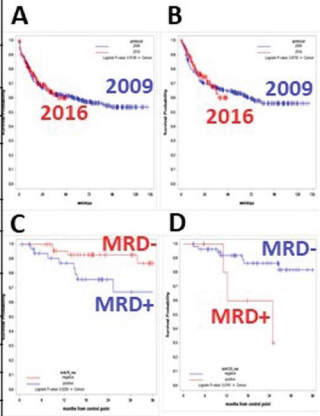
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Background: Since 2009 RALL-study group has conducted two clinical multicenter trials on the treatment of adult patients with Ph-negative ALL. The majority of adult ALL studies are highly intensive with substantial numbers of allogeneic HSCT in 1CR and tailor their treatment according to MRD levels after the induction phase. RALL studies were based on the non-intensive, but non-interruptive approach without high dose consolidations and without many allo-HSCTs but with autologous HSCT for T-cell ALL as late consolidation. Pregnant women were included in both trials. MRD measurement was carried out only in the second RALL-2016 study.
Aims: to present the comparison of long-term results of both studies and evaluate the impact of MRD measurement in RALL-2016.
Methods: From Jan, 2009, till Dec, 2016, 30 centers had enrolled 330 and since Dec 2016 till Jan 2021, 10 centers included 207 acute Ph-negative lymphoblastic leukemia patients. The main trials characteristics are presented in Table 1. There were no difference between two trials in numbers of autologous HSCTs for T-ALL (42/125 (33%) pts in RALL-2009 and 23/85 (27%) in RALL-2016); no difference in numbers of allo-HSCTs in 1CR (19/281 (6,8%) in RALL-2009 and 19/170 (11,2%) in RALL-2016). But the total number of allo-HSCTs was somewhat higher in RALL-2016: 21/305 (6,9%) in RALL-2009 and 25/186 (13,5%), p=0,02).
Results: Two trials look quite similar in main characteristics, though pts in RALL-2016 were older. Both trials have demonstrated identical stable results with optimistic long-term outcome (Pic.1. A,B). High early death rate (~10%) remains an obstacle that decreases CR rate and overall survival especially in Regional centers. MRD-positivity discriminated BCP-ALL patients at day+70 (Pic.1C) and T-ALL patients at day +133 (Pic.1D) to a poor prognostic group.

Table 1

	RALL-2009, n=330	RALL-2016, n=207	p, χ^2
m/f	m-182 (55%) f-148 (45%)	m-133 (64%) f-74 (36%)	0.037
Age	28 (15-55)	32.5 (18-55)	0.0003
BCP-ALL T-ALL biphenotypic unknown	195 (59%) 125 (38%) 4 (1%) 6 (2%)	112 (54%) 85 (41%) 9 (4.5%) 1 (0.5%)	0.0506
L x10^9/l, median, range	13.2 (0.4-899)	12.13 (0.66-833.94)	0.89
L>30x10^9/l, BCP-ALL,	48 (27%)	22 (20%)	0.24
L>100 x10^9/l, T-ALL,	50 (42%)	43 (53%)	0,12
Cytogenetics was done Normal karyotype t(4;11)	193 89 (46%) 9	168 71 (42%) 7	0.74
LDH, IU, >2N <2N	169 (58%) 122 (42%)	114 (60%) 76 (40%)	0.67
Pregnancy at time of diagnosis	15 (4,5%)	8 (3,9%)	0.34
Early death (during induction)	25 (8%)	21 (10%)	0.3
Late CR (on day 70)	27 (10%) of 281 CR	19 (11%) of 170 CR	0.59
MRD+ on day 70, n,%	NA	57 / 161 (35%)	
MRD+ on day 133, n, %	NA	23 / 140 (23%)	
Site of treatment: Academical centers Regional Centers	142 (43%) 188 (57%)	89 (43%) 118 (57%)	0.99

Picture 1. Overall survival according to the study (A). Disease free survival according to the study (B). Disease-free survival according MRD on day +70 for BCP-ALL (C). Disease-free survival according MRD on day +133 for T-ALL (D).



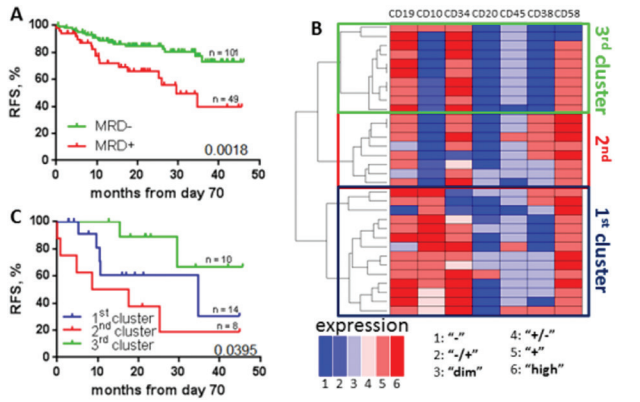
Summary/Conclusion: It was shown that disregard the absence of high-dose consolidations with high-dose methotrexate/ARA-C and low numbers of allo-HSCT in 1CR, both trials had demonstrated stable, high and reproducible results regarding overall and disease-free survival. In our setting MRD-positivity at day+70 for BCP-ALL and at day 133+ for T-ALL identifies patients that need different approach aimed to early MRD treatment with targeting drugs followed by allo-HSCT.

EP361 IMMUNOPHENOTYPE OF RESIDUAL BLASTS, NOT ONLY MRD-POSITIVITY, DOES MATTER IN LONG-TERM PROGNOSIS OF B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Measurable residual disease (MRD) is an independent prognostic factor in numerous acute lymphoblastic leukemia (ALL) studies. An unfavorable outcome may be dependent not only on the persistence of MRD, but on immunophenotype of residual blasts too. Immunophenotype could reflect the biology of tumor cells, especially their genetics (Gupta N. et al., 2019).
Aims: The aim was to investigate a significance of MRD and immunophenotype of residual blasts at the end of induction in Russian treatment protocol RALL-2016.
Methods: The multicenter study RALL-2016 (NCT03462095) included 207 adult patients from 2016 to 2020 years. The MRD was assessed at the end of induction (day 70) in 150 patients (80 patients with B-ALL and 70 patients with T-ALL) who achieved a complete remission. Analysis of MRD was performed in the bone marrow samples by flow cytometer instruments FACSCanto II (Becton Dickinson) or CytoFLEX (Beckman Coulter). The sensitivity was at least 0.01%. Seven basic antigens (CD19, CD34, CD10, CD20, CD38, CD45 and CD58) were analyzed to detect MRD and were used to describe the immunophenotype of residual blasts in B-ALL at day 70. The relative expression of these antigens was determined compared to normal cells of bone marrow (Dworzak M.N. et al., 2017) and translated into numerical equivalent as it was described earlier (Davydova Y. et al, HemaSpere – materials of EHA 2020). A dendrogram was constructed using the "ward.D2" method in R 3.4.4. The probability of relapse-free survival (RFS) was estimated with the Kaplan–Meier method, and comparisons were assessed using the log-rank test. A $p < 0.05$ was considered significant.
Results: At the end of induction 101 (67.3%) patients (48 B-ALL, and 53 T-ALL) were MRD-negative, and 49 (32.7%) patients (32 B-ALL, and 17 T-ALL) remained residual blasts. RFS was higher in MRD-negative than in MRD-positive patients (median undefined vs 29.5 months, p=0.002) in whole ALL cohort (fig. A). Analyzing B-ALL cohort, the RFS was depended on MRD (median undefined vs 29.5 months, p=0.004), but in T-ALL MRD was not significant (medians undefined, p=0.25).
Cluster analysis revealed 3 clusters in B-ALL MRD based on immunophenotype of residual blasts (fig. B). The 1st cluster (n=14) included cases with presence of CD10 while 2nd (n=8), and 3rd (n=10) clusters included CD10-negative cases. The expression of CD38, and CD58 was higher in 2nd than in 3rd cluster.
RFS probability differed in these 3 clusters: medians were 34.7 months, 13.1 months, and undefined in 1st, 2nd, and 3rd clusters, respectively (p=0.04) (Fig.C).



Summary/Conclusion: MRD measured by flow cytometry at the end of induction was confirmed as an important prognostic factor in RALL-2016 protocol among B-ALL patients. Immunophenotype of residual blasts was in association with the RFS. The most unfavorable prognosis was in cases that lack CD10 expression but have relatively high expression of CD58, and CD38.

EP362 PEG ASPARAGINASE INDUCED SEVERE HYPERTRIGLYCERIDEMIA IN ADULTS ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH PEDIATRIC-INSPIRED REGIMEN: IS IT SAFE TO RECHALLENGE THESE PATIENTS?

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Background: PEG-asparaginase, a long-acting formulation of L-asparaginase, is used as part of treatment protocols for Philadelphia negative acute lymphoblastic leukemia (ALL). In pediatric studies,

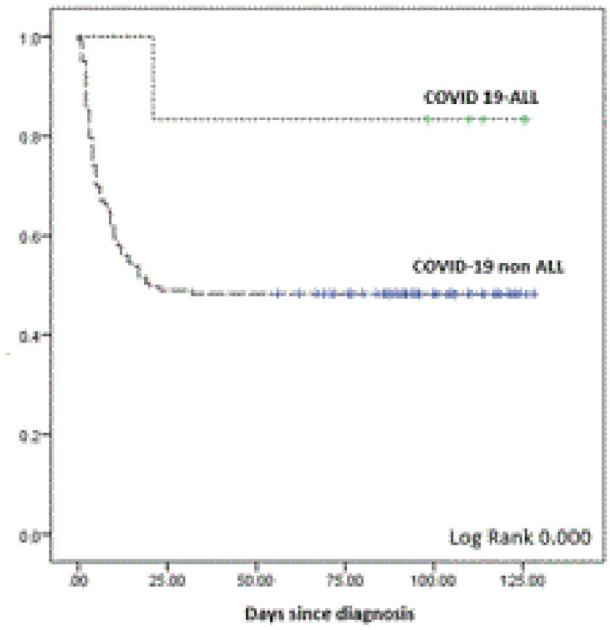
triglycerides were more affected by PEG asparaginase compared to native L-asparaginase (10.0% vs 5.5%). Using PEG asparaginase for ALL was associated with a higher incidence of hypertriglyceridemia up to 50% in adult patients. The clinical significance of this and if re-challenging these patients is safe or not is not clear.
Aims: We sought to determine the safety of re-challenging adult patients with PEG asparaginase after experiencing an episode of severe hypertriglyceridemia (> 1000mg/dl or 11.4mmol/L).
Methods: At Princess Margaret Cancer Center, we recently switched from native E. coli asparaginase to PEG asparaginase using modified pediatric Dana Farber Cancer Institute (DFCI) protocols. 46 consecutive adult patients received PEG-asparaginase as part of DFCI protocol for first-line treatment of Philadelphia negative ALL between February 2020 and December 2020. We analyzed the incidence of hypertriglyceridemia and their subsequent outcomes.
Results: The median age of the patients was 38 years, and 17 (36.9%) were female. 11 patients out of 46 (23.9%) have elevated triglycerides with levels above 2.2mmol/L. Elevated triglycerides occurred a median of 2 weeks after initial treatment; 4 out of 46 patients had severe hypertriglyceridemia with levels above 11.4 mmol/L (8.7%). The management of these patients was supportive in the form of a low-fat diet, hydration and fenofibrate or gemfibrozil. Their next treatment cycle with PEG-asparaginase was delayed by two weeks on average (range 1-3) until normalizing their triglycerides level. None of these patients required plasmapheresis or insulin infusion as a treatment for hypertriglyceridemia. Only one of 11 patients (9%) developed acute pancreatitis after the second cycle of intensification; he had severe hypertriglyceridemia with the first intensification cycle and proceeded to the next cycle before normalizing the triglyceride. This patient did not re-challenge subsequently with PEG-asparaginase. The remaining ten patients were re-challenged after dropping triglyceride levels without developing pancreatitis. Among the 4 patients with severe hypertriglyceridemia, two completed their intensification phase therapy with PEG asparaginase. One patient continues to receive PEG asparaginase as part of the intensification treatment and one patient was not re-challenged as he developed acute pancreatitis as mentioned above.
Three patients with severe hypertriglyceridemia were noted to have high anion gap metabolic acidosis with hypobicarbonatemia and or hyperammonemia. This was normal on repeat testing using venous blood gas and testing with an alternative device for ammonia. The evaluation revealed that the low bicarbonate level was fictitious and was related to lipemic serum.
Summary/Conclusion: With moving from native asparaginase to PEG asparaginase in adult patients with ALL, hypertriglyceridemia incidence was high. Checking triglycerides at baseline and monitoring levels while receiving PEG asparaginase is needed to safely receive their treatment on subsequent cycles after the initial PEG asparaginase exposure. In patients with hypertriglyceridemia not complicated by acute pancreatitis, re-challenging these patients who did not have pancreatitis is safe once the triglycerides level normalizes.

EP363 ACUTE LYMPHOBLASTIC LEUKEMIA AND SARS-COV-2, RESPONSE TO TREATMENT AND SPONTANEOUS REMISSIONS. EXPERIENCE OF TWO COVID-19 HOSPITALS IN MEXICO CITY.

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Background: From the end of December 2019, the new beta coronavirus named COVID-19 has significantly affected the greater number of countries in the world. The major part of the recommendations for the treatment of ALL in the era of COVID-19 includes delaying as long as possible chemotherapy, except in cases of high risk of complications or disease progression. In Mexico, the number of cases of leukemia has diminished due to hospital conversion such as limited access to treatments. The object of this study was to describe the cases with *de novo* acute lymphoblastic leukemia in two institutions assigned as COVID-19 hospitals in Mexico City
Aims: Describe patients' clinical and prognostic behavior with ALL and COVID-19 infection at diagnosis as at any stage of treatment.
Methods: A prospective, observational study in patients *de novo* diagnosed with ALL according to the WHO criteria, cared for in the Hematology Department of the Hospital Regional de Alta Especialidad de Ixtapaluca and the Hospital General de México. The clinical records of the patients diagnosed with ALL from April to December 2020 were included; they received treatment based on intermediate intensity program (CALGB-10403) or high-intensity program (Hyper-CVAD), maintaining the majority of patients as outpatients. ALL the confirmed COVID-19 cases with ALL were compared with non-cancer COVID-19 cases to describe the difference. Support treatment for COVID-19 was based on local considerations. This research was registered on the ClinicalTrials platform (NCT04745416).
Results: Thirty patients were studied (April to December 2020); one case was excluded from the analysis (spontaneous remission). Of the 29 cases, 6 (20.7%) were COVID-19 confirmed cases, four at diagnosis and two during the induction period.There were no differences in gender, age (24 vs. 30 years, p=0.261), or mean leukocyte count at diagnosis (156.3 vs. 116.5 x109/L, p=0.564, 95%CI). BCR-ABL was detected in one case with COVID-19; two cases with COVID-19 showed AF4-MLL and ELN-MLL. According to risk, 66.7% (n=4) of the cases with COVID-19 were considered high risk.
The treatment for COVID-19 was high-flow oxygen, azithromycin, anticoagulation. Upon analyzing the response to induction, the group negative to COVID-19 showed a higher proportion of response than the cases with a background of COVID-19 (78.3% vs. 66.7%), but without statistical significance (p=0.628). The group with COVID-19 showed a higher proportion of leukemia refractory to induction (33% vs. 17.4%), requiring a second treatment program. There were no deaths in the COVID-19 arm.
Comparing the survival with non-cancer COVID-19 patients, the mortality was 51.7% for individuals without leukemia and 16.7% (n=1) for leukemia COVID-19 cases.
Two female patients showed ALL patients' morphological remission: (19 years and 38 years of age). Both debuted with fever as the main manifestation, cytopenias (patient 1: WBC 0.5 x 109/L, platelets 13 x109/L; patient 2: 0.7 x109/L, platelets 123 x109/L) without cytogenetic abnormalities. From day 10 of hospital stay, they showed improvement in leukocyte and platelet counts, reaching the normal range by day 21, requiring evaluation of extended bone marrow, which showed an absence of blasts. Patient 1 had a negative finding after beginning an induction program, and patient two is still without treatment.



Summary/Conclusion: The prognosis of individuals with COVID-19-ALL is better due to the null development of cytokine storm; similar to

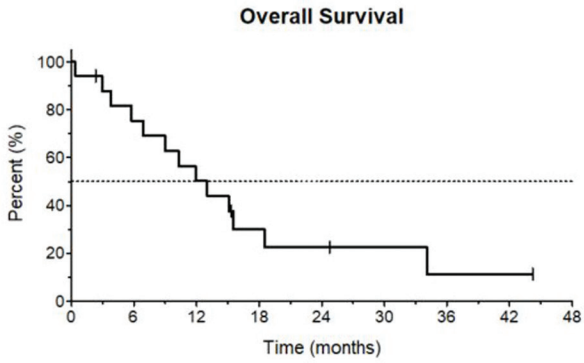
other tumors, spontaneous remission can be seen, especially in young individuals, and decreased tumor burden.

EP364 OUTCOME OF RELAPSED OR REFRACTORY ACUTE B-LYMPHOBLASTIC LEUKEMIA PATIENTS WITH EXTRAMEDULLARY DISEASE RECEIVING INOTUZUMAB OZOGAMICIN

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Background: Extramedullary involvement of B-cell acute lymphoblastic leukemia (EM-ALL) is a rare occurrence, characterized by dismal outcome and the lack of a defined and shared therapeutic approach. Inotuzumab ozogamicin (InO) is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin. It was developed as a targeted therapy for B-cell malignancies.
Aims: To characterize a series of relapsed/refractory (r/r) adult EM-ALL patients (pts) and evaluate outcome after InO treatment.
Methods: We studied 17 r/r pts (median age, 31 years; range, 19-68 years), who were treated with InO between 2015 and 2020 within a compassionate use program (n=7) or in-label after EMA approval (n=10). Three of the 17 pts were previously treated with tyrosine kinase inhibitors for chronic myeloid leukemia and progressed to blast crisis of B-lymphoid lineage. Bone marrow evaluation and immunophenotyping by flow cytometry revealed acute B-lymphoblastic leukemia in all three pts. All 17 pts were CD22 positive at relapse/progressive disease. Up to six InO cycles (≤2 cycles, n=11; 3-4 cycles, n=4; 5-6 cycles, n=2) were administered according to the previously approved regimen. EM response assessment was performed by CT or PET-CT.
Results: Localization of EM disease included lymph nodes (in total, n=9; including gastric and skin; bone and skin; lung, bone and skin; hepatic and bone; hepatic, n=1 in each of these combinations), bones (n=4), kidney (n=1), peripheral nerves (n=1), pancreas and bone (n=1), and ovary (n=1). At the time of r/r EM-ALL median white blood cell and platelet counts were 4.9/nl (range, 0.7-10.3/nl) and 94.5/nl (range, 11-515/nl), respectively. Eleven pts (49%) were female; ECOG was ≤ 2 in all pts. Cytogenetic analysis at the time of r/r EM-ALL was available in five pts. One patient had a normal karyotype, two were complex and two pts displayed a t(9;22). Complete remission assessed by PET-CT (CR; including EM and hematological/bone marrow CR) after the first InO cycle was achieved in 7 pts (41%), 7 pts had a partial remission (PR) (41%), one (6%) had stable disease (SD) and one patient (6%) died at day 11 of the first InO cycle due to cerebral hemorrhage. One patient had no response assessment after the first induction cycle (6%). After two InO cycles, overall response rate was 94% (n=16), including CR in 9 pts (56%) and PR in six (38%); the patient with SD did not receive further InO treatment (6%). Median follow-up was 12.1 months (range, 0.4-44.9 months) and median overall survival (OS) 11.9 months (95%>CI, 8-20 months; Figure 1). One-year and two-years OS rates were 50% (95%>CI, 25-71%) and 23% (95%>CI, 6-46%), respectively. Age above 60 years had no impact on OS (p=0.48). Seven pts proceeded to allogeneic hematopoietic stem cell transplantation (allo-SCT; CR, PR, n=3, each; progressive disease, n=1). Prior to allo-SCT four pts received ≤2 cycles InO and three pts ≤4 cycles. No occurrence of veno-occlusive disease was reported. Relapse/progressive disease occurred in nine pts and all pts succumbed of their disease. Cumulative incidence of relapse after 12 months was 38%. One patient experienced a molecular relapse, which could be successfully treated with InO again. Four pts died in remission and four pts are in ongoing CR including the patient with prior molecular relapse and InO re-exposure.



Summary/Conclusion: This outcome analysis demonstrates that treatment with InO is an effective and promising approach including a successful bridge-to-transplant strategy in this rare subgroup of patients with r/r EM-ALL and abysmal prognosis.

EP365 ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE: A SINGLE CENTRE RETROSPECTIVE REVIEW OF DISEASE CHARACTERISTICS, TREATMENT STRATEGIES, OUTCOMES AND NOVEL THERAPEUTIC TARGETS

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Background: Acute leukemia of ambiguous lineage (ALAL) is a rare form of acute leukemia, with a reported incidence of 1-6%, associated with a poor prognosis with median survival of 14.8 to 18 months. The World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues 2016 Revised Edition classifies ALAL as a separate category from acute myeloid leukemia and acute lymphoblastic leukemia.
Treatment generally consists of acute myeloid leukemia (AML) induction, acute lymphoblastic leukemia (ALL) induction or hybrids of AML and ALL induction. Patients with t(9;22) are generally treated with a tyrosine kinase inhibitor. Eligible patients who achieve complete remission after induction are often treated with a consolidative allogeneic hematopoietic stem cell transplant (HSCT). Little evidence is available for the use of novel therapeutics such as antibody-drug conjugates, bispecific T-cell engagers or chimeric antigen receptor T-cells (CAR-T) in ALAL.
Aims: 1. To determine the incidence of ALAL in a single center
2. To determine the characteristics of ALAL patients and their disease
3. To review the treatment employed in ALAL patients
4. To report outcomes of ALAL patients
5. To report incidence of specific immunophenotypic markers which may be therapeutic targets in ALAL
Methods: Using the British Columbia Cancer Agency Leukemia Database, patients with diagnosed the an ALAL between 2000 and 2020 were identified. Information including demographics, date of diagnosis, pathology results, treatment employed and survival data from the database was reviewed by two clinical hematologists. If the diagnosis was felt to meet another diagnosis other than ALAL, the patient was excluded from the analysis. Patient sex, age at diagnosis, immunophenotypic markers, first treatment regimen and bone marrow transplant status were quantified. A survival analysis was performed using a Kaplan-Meier analysis.
Results: 63 patients were identified as having ALAL. 16 patients were removed from analysis because of the diagnosis meeting another WHO leukemia classification.
The characteristics of patients, disease and treatment strategies employed for these patients is demonstrated in **Table 1.** CD33 and CD19 were the most common immunophenotypic targets, with more than 40% of patients being positive, respectively.

The median overall survival was 30.2 months (12.4-48.0 months, CI 95%) with a median follow-up time of 22.1 months. Three-year overall survival was 42.6%. Three-year overall survival was 59.9% and 24.8% in the transplant group and non-transplant group, respectively.

Table 1: Characteristics of ALAL Patients

Median Age at Diagnosis (N=47)	Range
55	5-79
Male Sex (N=47)	
38	
Median Presenting White Blood Cell Count	Range
13.2	0.2-259.1
WHO ALAL Category (N=47)	
Acute Undifferentiated Leukemia	6
MPAL with t(9;22)(q34.1;q11.2);BCR-ABL1	10
MPAL with t(v;11q23.3);KMT2A-rearranged	3
MPAL, B/myeloid, NOS	6
MPAL, T/myeloid, NOS	9
MPAL,NOS, rare types	3
Acute Leukemia of Ambiguous Lineage	5
Missing Data	5
Immunophenotypic Marker (N=47)	Number Positive (%)
CD19	21 (44.7)
CD20	3 (6.4)
CD22	12 (27.7)
CD33	22 (46.8)
Missing Data	5 (10.6)
Initial Treatment (N=47)	
AML Induction Chemotherapy	14
ALL Induction Chemotherapy	12
Cytarabine/Anthracycline-based Chemotherapy	8
Other	8
No Treatment	5
Bone Marrow/Stem Cell Transplant (N=47)	
Yes	24
No	23

Summary/Conclusion: This single-centre, retrospective cohort study offers the first data of ALAL using the updated WHO 2016 criteria for ALALs. That 16 patients were deemed to have alternative diagnoses demonstrates the advances in understanding of acute leukemias and may indicate that the incidence of ALALs is decreasing as more refined diagnostics are used.
MPAL with t(9;22) was the most common subtype of ALAL that was demonstrated. Further review of data is required to determine what percentage of these patients received tyrosine kinase inhibitors. The majority of the patients in our cohort received either an AML or ALL type induction regimens with 51% of the patients going on to receive an allogeneic transplant. This is consistent with previously reported treatment strategies. Most patients had an immunotherapeutic target. This supports the future study of novel immunotherapeutics such as gemtuzumab ozogomicin, blinatumomab, CD19-directed CAR-T products and inotuzumab ozogamicin in ALAL.

EP366 HETEROGENEITY OF TREATMENT RESPONSE DEFINITIONS IN REFRACTORY/RELAPSED ADULT ACUTE LYMPHOBLASTIC LEUKEMIA (R/R ALL): FINDINGS FROM A SYSTEMATIC LITERATURE REVIEW (SLR) OF CLINICAL TRIALS

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Background: Treatment response measures for R/R aALL have evolved with improved understanding of ALL characteristics, which has led to different definitions in clinical trials.
Aims: This study aimed to examine the comparability of response measurements used in trials of current standard of care (SoC) treatments for R/R aALL, with a focus on complete remission (CR) and CR with incomplete hematologic recovery (CRi).
Methods: An SLR was conducted to identify clinical trials reporting treatment response with SoC for R/R aALL. Searches of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases as well as conference proceedings/trial registries were conducted in November 2020. Inclusion criteria were applied to restrict to trials of licensed and recommended treatments for R/R aALL, i.e. blinatumomab, inotuzumab ozogamicin, tyrosine kinase inhibitors (imatinib, dasatinib, ponatinib), and chemotherapies (fludarabine-, cytarabine-, alkylator-containing regimens). Additionally, criteria were further applied to exclude clinical trials with no full-text publications that reported CR alone or both CR and CRi by search completion date.
Results: The SLR identified 15 treatment arms in 12 studies which reported CR, and 14 treatment arms in 11 studies which reported both CR and CRi. Across the 15 treatment arms reporting CR, the definitions were comparable, i.e., an absolute neutrophil count (ANC) response ≥1 x 10^9/l and platelet count ≥100 x 10^9/l along with ≤5% bone marrow blasts. For the 14 treatment arms in 11 studies with both CR and CRi, the CRi definitions varied in hematologic criteria. Many of the 11 studies were heterogenous in terms of specific ANC and platelet thresholds employed for CRi. Moreover, some studies did not require hematologic recovery. Specifically, six studies included a hematological recovery requirement in ANC and/or platelets for CRi with variant thresholds. Three studies did not have a minimum requirement for ANC or platelets, and two studies did not explicitly describe the hematological criteria. Among all studies with CRi hematological recovery thresholds, the most stringent criteria were used in the TOWER trial, defined as ANC ≥1 x 10^9/l or platelet count ≥100 x 10^9/l. The differences in CRi definitions were clinically meaningful and led to significantly different response rates.
Summary/Conclusion: Whereas CR definitions were comparable across trials, CRi definitions were very heterogenous in terms of hematologic recovery criteria, with older definitions being less stringent or requiring no hematological recovery. The lack of standardized CRi definitions make it challenging for cross-trial efficacy comparisons with composite response endpoints such as CR+CRi due to the different levels of stringency in criteria for CRi. This suggests that treatment response outcome measures for historical control studies should be based on CR alone. Outcomes with comparable definitions across trials such as CR and standard efficacy measures such as overall survival are likely to provide more robust and clinically relevant cross-trial efficacy comparisons.

EP367 A PHASE II STUDY OF BLINATUMOMAB FOR THE TREATMENT OF MEASURABLE RESIDUAL DISEASE-POSITIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Persistent or recurrent measurable residual disease (MRD) is associated with high rates of relapse in B-cell acute lymphoblastic leukemia (ALL). We evaluated the CD3-CD19 bispecific T-cell engaging antibody, blinatumomab, in patient (pts) with B-cell ALL in complete remission (CR) who did not achieve MRD negativity with standard therapy or who experienced MRD relapse.
Aims: We evaluated the efficacy and safety of blinatumomab in pts with B-cell ALL and MRD-positive disease.
Methods: This is a single-arm, phase II trial of pts with B-cell ALL in CR who did not achieve MRD negativity or had MRD relapse after at least 3 months of frontline therapy (i.e. CR1) or after at least 1 month of salvage therapy (i.e. CR2 and beyond). Positive MRD was defined as ≥0.01% by flow cytometry in pts with Philadelphia chromosome (Ph)-negative ALL and a *BCR-ABL1/ABL1* transcript ratio by PCR of ≥0.01% for pts with Ph-positive ALL. MRD negativity was defined as undetectable MRD by flow and PCR at a sensitivity of 10^{-4}. Blinatumomab was given at standard doses (up to 28 µg/day, if tolerated) in 42-day cycles for up to 5 total consolidation cycles. Pts

who did not proceed with ASCT could receive blinatumomab maintenance with one cycle every 3 months for up to 4 maintenance cycles (9 cycles total). A TKI of the treating physician's choice was added to the regimen for pts with Ph-positive ALL.

Results: Between 12/2015 and 2/2021, 31 pts with MRD-positive B-cell ALL in CR were enrolled. The median age was 42 years (range, 22-84 years). Thirteen pts (42%) had Ph-positive ALL; 10 pts received concomitant ponatinib, 2 received dasatinib, and 1 received imatinib. Twenty-three pts (74%) were in CR1, and 8 (26%) were in CR2 and beyond (5 in CR2 and 3 in CR3). Nineteen pts (61%) had persistent MRD and 12 (39%) had MRD relapse. Two pts had undergone prior ASCT.

Pts received a median of 3 cycles of blinatumomab consolidation (range, 1-5 cycles). Overall, 23 pts (74%) achieved MRD negativity at any time. Fifteen of 18 pts (83%) with Ph-negative ALL achieved MRD negativity, and 8 of 13 pts (62%) with Ph-positive ALL achieved MRD negativity. Three additional pts with Ph-positive ALL achieved a major molecular response as best response. Among the 23 MRD responders, 21 (91%) responded after 1 cycle; 1 after 2 cycles, and 1 after 4 cycles. MRD response occurred in 65% of pts in CR1 and 100% in CR2+. Eight pts (35% of MRD responders) proceeded to ASCT (5 in CR1 and 3 in CR2+) with median time to ASCT of 3 months (range, 2-6 months).

Blinatumomab-related adverse events were as expected, with adverse events of any grade observed in 12 pts (39%). All resolved with supportive management. One pt discontinued blinatumomab due to adverse event (grade 3 altered mental status). There were no grade 4 or 5 adverse events.

With a median follow-up of 25 months (range, 5-60 months), 7 pts have relapsed (30% of MRD responders). One relapse was in a pt who underwent ASCT and 6 were in pts who did not undergo ASCT (3 in CR1, 2 in CR2, and 1 in CR3). Four relapses were hematologic only, 1 was hematologic plus CNS, 1 was extramedullary only, and 1 was MRD only. The 3-year overall survival (OS) and relapse-free survival (RFS) rates were both 63%. The 3-year OS rates were similar for pts who underwent ASCT and those who did not (75% vs. 63%; P=0.95). The 3-year OS rates for pts with an MRD level of 0.01%>0.1% (n=10) and those >0.1% (n=21) were 72% and 60%, respectively.

Summary/Conclusion: Blinatumomab is well-tolerated and highly effective in eradicating MRD in pts with B-cell ALL who have persistent MRD or who experience MRD relapse.

EP368 EPIDEMIOLOGY, TREATMENT PATTERNS AND CLINICAL OUTCOMES OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS IN TAIWAN: A POPULATION-BASED COHORT STUDY

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Background: Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children. However, the epidemiology, treatment patterns, and clinical outcomes of pediatric ALL in Asian population are still limited.

Aims: To investigate the incidence of ALL in pediatric population and their baseline characteristics, treatment patterns as well as clinical outcomes in Taiwan.

Methods: We conducted a nationwide population-based retrospective cohort study using the Taiwan Cancer Registry (TCR) and National Health Insurance Research Database (NHIRD). In the first part of our analysis, pediatric patients newly diagnosed with ALL from 2002 to 2017 were identified from the TCR and the annual incidence of ALL were reported. In the second part of our analysis, we further focused on the pediatric patients diagnosed with B-cell ALL during 2009 to 2015 and investigated their baseline characteristics, treatment patterns and clinical outcomes. Outcomes of interest included refractory disease, disease relapse and all cause mortality. Kaplan-Meier survival analysis were performed with stratification by induction therapy or not, age at diagnosis and response of induction therapy.

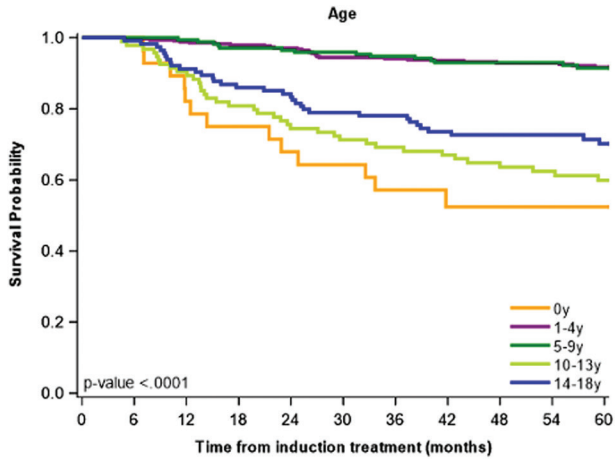
Results: The annual incidence of ALL in pediatric population ranged from 2.36 to 3.19 cases per 100,000 persons, with the highest incidence in the age group of 1 to 4 years. Mean age at diagnosis was 7.1 years.

Among 787 pediatric patients with B-cell ALL identified in TCRD, 761 (96.7%) patients received their induction therapy within 4 months after diagnosis of ALL and were identified for further analysis. Their median age ranged from 3 to 5 years old in the different fiscal year. Most of the patients (97.4 %) were treated in a medical center and initiated induction therapy within the first week after diagnosis, with median time internval ranging from 0 to 7 days.

The proportion of the patients who achieved remission state increased steadily over the years and achieved 97.0% in 2015. In patients who achieved remission state, approximately 20% of them encountered relapse. The cumulative mortality were 26.4% in 2009 and 8.0% in 2015. The proportion of patients received stem cell transplantation (SCT) were 11.2% in 2009 and 7.0% in 2015.

As for the survival analysis, the 3-year survival rate is 87% in patients with induction therapy, with best 3-year survival rate of 94% and 95% in age groups of 1 to 4 and 5 to 9.

The survival of patients who received induction therapy were significantly better than those who did not. The survival were also significantly different in different age at diagnosis, with age groups ranging from 1 to 4 and 5 to 9 having the best survival. Patients who did not encountered refractory disease also showed better survival. Similar trend were observed in relapse-free survival, with better survival in age group 1 to 4 and 5 to 9.



Summary/Conclusion: Our study, with the advantage of 16 years of longitudinal data, has provided epidemiology, treatment patterns and survivals of pediatric ALL in the past decades in Taiwan. The annual incidence of ALL were approximately 2.8 per 100,000 person in Taiwanese pediatric population, with the highest incidence in the age group of 1 to 4 years. Most of the patients achieved remission state after induction therapy, of whom approximately 20% encountered relapse. The 3-year survival rate is 87% in patients with induction therapy. Best survival were observed in the age groups of 1 to 4 and 5 to 9, with 3-year survival rate of 94% and 95%.

EP369 CORRELATION OF BLINATUMOMAB THERAPY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA OUTCOME WITH MINIMAL RESIDUAL DISEASE, CYTOGENETICS AND ABSOLUTE LYMPHOCYTE COUNT:RETROSPECTIVE MULTICENTER STUDY.

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Background: The management of Refractory/Relapsed B cell Acute Lymphoblastic Leukemia (R/R ALL) is still challenging. The use of Blinatumomab in such patients is an option with encouraging results.
Aims: To study the outcome of pediatric patients with R/R ALL or persistent Minimal Residual Disease (MRD) in three centers and correlate their outcome with MRD level, Cytogenetics and Absolute Lymphocyte Count(ALC) prior to Blinatumomab therapy.
Methods: A total of 33 patients with R/R ALL or persistent Minimal Residual Disease (MRD) in three different centers who received Blinatumomab therapy.Their outcome was studied based on MRD level, Cytogenetics and Absolute Lymphocyte Count(ALC) prior to Blinatumomab therapy.MRD measurement was done using flowcytometry method. Results were described and associaction analysis was done using chi-square and Fisher's tests.
Results: Clinical characteristics and outcome are demonstrated in Table attached. Complete remission (CR) with MRD <0.01 after one or two cycles was achieved in 25 patients then proceeded with other assigned treatment. 20 patients (60%) remained alive without disease recurrence. MRD levels, cytogenetics abnormalities and Absolute Lymphocyte Count (ALC) prior to Blinatumomab therapy in relation to disease response are shown in Table. In addition, patients with t(1,19) had worse outcome compared to other cytogenetic abnormalities.Follow-up duration was (0.4–5) years.

Characteristics	N	Disease response (%)	
NCI risk at diagnosis			
Standard risk	19	13 (68)	
High risk	14	12 (85)	p=0.4
Gender			
Male	20	14 (70)	
Female	13	11(85)	p=0.43
Age at relapse(years)			
1-9.9	24	17(70)	
>10	9	8 (88)	p=0.73
Molecular/Cytogenetics:			
ETV6/RUNX1	6	4 (66)	
Hyperdiploidy	5	5 (100)	
t (1;19)	5	1(20)	
iAMP21	5	5(100)	
KMT2A-rerrangement	2	2(100)	
BCR ABL	2	1(50)	
Negative	3	3(100)	
others	5	4 (80)	p=0.24
ALL relapse :			
1st Relapse/Very early	4	3 (75)	
1st relapse/Early	7	3 (42)	
1st Relapse/Late	4	4(100)	
2nd Relapse including after HSCT	7	6(85)	
Relapse Site:			
BM only	19	13 (68)	
BM + CNS	2	2 (100)	
BM + testicular	1	1 * (only cleared BM)	p=0.32
Persistent MRD	8	7 (87)	p=0.32
Refractory disease	3	2 (66)	p=0.32
MRD prior to Blinatumomab			
<0.01	5	5 (100)	
0.01-0.09	8	7 (87)	
0.1-1	9	7 (77)	
1.1-5	3	2(66)	
>5	8	4 (50)	p=0.3
ALC prior to blinatumomab			
< 500	8	4 (50%)	
500-1000	4	2 (50%)	
1000-1500	7	7 (100%)	
>1500	9	8 (88%)	p=0.05
Not available	4		
Post Blinatumomab therapy			
HSCT	11	9 (81)	
CART	4	3 (75)	
Chemotherapy/awaiting HSCT	17	13(76)	p=0.55
Overall outcome	20	60%	
Disease free	5	15%	
Alive with disease	8	24%	
Deceased			p=0.002

Summary/Conclusion: Blinatumomab therapy was associated with excellent response especially in ALL patients with positive MRD. MRD level <0.1% and Absolute Lymphocyte Count (ALC) > 1000/ul prior to Blinatumomab therapy were associated with better outcome. Large prospective studies are ongoing to study Blinatumomab upfront therapy in pediatric ALL patients with persistent MRD.

EP370 THE PATIENT EXPERIENCE OF ACUTE LYMPHOBLASTIC LEUKEMIA AND ITS TREATMENT: A SOCIAL MEDIA REVIEW

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Background: Adult patients with acute lymphoblastic leukemia (ALL) report substantial disease- and treatment-related impacts on their health-related quality of life (HRQOL) despite improvements in treatment strategies over the past 10 years. As novel therapies are developed, greater insight into patients' experiences of current ALL treatments is needed. Patient-reported information (PRI) shared on social media provides a distinct opportunity to understand patients' perspectives outside of the formal research context.
Aims: This study—to our knowledge the first of its kind in ALL—thematically analyzed PRI shared on patient advocacy websites and YouTube to better understand patients' experiences of ALL and its treatment.
Methods: Searches were conducted of 3 patient advocacy websites (Patient Power, The Patient Story, and Leukemia Care) and YouTube to identify individual social media posts describing self-reported PRI on experiences of ALL and/or ALL treatments. English-language posts were included for review if posts were shared by adults (aged ≥ 18 years) with a self-reported ALL diagnosis and if content was relevant to patient ALL and treatment experience. Patients' demographic and disease characteristics were extracted from posts (where available), and the posts were analyzed thematically. A network analysis was conducted to delineate relationships among ALL symptoms, HRQOL impacts, and treatment-related symptoms and impacts.
Results: Of the 935 social media posts identified, 63 met the review criteria: 40 videos, 5 comments posted in response to videos, and 18 blog posts. The 63 posts were contributed by 41 individual patients. Twenty-one (51%) of the patients were male. Fatigue (n=20, 49%), shortness of breath (n=13, 32%), and bruising (n=12, 29%) were the symptoms prior to treatment that were most frequently discussed by patients. Substantial HRQOL impacts were also recorded, with 26 (63%) patients discussing impacts on personal relationships, 25 (61%) discussing psychological and emotional impacts, and 16 (39%) discussing impacts on work. Key themes relating to patients' treatment experiences included perspectives on inpatient treatment, treatment expectations and preferences, and treatment decision-making. Although inpatient treatment restricted patients' independence and social functioning, it also provided a few patients with a sense of safety. Patients also preferred treatments that minimized impact on their HRQOL; treatment intensity and time commitment were key drivers of HRQOL impact. Patients frequently relied on their doctors to drive their treatment decisions but were also influenced by family members. The network analysis indicated that ALL symptoms primarily affected patients' physical functioning, activities of daily living, and ability to work, while treatment-related symptoms and impacts primarily affected patients' emotional well-being.
Summary/Conclusion: This study provides novel and valuable insight into the patient experience of ALL and its treatments through an analysis of PRI shared on social media. ALL and treatment-related symptoms have distinct and often detrimental impacts on patients' HRQOL. Results were largely intuitive, with treatment side effects being particularly burdensome for patients and impacting their HRQOL. Patients report that in-patient care is associated with certain challenges (e.g., restricted independence and social functioning) but is also appreciated by a few patients for providing them with a sense of security. Overall, patients hope for treatments with less severe impacts on their HRQOL.

EP371 INOTUZUMAB OZOGAMICIN IN RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKAEMIA: A REAL-WORLD RETROSPECTIVE STUDY IN THE UK

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Background: Inotuzumab ozogamicin (InO) is a CD-22 directed antibody-drug conjugate indicated for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia (R/R ALL). In the randomised phase 3 INO-VATE study (Kantarjian 2016), InO demonstrated increased efficacy compared to conventional chemotherapy. We sought to evaluate the safety and efficacy of InO in the Real-World setting.
Aims: We aimed to characterise patients with R/R ALL initiated on InO in the UK, and evaluate disease response, survival, and occurrence of adverse events, including the risk of veno-occlusive disease / sinusoidal obstruction syndrome (VOD/SOS).
Methods: We conducted a retrospective chart review of 19 adult patients diagnosed with R/R ALL and initiated on InO at 3 centres across the UK between 1st June 2016 and 31st December 2020 (interim analysis, data from 9 patients from an additional site to be added to the poster). The study received ethics approval prior to study set up and data collection. All data was extracted by the patients' medical team in pseudonymised format prior to data analysis, therefore informed consent was not required.
Results: In total, 10/19 (53%) patients were Females, median age at initiation of InO was 50.8 (range 22.7–85.1) years, and median time since ALL diagnosis was 8.5 (1.3–30.5) months.
At initiation of InO, 17/19 (89%,) patients were experiencing their first relapse. 2/19 (11%) patients were BCR-ABL positive.
At the time of InO treatment initiation, 3/19 (16%) patients had previously received blinatumomab, and 6/19 (32%) patients had undergone a prior haematopoietic stem-cell transplant (HSCT).
After InO discontinuation, 4/19 (21%) patients underwent HSCT, and all received 2 cycles of InO; whilst in the remaining 15 patients, the number of cycles ranged from 1 to 6 (median 3). Among the 4 patients who underwent HSCT, 1 experienced VOD/SOS. Of the 15 patients not proceeding to HSCT, 1 patient experienced VOD/SOS, and subsequently died of this complication. This gave an overall incidence of VOD/SOS of 11%. Additionally, 2/19 (11%) patients experienced a grade 3/4 treatment related adverse event, and 1/19 (5%) patient had abnormal liver function tests not due to VOD/SOS.
After InO discontinuation, in the 16 patients who had available response data, 12 (75%) patients achieved CR/CRi. Of 10 evaluable complete responders, 9 (90%), achieved minimal residual disease (MRD) negativity (8 by flow cytometry and 1 by molecular assessment at a level of 10^{-4}).
At last contact, patients had a median overall survival of 9.4 months (range: 0.1 -37.2). In total, 13/19 (68%) patients were known to be alive at 6 months after InO initiation, and 7/19 (37%) patients at 12 months. All 6/19 (32%) patients who were still alive at the time of data collection had achieved CR with a median follow-up of 14.6 months.
Summary/Conclusion: In this sample of UK patients, InO was an effective treatment for patients with R/R B-cell ALL. Response rates, MRD negativity and safety profile were broadly consistent with the established profile of InO in the published phase 3 INO-VATE study.
Reference: Kantarjian HM, et al. N Engl J Med 2016;375:740–753.

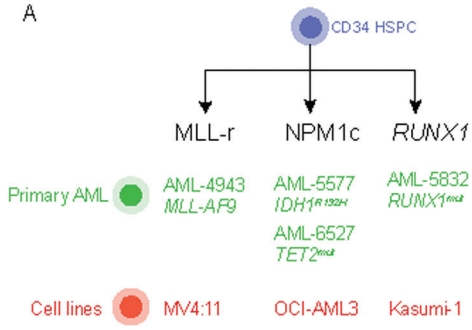
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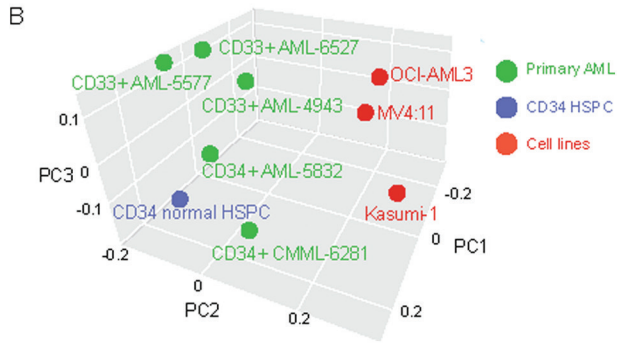
EP372 3D GENOMICS OF ACUTE MEYLOID LEUKEMIA REVEALS THE IMBALANCE BETWEEN DNA METHYLATION CANYON INTERACTIONS AND LEUKEMIC SPECIFIC ENHANCER NETWORK INTERACTIONS

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Background: Changes in 3D chromatin organization like enhancer hijacking are believed to the driver for disease development like leukemia. Here we performed high-resolution HiC assays on primary acute myeloid leukemia (AML) samples and cell lines to dissect the abnormal 3D chromatin organization in AML. We have recently generated a high-resolution map for normal human hematopoietic stem cells (HSC) (Zhang et al. Mole Cell. 2020).
Aims: To dissect the pathogenic alteration in 3D genomics of acute meyloid leukemia
Methods: We use *in situ* HiC to generate the high resolution HiC contact map. Our data set covers 5 AML samples and 3 AML cell lines. This dataset includes the common genetic abnormalities in AML: *MLL*-rearrangement, *NPM1* mutation, *RUNX1* mutation, and *IDH1/TET2* mutations (Figure 1A,B).
Results: In comparison with the HSC 3D chromatin organization, we found TADs and loops are very stable in both primary leukemia samples and cell lines. Less than 5% of all TADs in HSC without disruption of gene expression for genes located in the fused TAD. Interestingly, in *TET2* or *IDH1* mutated AML, two-fold more TAD fusion events occurred in comparison with *RUNX1* and *MLL-r* leukemia, with a hypermethylation on the TAD fusion break point regions.
Compared with normal HSC, we found in AML, the AML-specific H3K27ac marked regions form leukemia specific loops and transcription stripes in both cell lines and primary samples. Particularly in MLL-r primary leukemias, we found broad H3K27ac covered, hyperacetylated domains (10kb to 200kb). 22 such hyperacetylated domains were identified and associated with leukemogenic genes such as *SATB1*, *ZEB2* and *HOXA*. All these domains formed distinct 3D micro-TAD in the MLL-r primary leukemia in comparison with the HSPC, and CTCFs are not located at the border of these domains. Taken together, suggest active leukemia specific transcription created new 3D genomic interactions which is independent of cohesion-CTCF mediated loop extrusion. Particularly, we found the driving oncogenic transcriptional factor HOXA9 and MEIS1 is driving the leukemia specific 3D genomic interactions in *MLL-AF9* and *NPM1* mutant leukemias.
We previously found in HSC, the Polycomb marked DNA methylation Canyons (DMC) form multi-Mb size long-range interactions. DMC interactions in general decrease in primary AMLs. AMLs with *IDH1* or *TET2* mutations shows the biggest reduction in DMC interactions. Hypermethylation in the DMCs is observed in the all AML samples, but *IDH1* and *TET2* mutated AML shows the biggest reduction in the H3K27me3 enrichment in DMC regions, suggesting the level of H3K27me3 enrichment is directly correlated with the strength of DMCs. Remarkably, we found some DMCs switched to active state with gain of active chromatin market H3K27ac. Particularly, two Iroquois homeobox genes, which lies in proximity on chromosome 16 - *IRX3* and *IRX5* are activated in *NPM1c* leukemia. We found that *IRX3* and *IRX5* form the long-range stripe interactions with *FTO* intron enhancer as in the muscle and brain. Further test shows IRX3 and IRX5 is essential for the leukemia growth and the expression is directly maintained by NPM1c in a NPM1c targeted degradation system.





Summary/Conclusion: In summary, we have found in AML, specific 3D genomics interactions associated with leukemia specific transcription is established *de novo*. Particularly, we discovered the DNA methylation Canyon in AML switch from polycomb repressed state to activation state by direct activation of NPM1c.

EP373 FUNCTIONAL COOPERATION OF CEBPA AND TET2 MUTATIONS IN ACUTE MYELOID LEUKEMIA

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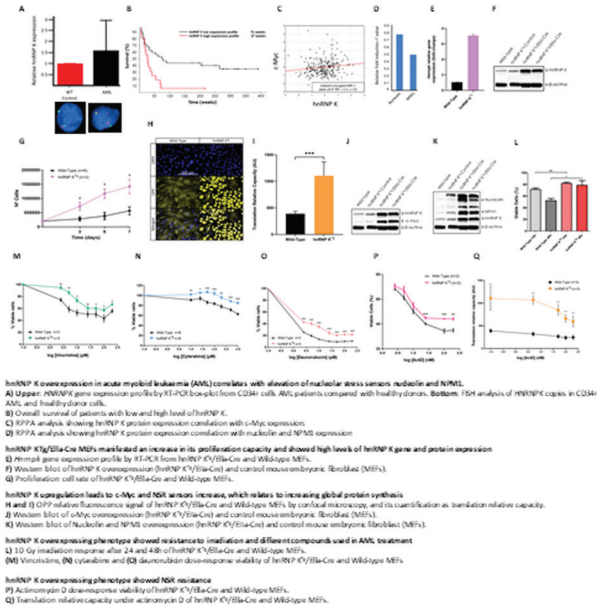
Background: The transcription factor CCAAT-enhancer-binding protein alpha (C/EBPα) is a master regulator of granulopoiesis. Usage of two alternative translation initiation sites in the *CEBPA* mRNA results in expression of a full-length C/EBPα protein, termed p42 (42 kDa) and a shorter p30 isoform (30 kDa). *CEBPA* is mutated in 10-15 % of Acute Myeloid Leukemia (AML) patients. While N-terminal frameshifts that ablate the expression of p42 represent the predominant type of lesions, mutations in the C-terminal basic-region leucine zipper (bZip) that disrupt the DNA-binding ability of C/EBPα are also found. AML patients harbor either mono- or biallelic *CEBPA* mutations (CEBPAmo or CEBPAbi) and both genotypes are frequently associated with concurrent mutations in other genes. The most commonly co-occurring mutations in both groups are loss-of-function mutations in the methylcytosine dioxygenase TET2 (44.4 % in CEBPAmo / 34.8 % in CEBPAbi), resulting in adverse overall survival. We hypothesized that combinatorial effects of *CEBPA* mutations together with *TET2* loss specifically rewire transcriptional and epigenetic circuitries in AML cells, thereby strongly influencing disease outcome.
Aims: We aimed to elucidate the molecular mechanisms behind cooperative effects of *CEBPA* and *TET2* mutations through state-of-the-art transcriptomic and epigenomic analyses of relevant *in vitro* and *in vivo* models as well as data from AML patients.
Methods: We used the CRISPR-Cas9 technology to introduce *Tet2* mutations into murine cell lines expressing only the p30 isoform (*Cebpa*$^{p30/p30}$) or mimicking biallelic *CEBPA* mutations (*Cebpa*$^{p30/C\text{-}mut.}$) to study functional cooperation of these mutations *in vitro*. A *Cebpa*$^{-/p30}$ *Tet2*$^{-/-}$ mouse model was used to study effects of *Tet2* loss in *CEBPA* mutated AML. We performed RNA-, C/EBPα-ChIP-, ATAC- and Bisulfite-seq to generate a comprehensive dataset for in-depth comparative analysis and correlation with relevant patient data from the beatAML collection.
Results: CRISPR/Cas9-mediated introduction of *Tet2* mutations into *Cebpa*$^{p30/p30}$ and *Cebpa*$^{p30/C\text{-}mut.}$ cell lines conferred a strong proliferative advantage to *Tet2*-targeted cells *in vitro*. In line, loss of *Tet2* in a mouse model of *CEBPA* mutant AML shortened leukemia latency. TET2 loss caused decreased global chromatin accessibility and increased DNA methylation, which was accompanied by downregulated expression of numerous genes. Integration of transcriptomic and epigenomic data from *in vitro* and *in vivo* models with gene expression analyses in AML patients harboring *CEBPA* and *TET2* mutations identified the transcription factor GATA2 as a conserved target of the CEBPA-TET2 axis. ChIP-seq showed that p30 binds to multiple regions in the *Gata2* locus, and Tet2 loss caused reduced accessibility and increased DNA methylation of the *Gata2* promoter. RNAi-mediated silencing revealed a dose-dependent effect of *Gata2* expression on leukemia cell fitness *in vivo*. Furthermore, treatment with the demethylating agent 5-azacytidine restored *Gata2* expression in an AML model with *Cebpa* and *Tet2* mutations and caused a significant survival benefit.
Summary/Conclusion: The datasets generated from these novel models enable deeper insights into the global epigenetic and transcriptomic changes that depend on *CEBPA* and *TET2* mutations in a physiologically relevant mutational context. Our results reveal deregulated *GATA2* expression as a result of mutational disruption of *CEBPA* and *TET2* in AML and show that restoration of *GATA2* expression can be beneficial for AML patients with *CEBPA* and *TET2* mutations.

EP374 HNRNP K OVEREXPRESSION CONTRIBUTES TO POOR PROGNOSIS AND CHEMORESISTANCE IN AML BY DEVELOPING SUPER-NUCLEOLUS

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Background: hnRNP K is a ribonucleoprotein involved in processing hnRNAs into mature mRNAs, transcription, and translation control. hnRNP K participates in the nuclear-cytoplasmic shuttling and transmission of information from the nucleus to the cytoplasm. In previous studies, we noticed that *HNRNPK* overexpression is linked with acute myeloid leukaemia's (AML) poor prognosis, which is also related to an oncogenic event, i.e. Nucleolar Stress Response (NSR) resistance. Thus, our objective is to decipher the underlying molecular mechanism by which hnRNP K is related to AML's poor outcomes.
Aims: Our aim is to test the impact on proliferation and tumour development of hnRNP K overexpression due to the generation of NSR resistance
Methods: Clinical bone marrow samples from AML patients with high and low levels of hnRNP K (n=415) were used to study HNRNPK protein expression. Additionally, we analyzed *HNRNPK* copy number by FISH (n=205). Moreover, reverse-phase protein array (RPPA) of AML patients was performed and showed HNRNPK and C-MYC overexpression correlation. hnRNP K overexpression mice models, hnRNP K^{Tg}/EIIa-Cre and hnRNP K^{Tg}/UBC-Cre were used as validation of human samples. Molecular analysis (RT-qPCR, WB and Confocal Microscopy) of hnRNP K, c-Myc, B23 and NPM1 were performed using Mouse Embryonic Fibroblast (MEFs) from our mice models. Also, we analyzed protein synthesis capacity (OPP assay) and NSR sensors by confocal microscopy. Finally, viability and dose-response assays with genotoxic compounds were performed using trypan blue and WST-1
Results: AML patient samples revealed an amplification in the copy number of *HNRNPK* and the consequent gene overexpression and poor outcomes. Moreover, HNRNPK overexpression correlates with c-MYC and NSR sensors (B23 and C23) overexpression (Fig. A, B, C, D). MEFs showed gene and protein high levels of hnRNP K, which correlates with an increase in its proliferation capacity (Fig. E, F, G). Molecularly, this increase leads to c-Myc and NSR sensors upregulation, contributing to increasing global protein synthesis (Fig. H, I, J, K). In addition, these cells showed resistance to irradiation and genotoxic compounds such as vincristine, cytarabine and daunorubicin (Fig. L, M, N, O). Furthermore, this hnRNP K upregulated phenotype manifests NSR resistance when we exposed these MEFs to Actinomycin D. This event could correlate with an increase in NSR sensors such as B23 and C23 (Fig. P, Q).



hnRNP K overexpression in acute myeloid leukaemia (AML) correlates with elevation of nucleolar stress sensors nucleolin and NPM1.
A) Upper: *HNRNPK* gene expression profile by RT-PCR box-plot from CD34+ cells. AML patients compared with healthy donors. **Bottom:** FISH analysis of HNRNPK copies in CD34+ AML and healthy donor cells.
B) Overall survival of patients with low and high level of hnRNP K.
C) RPPA analysis showing hnRNP K protein expression correlation with c-Myc expression.
D) RPPA analysis showing hnRNP K protein expression correlation with nucleolin and NPM1 expression

hnRNP K Tg/EIIa-Cre MEFs manifestated an increase in its proliferation capacity and showed high levels of hnRNP K gene and protein expression
E) *Hnrnpk* gene expression profile by RT-PCR from hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs.
F) Western blot of hnRNP K overexpression (hnRNP K^{Tg}/EIIa-Cre) and control mouse embryonic fibroblast (MEFs).
G) Proliferation cell rate of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs.

hnRNP K upregulation leads to c-Myc and NSR sensors increase, which relates to increasing global protein synthesis
H and I) OPP relative fluorescence signal of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs by confocal microscopy, and its cuantification as translation relative capacity.
J) Western blot of c-Myc overexpression (hnRNP K^{Tg}/EIIa-Cre) and control mouse embryonic fibroblast (MEFs).
K) Western blot of Nucleolin and NPM1 overexpression (hnRNP K^{Tg}/EIIa-Cre) and control mouse embryonic fibroblast (MEFs).

hnRNP K overexpressing phenotype showed resistance to irradiation and different compounds used in AML treatment
L) 10 Gy irradiation response after 24 and 48h of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs.
(M) Vincristine, **(N)** cytarabine and **(O)** daunorubicin dose-response viability of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs

hnRNP K overexpressing phenotype showed NSR resistance
P) Actinomycin D dose-response viability of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs.
Q) Translation relative capacity under actinomycin D of hnRNP K^{Tg}/EIIa-Cre and Wild-type MEFs.

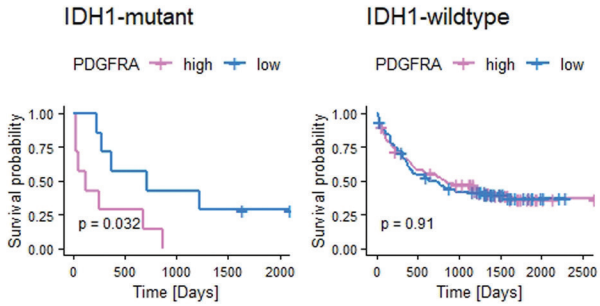
Summary/Conclusion: HNRNPK is amplified and overexpressed in AML patients, which manifest less survival than patients without this upregulation. Moreover, hnRNP K regulates c-Myc that triggers the global translation process. Therefore, the c-Myc upregulation leads to an increase in ribosome biogenesis and function, enhancing global translation. In addition, overexpression of hnRNP K drives B23 and C23 increase, which could establish a hyperactivated nucleolus. These events evoke an oncogenic event known as "Nucleolar Stress". Moreover, hnRNP K overexpression showed NSR resistance. Super-nucleolus drives the NSR resistance that promotes the chemo-resistance to different AML treatments, explaining these poor outcomes. Thus, the development of a specific hnRNP K inhibitor would potentially open the door to new treatments of AML patients that do not respond to treatment due to hnRNP K overexpression.

EP375 IDH MUTATIONS DRIVE LEUKEMOGENESIS BY ONCOGENIC ACTIVATION DUE TO INSULATOR DYSFUNCTION

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Background: Acute myeloid leukemia (AML) is a heterogenous disease, characterized by complex patterns of molecular alterations and somatic driver mutations in genes of numerous functional categories, such as *NPM1*, *DNMT3A* or *IDH1/2*. In younger adults, *IDH1* mutations occur in 6-10% of AML cases, whereas elderly AML patients show a significantly higher *IDH1* mutation frequency of 17.2% accompanied by DNA hypermethylation. Despite advances in targeted therapy due to the recent approval of *IDH* inhibitors (Enasidenib, Ivosidenib), elderly AML patients with *IDH* mutations still have an inferior outcome irrespective of cytogenetic group with high rates of chemotherapy resistance and relapses. Recently, the *IDH1* p.R132H mutation was linked to altered DNA loop formation by disrupted CTCF binding, leading to oncogene activation in glioma cells, which correlated with inferior outcome.
Aims: Here, we investigate the role of the *IDH1* p.R132H mutation in altering 3D DNA architecture and subsequent activation of oncogene expression in AML.
Methods: To identify upregulated oncogenes in *IDH1*-mutant (-mut) AML, differential gene expression was analyzed in two independent AML datasets, the BeatAML RNA-Seq dataset with n = 264 patients with annotated *IDH1*-status (Tyner et al. 2018) and a microarray dataset with n = 247 patients (Verhaak et al. 2009). To validate enhanced oncogene expression by RT-qPCR and investigate DNA loop formation, we generated a KG1a-based cellular model containing the *IDH1* p.R132H point mutation using CRISPR base editing. Confirmed oncogenes were correlated with differential occupancy and methylation of corresponding CTCF binding sites using chromatin immunoprecipitation (ChIP) and methylation-sensitive restriction followed by RT-qPCR. Clinical relevance of identified oncogenes was investigated by comparing survival of patients with high or low oncogene expression with or without *IDH1* mutation in two independent clinical datasets (BeatAML and Bamopoulos et al. 2020, n = 246).
Results: Differential expression analysis of AML datasets identified 179 genes upregulated by >1.5 fold (ANOVA, $p < 0.05$) in *IDH1*-mut AML patients compared to *IDH1*-wildtype (-wt) patients, including 13 oncogenes. Upregulated oncogene expression was confirmed in the KG1a *IDH1* p.R132H model revealing highest upregulation (2.5 fold) of the receptor tyrosine kinase gene *PDGFRA*. Quantification of CTCF occupancy identified decreased CTCF binding by 30% at the CTCF anchor region 1.7 Mb upstream of the *PDGFRA* locus. In addition, DNA methylation of the identified CTCF binding site was increased by 2-fold in cells harboring the *IDH1* p.R132H mutation. Analysis of AML clinical data revealed significantly decreased survival of AML patients with high *PDGFRA* expression among *IDH1*-mut but not *IDH1*-wt patients (Fig. 1, OS of *IDH1*-mut/-wt patients with high/low *PDGFRA*, data: Bamopoulos). Interestingly, *IDH1*-mut KG1a cells showed higher sensitivity towards the tyrosine kinase inhibitor Dasatinib in a WST-based drug screen, supporting Dasatinib as novel candidate for treatment of AML patients with *IDH1* mutation.



Summary/Conclusion: Our data suggest that *IDH1* p.R132H mutation leads to 3D conformational changes in AML, disrupting DNA loop formation and insulation of the tyrosine kinase *PDGFRA*, which subsequently results in upregulated *PDGFRA* oncogene expression. As high *PDGFRA* expression correlated with poor prognosis, treatment with tyrosine kinase inhibitor Dasatinib may be an option for *IDH1* p.R132H mutant AML patients. Our findings offer a base for novel treatment strategies and tackling resistance in AML patients with *IDH1* mutations.

EP376 NEXT-GENERATION SEQUENCING (NGS)-BASED MEASURABLE RESIDUAL DISEASE (MRD) MONITORING IN ACUTE MYELOID LEUKEMIA WITH FLT3 INTERNAL TANDEM DUPLICATION (FLT3-ITD+ AML) TREATED WITH ADDITIONAL MIDOSTAURIN

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Background: *FLT3*-ITD occurring in ~25% of adult AML patients (pts) is associated with poor prognosis. *FLT3*-ITD represents an attractive target for MRD monitoring particularly in pts treated with a tyrosine kinase inhibitor. We have recently demonstrated that NGS can overcome the limitations of the broad heterogeneity of ITD length and insertion site (IS) offering the opportunity for MRD monitoring in *FLT3*-ITD$^+$ AML.
Aims: To validate our NGS-based *FLT3*-ITD MRD assay and to evaluate the prognostic impact of *FLT3*-ITD MRD monitoring in *FLT3*-ITD$^+$ AML treated within the AMLSG16-10 trial (NCT01477606) combining intensive chemotherapy with midostaurin followed by midostaurin maintenance.
Methods: Using *FLT3*-ITD paired-end NGS (Illumina MiSeq) and getITD with a variant allele frequency (VAF) sensitivity of 10^{-4}-10^{-5}, 336 bone marrow (BM) and 36 peripheral blood samples from 96 *FLT3*-ITD$^+$ AML pts were analyzed at diagnosis (Dx), after two cycles of chemotherapy (Cy2), at end of treatment (EOT), and during 3-12 months follow-up (FU). All pts achieved complete remission (CR) after Cy2. Allogeneic hematopoietic cell transplantation in first CR (HCT in CR1) was performed in 72 (75%) pts. *NPM1* and *DNMT3A* mutation status were available for all pts (*NPM1*^{mut}, n=74; *DNMT3A*^{mut}, n=48; *NPM1*^{mut}/*DNMT3A*^{mut}, n=46); *NPM1*^{mut} MRD data in 67 pts.

Results: At Dx we identified 296 ITDs; with 71% of the pts exhibiting >1 ITD at Dx (median 2; range, 1-15). Median length was 48 nucleotides (range, 9-240) and median VAF 0.280% (0.006-90.21). Of the 296 ITDs, 69% located in the juxtamembrane domain and 31% in the tyrosine kinase domain-1. VAF did not correlate with length or IS, whereas ITD length correlated with IS: the more 3´ the IS, the longer the ITD (Rho=0.51; p<.001). Median total ITD VAF per pt was 32.6% (0.57-90.21) and correlated positively with white blood cell count (WBC, Rho=0.233; p=.024), and inversely with ITD number (Rho=-0.221; p=.03). There were no correlations with other clinical or genetic features. Pts' total ITD VAF significantly decreased after Cy2 and at EOT (median $\log_{10}$ reduction: 4.4 and 4.7; p<.001, each), and MRD negativity (MRD^-) was achieved in 64% and 87%, respectively. Concurrent *NPM1*^{mut} favorably impacted on $\log_{10}$ VAF reduction (median, 4.7 for *NPM1*^{mut} vs 4.7 for *DNMT3A*^{mut}/*NPM1*^{mut} vs 2.9 others; p<.001) and MRD^- (78 vs 72 vs 30%; p=.001) after Cy2, but exerted no impact at EOT. *NPM1*^{mut} and *FLT3*-ITD MRD course correlated positively after Cy2 (Rho=0.423; p=.001), but not at EOT, likely due to the higher sensitivity of the *NPM1*^{mut} MRD assay (qRT-PCR).
Median follow-up was 3.8 years (95% CI, 3.0-4.7). Survival analyses for cumulative incidence of relapse (CIR) and overall survival (OS) revealed in strong trend lower CIR for total VAF per pt at Dx >32.6% (p=.055), significantly lower CIR for VAF reduction >4.4 $\log_{10}$ ($MR^{4.4}$) after Cy2 (p=.028), $MR^{4.7}$ at EOT (p=.007), and for MRD^- at EOT (p<.001). There was no impact on OS. In exploratory Cox regression (n=72), including BM blasts, WBC, lactate dehydrogenase, age, *NPM1*^{mut}, and HCT in CR1 as time dependent variable, MRD^- at EOT was the only consistent favorable variable for CIR (HR, 0.1; p=.001) and OS (HR, 0.33; p=.046). *NPM1*^{mut} (HR, 0.04; p<.001) and HCT in CR1 (HR, 0.1; p=.002) were favorable for CIR.
Summary/Conclusion: In this cohort of *FLT3*-ITD$^+$ AML treated with intensive chemotherapy and midostaurin we could demonstrate that a large proportion of pts became MRD^- at EOT by *FLT3*-ITD NGS-based MRD monitoring which reveals as a promising tool to monitor therapy response and to identify pts at a higher risk of relapse.

EP377 AGEING MIMICS LEUKEMIC ADAPTATION OF BONE MARROW STROMAL CELLS AND PROMOTES ACUTE MYELOID LEUKEMIA INITIATION

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Background: The incidence of acute myeloid leukemia (AML) increases with age and elderly patients display increased frequency of unfavorable cytogenetics. However, when compared to similarly-treated younger patients from the same cytogenetic risk group, elderly patients still experience lower overall survival, indicating that age-related differences extrinsic to hematopoietic cells contribute to AML therapy resistance and disease relapse. Interactions between leukemic cells and the bone marrow (BM) microenvironment are crucial for myeloid leukemia progression. Indeed, leukemic cells have the ability to shape their microenvironment in order to support their expansion and BM stromal cells can support malignant hematopoiesis at the expense of normal hematopoiesis. The BM microenvironment also changes during ageing, contributing to the age-associated decline in adaptive immunity, and platelet-myeloid bias of cellular output. These changes can potentially contribute to the increased prevalence of myeloid malignancies seen in the elderly population.
Aims: Address the potential role of the aged microenvironment in myeloid leukemogenesis by investigating the correlation between AML- and ageing-related changes in the BM microenvironment.
Methods: We developed a murine model of *Cebpa* mutant AML, where *Cebpa* mutant leukemic initiating cells (LICs) were injected into sub-lethally irradiated young mice, reproducibly leading to AML in 4 weeks. Flow cytometry was used to study the changes that occur to the abundance of BM niche during AML development. Molecular profiling of leukemic cells and BM stromal cells during leukemogenesis was performed, and the identified changes were overlaid with those occurring during physiological ageing.
Results: In our *Cebpa* mutant AML model, the 2-, 3- and 4-week time points represented 3 key stages of leukemia progression: i) an early expansion phase with no overt leukemia; ii) a late expansion phase with leukemia cells highly abundant in hematopoietic organs, and iii) a terminal phase where normal BM hematopoiesis is displaced (Figure 1A). As most AML cells occupy the central BM (CBM), we focused on CBM vascular endothelial cells (VECs) and perivascular cells (PVCs). We observed a decrease in the number of CBM VECs in leukemic, compared to mock transplanted mice, which was similar to that observed during normal ageing. CBM VECs and PVCs were profiled by RNA sequencing at the 3 key time points after LIC transplantation, with cells from mock transplanted mice profiled as controls. In CBM VECs, we observed a significant overlap between the genes and process networks altered during ageing and those altered at week 3 of AML (Figure 1B). In addition, several cytokines produced by leukemic cells were capable of expanding myeloid progenitors (the closest normal counterpart of LIC) *in vivo*. These cytokines were also upregulated in aged BM stromal cells, consistent with the aged BM microenvironment sharing characteristics with that adapted to AML (Figure 1C-D). This hypothesis was confirmed when we observed leukemia engraftment only in non-irradiated aged mice injected with *Cebpa* mutant LICs but not in young mice (Figure 1E).

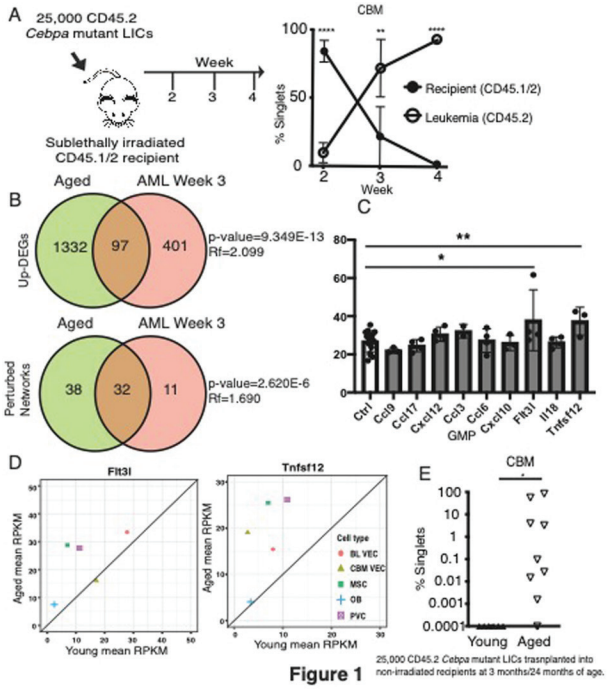


Figure 1

Summary/Conclusion: Molecular and functional similarities exist between the BM microenvironment generated during leukemia progression and physiological ageing. These similarities may contribute to increased AML incidence and progression by providing support for the expansion of myeloid progenitors, including LICs.

EP378 SELECTIVE REQUIREMENT OF MYB FOR ONCOGENIC HYPERACTIVATION OF A TRANSLOCATED ENHANCER IN ACUTE MYELOID LEUKEMIA

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Background: Chromosomal inversion or translocation between 3q21 and 3q26 (inv(3)/t(3;3)) results in the aberrant expression of the proto-oncogenic transcription factor *EVI1* located at 3q26, causing the development of Acute Myeloid Leukemia (AML). It has been shown that in those AMLs a single *GATA2* enhancer at chromosome 3q21

translocates to 3q26 and turns into a hyperactive super-enhancer, driving overexpression of *EVI1*. AMLs with inv(3)/t(3;3) are dependent on *EVI1* and are characterized by an aggressive course and are refractory to therapy.
Aims: In this study we aimed to investigate how the hijacked *GATA2* enhancer leads to *EVI1* activation. To this purpose, we identified sequence motifs in this enhancer essential for *EVI1* transcription in inv(3)/t(3;3) AML.
Methods: We generated a model to study *EVI1* regulation in inv(3)/t(3;3) AML cells by inserting a *GFP* reporter 3' of endogenous *EVI1* into the inv(3) MUTZ3 cell line. To uncover important transcription factor binding elements essential for driving *EVI1* transcription in the *GATA2* hijacked enhancer, we applied an unbiased CRISPR/Cas9 enhancer scan. To this end, we constructed a lentiviral library containing all sgRNAs covering the translocated region and transduced it into MUTZ3-EVI1-GFP cells at a low multiplicity of infection to analyze the effect of single mutations in the enhancer on *EVI1* expression.
Results: The unbiased CRISPR/Cas9 scan of the translocated *GATA2* enhancer in 3q26-rearranged AMLs pinpointed a single regulatory element of approximately 1 kb of open chromatin that is critically required for aberrant *EVI1* expression. This element contained a DNA binding motif for the transcription factor MYB, which specifically occupied this site at the translocated allele. This motif was required for *EVI1* expression but dispensable for *GATA2*. *MYB* knockout as well as peptidomimetic blockade of CBP/p300-dependent MYB functions resulted in downregulation of *EVI1* but not of *GATA2*. Targeting *MYB* or mutating its DNA-binding motif within the translocated *GATA2* enhancer resulted in myeloid differentiation and cell death.
Summary/Conclusion: Our data show an essential role for MYB in the regulation of *EVI1* expression via the translocated *GATA2* enhancer. This is a novel paradigm in which chromosomal aberrations reveal critical regulatory elements that are non-functional at their endogenous locus. This knowledge provides a rationale to develop new compounds to selectively interfere with oncogenic enhancer activity.

EP379 MENIN INHIBITION DECREASES BCL-2 AND SYNERGIZES WITH VENETOCLAX IN NPM1/FLT3-MUTATED AML

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Background: Nucleophosmin (NPM1) is the most commonly mutated gene in adult AML (approximately 30%), which results in its aberrant cytoplasmic localization (NPM1c). The interaction of mixed-lineage leukemia (MLL1) with menin in NPM1 mutated AML shares a common HOX gene signature and dependencies as that of MLL-rearrangements (MLL1-r) with menin. Indeed, inhibition of menin has demonstrated anti-leukemia activity in both NPM1c and MLL-r AML. NPM1 mutations in AML frequently occur in patients with other mutations, such as FLT3-ITD and FLT3 tyrosine kinase domain (TKD) mutations. Co-inhibition of menin and FLT3 has demonstrated enhanced anti-leukemia activity in MLL-r/FLT3- and NPM1c/FLT3-mutated AML.
Targeting Bcl-2, a critical factor for AML cell and AML stem/progenitor cell survival, has emerged as a promising therapeutic option for patients with AML. However, despite the major improvement of combining the Bcl-2 inhibitor venetoclax with hypomethylating agents, most patients develop resistance and ultimately relapse.
Aims: To investigate the anti-leukemic activity and potential synergism and mechanisms of the combination of the menin-MLL1 inhibitor SDNX-50469, an equipotent surrogate of the clinical compound SNDX-5613 and venetoclax *in vivo* in an NPM1c/FLT3-ITD/TKD patient-derived xenograft (PDX) model.
Methods: The PDX cell engrafted NSG mice were treated with 0.05 or 0.1% SNDX-50469-spiked chow, venetoclax (50 mg/kg), or 0.1% SNDX-50469 plus venetoclax for one month. Engraftment and disease progression were assessed by flow cytometric measurement of human $CD45^+$ cells in mouse peripheral blood. Survival was monitored. The treatment effects on various leukemia cell populations and their protein expression levels were determined by CyTOF mass cytometry.
Results: Menin inhibition exhibited strong anti-leukemia activity and significantly prolonged mouse survival, which was further enhanced when combined with venetoclax, while venetoclax alone had minimal effect. The combination was most effective in extending mouse survival (143 d for 0.1% SNDX-50469 plus venetoclax, $P = 0.0003$; 131 d and 125 d for 0.1% or 0.05% SNDX-50469, respectively, $P = 0.0001$ for both; 69 d for venetoclax, $P = 0.025$; vs. 61 d for controls). At the end of treatments, bone marrow cells were collected and CyTOF analysis demonstrated that menin inhibition preferentially targeted $CD34^+CD38^+$ cells, while venetoclax targeted $CD34^+CD38^-$ cells. Only the combined inhibition of menin and Bcl-2 effectively eliminated bulk and $CD34^+CD38^+$/$CD34^+CD38^-$ stem/progenitor cells. Menin inhibition also increased the $CD11b^+$ myeloid cell population. Mechanistically, menin inhibition decreased multiple anti-apoptotic Bcl-2 proteins including Bcl-2 and Bcl-xL, and concomitantly increased pro-apoptotic Bcl-2 proteins such as Bax that seemingly enhanced the activity of Bcl-2 inhibition by venetoclax. However, we observed increases of p-FLT3 in the surviving leukemia cells at the end of the treatments, particularly in the combination treated group, which may contribute to the regrowth of leukemia cells.
Summary/Conclusion: Our study further validated menin as a therapeutic target and demonstrated that its inhibition synergizes with venetoclax in NPM1/FLT3-mutated AML, which warrants further clinical evaluation. Inhibition of FLT3 may further enhance the therapeutic efficacy of menin and Bcl-2 co-targeting in NPM1 and FLT3 mutated AML.

EP380 IDENTIFICATION OF FUNCTIONAL GENETIC DEPENDENCIES AND DIRECT TRANSCRIPTIONAL TARGET GENES OF NUP98-JARID1A IN ACUTE MYELOID LEUKEMIA

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Background: The Nucleoporin 98 (*NUP98*) gene is recurrently involved in the formation of oncogenic fusion proteins in acute myeloid leukemia (AML). While more than 30 partner genes have been identified to participate in *NUP98* gene fusions, NUP98-JARID1A is the most frequent NUP98-rearrangement in infant leukemia and is associated with particularly poor prognosis. As no targeted therapy exists, there is an urgent need for a better understanding of the molecular mechanisms of NUP98-fusion-protein-dependent leukemogenesis to enable the development of tailored treatments. We and others have shown that oncogenic NUP98-fusion proteins act as transcriptional regulators, but it is incompletely understood how NUP98-fusion proteins directly regulate gene expression to drive leukemia.
Aims: To unravel critical effectors of NUP98-fusion-driven leukemogenesis we aimed to identify direct transcriptional targets of NUP98-JARID1A and characterize their requirements for the development and maintenance of NUP98-JARID1A-expressing AML.
Methods: To investigate functional genetic dependencies we conducted a genome-scale CRISPR/Cas9 loss-of-function screen in a cellular model of NUP98-JARID1A-dependent AML. Next we reasoned that a detailed understanding of the underlying transcriptional circuitries is critical to understand NUP98-fusion-dependent gene regulation. Using a newly developed model for ligand-induced degradation of the NUP98-JARID1A protein via the degradation tag (dTAG) system and performing nascent RNA-seq (SLAM-seq), we measured immediate transcriptional changes upon acute NUP98-JARID1A degradation.
Results: Analysis of the CRISPR/Cas9 screen identified 2550 genes that are required for the proliferation and survival of a NUP98-JARID1A AML cells. With the newly established model for ligand-induced NUP98-JARID1A loss we achieved complete degradation of the fusion protein within one hour after ligand addition, leading to terminal differentiation and apoptosis of leukemia cells. Global analysis of nascent mRNA expression by SLAM-seq revealed that 45 genes were significantly downregulated upon NUP98-JARID1A degradation. By intersecting these candidates with the 2550 genes that were required for NUP98-JARID1A-AML cell growth, we identified 12 high-confidence essential direct targets of NUP98-JARID1A.
Summary/Conclusion: This approach allows the identification of functional genetic dependencies and direct transcriptional target genes of NUP98-JARID1A in AML. Multi-layered validations of high-confidence candidates in a variety of models, including primary patient samples, will provide new insights into the molecular mechanisms and transcriptional circuitries of NUP98-JARID1A-driven leukemia and might identify novel actionable gene targets.

EP381 FUNCTIONAL ANALYSIS OF ABERRANT GENE REGULATORY PROGRAMS AND SELECTIVE DEPENDENCIES IN EVI1/MECOM-DRIVEN ACUTE MYELOID LEUKEMIA

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Background: With a two-year survival of <10% chromosomal rearrangements involving EVI1/MECOM represent the most adverse genetic event in acute myeloid leukemia (AML). As established treatment options commonly fail in these patients, there is an urgent need for rational therapeutic concepts that will require a better understanding of molecular and cellular functions of the EVI1 oncogene in AML.
Aims: This study aimed to identify transcriptional programs and genetic dependencies evoked by aberrant EVI1/MECOM expression in AML.
Methods: We have developed a panel of murine and human models of EVI1-driven AML that recapitulate common phenotypic and transcriptional features of human EVI1-rearranged AML, enable conditional expression of EVI1 itself, as well as the RNAi- and CRISPR/Cas9-based genetic exploration of EVI1-associated candidate targets.
Results: We have characterized transcriptional programs evoked by EVI1 in cell culture models and in vivo, and systematically identified genetic dependencies through comparative CRISPR/Cas9-based screens. By integrating orthogonal data from transcriptome profiling, we identify factors that are both, aberrantly expressed and specifically required in EVI1-driven AML. Among these, we identify aberrant activation of ERG, an ETS-related transcription factor that is overexpressed in subgroups of patients suffering from AML and T-ALL, as highly selective dependency in EVI1-driven AML. Suppression of ERG triggers potent and selective anti-leukemic effects and terminal differentiation in human and murine models of EVI1-driven AML, while ectopic expression of ERG functionally rescues loss of the EVI1 oncogene.
Summary/Conclusion: We find that a major oncogenic function of EVI1 is to drive aberrant expression of ERG and thereby maintain leukemia cells in an immature state. Interfering with this regulatory axis may provide new entry points for rational therapies that are urgently needed for this group of AML patients.

EP382 NUP98/NSD1-POSITIVE AML IS ADDICTED TO A FUNCTIONAL MENIN-MLL INTERACTION

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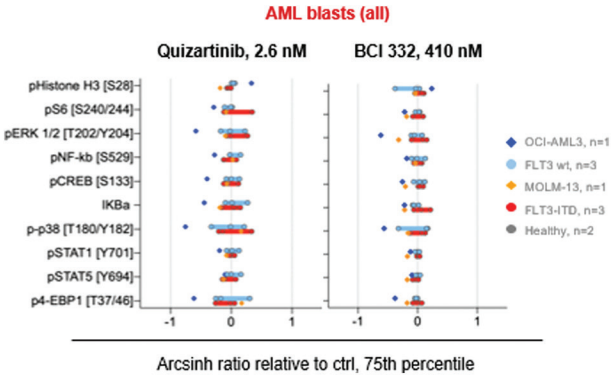
Background: The chromosomal translocation t(5;11)(q35;q15.5) encoding the *NUP98/NSD1* fusion gene is a frequent rearrangement in pediatric high-risk AML. In more than 80% of all cases, *NUP98/NSD1* co-occurs with *FLT3-ITD* or *WT1* mutations. This AML subtype is characterized by a *HOXA/B* programme, where MLL binds to the N-terminus of the NUP98/NSD1 fusion protein and recruits it to the *HOXA* and *MEIS1* loci. In general, transcriptional activation by MLL depends on its interaction with its cofactor Menin. SNDX-5613 is a novel selective Menin-MLL inhibitor that resides with high affinity in the binding pocket of Menin and disrupts the Menin-MLL interaction. This inhibitor has recently been shown to have substantial single agent activity against MLL-rearranged and NPM1 mutant leukemia. Based on these combined findings, we hypothesized that the NUP98/NSD1 leukaemic programme depends on a functional Menin-MLL interaction that can be targeted by SNDX-5613.
Aims: The aim of this study was to examine the significance of the MLL – MEN1 interaction for *NUP98/NSD1*-driven gene expression and to explore the potency of SNDX-5613 to interfere with t(5;11)-AML propagation.
Methods: Patient AML samples positive for *NUP98/NSD1* were provided by the Princess Maxima Center for Pediatric Oncology. All samples were also positive for FLT3-ITD with VAFs > 0.35. AML samples were co-cultured with bone marrow-derived mesenchymal stromal cells (MSCs) and treated with different concentrations of SNDX-5613 (Syndax Pharmaceuticals) followed by evaluation of proliferation, gene and protein expression, clonogenicity and differentiation. Changes in cell surface marker expression were investigated after 2 weeks using flow cytometry.
Results: Co-culture of *NUP98/NSD1*-positive patient samples resulted in a 3 – 6-fold expansion of total cells and a 15 – 200-fold expansion of immature CD34+ CD38- CD117+ CD45RA+ leukaemic cells over a period of 14 days. Treatment of four different *NUP98/NSD1*-positive AML samples in this setting resulted in a profound dose-dependent inhibition of proliferation with latency of 10 days and IC50 values between 2 and 50 nM. On the contrary, primary AML cells lacking *NUP98/NSD1* translocation were not affected even by 250 nM of SNDX-5613, demonstrating on-target mechanism of action of this compound. This growth inhibitory effect was associated with a 70% reduction in clonogenicity both by colony number and size when compared with DMSO-treated cells. Furthermore, SNDX-5613 treatment induced myeloid differentiation in AML blasts as demonstrated by diminished expression of CD34 and CD45RA and concomitant elevated expression of CD11b, CD14 and MNDA. Transcriptional profiling upon SNDX-5613 treatment revealed specific changes in leukemogenic gene expression with downregulation of *HOXA7 – 10* and *MEIS1*. SNDX-5613 also reduced *CDK6* levels, a key regulator of cell cycle progression and an established direct transcriptional target of MLL and NUP98/NSD1. Notably, we found that and its potential target gene *FLT3* are uniformly downregulated in a dose dependent manner suggesting an impact of this drug on a secondary leukaemic driver.
Summary/Conclusion: This study demonstrates the relevance of the Menin-MLL interaction for NUP98/NSD1-driven leukemogenesis in primary patient cells and highlights the pharmacologic inhibition of this interaction as a promising therapeutic option for this poor prognosis AML.

EP383 MECHANISTIC STUDIES OF TENOFOVIR-DERIVED TYROSINE KINASE INHIBITORS TARGETING FLT3 IN ACUTE MYELOID LEUKEMIA

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Background: About 25% of patients with acute myeloid leukemia (AML) have internal tandem duplications (ITDs) in the Fms-Like Tyrosine kinase-3 (FLT3) receptor, leading to constitutive activation of the receptor and downstream signaling pathways, and uncontrolled cell division. Several approved and investigational small molecule kinase inhibitors are available, although all kinase inhibitors show off target effects.
Aims: We investigated a novel library of highly selective FLT3-targeting inhibitors built on the chemical backbone of the anti-HIV drug tenofovir, aiming to identify new clinically safe inhibitors with superior FLT3-specificity and reduced off-target effects.
Methods: A panel of 40 analogs with kinase inhibitory properties were synthetized and screened in multiple cell lines expressing wild type (wt) and ITD-mutated FLT3 receptor using the WST-1 assay to define anti-leukemic effect IC_{50}, validated by Hoechst. The novel inhibitor BCI 332 was selected for further evaluation, using quizartinib as a reference compound. BCI 332 was investigated for in vivo toxicity and efficacy in an NSG (NOD/SCID IL2rγ^{null}) subcutaneous mouse model using MV4-11 (ITD/null) cells. Functional assessments of anti-leukemic effects (Annexin V/PI and cell cycle analysis) were performed by flow cytometry in MOLM-13 (FLT3 ITD/wt) and OCI-AML3 (FLT3 wt/wt) cells. Downstream effects of FLT3-inhibition were assessed by mass cytometry (CyTOF) in ex vivo treated mononuclear cells (bone marrow) from healthy donors and FLT3 wt (n=3) and FLT3-ITD mutated (n=3) AML patients, in addition to the cell lines MOLM-13 and OCI-AML3. Samples were stained with a panel of 19 extracellular and 13 intracellular antibodies, and cell subsets were identified by unsupervised clustering based on surface marker expression using the phenograph algorithm.
Results: We identified several potent inhibitors with differential effect on cells expressing FLT3 wt and FLT3-ITD. The inhibitor BCI 332 showed selectivity towards FLT3-ITD, and was therefore further assessed. *In vivo* toxicity and efficacy studies demonstrated low toxicity and potent anti-leukemic effect. Functional assays of MOLM-13 and OCI-AML3 cells showed that BCI-332 induced apoptosis in FLT3-ITD cells, although less potent than quizartinib. CyTOF analyses of healthy (monocytes and CD4 T cells) and leukemic cell subsets revealed heterogeneous response profiles in patient samples, although we did not identify significant differences between FLT3 wt and -ITD mutated samples (Figure).



Summary/Conclusion: The novel inhibitor BCI 332 induced apoptosis in FLT3-ITD mutated cells, and our results indicate higher specificity towards FLT3-ITD than the reference compound quizartinib. Our analyses did not reveal an ITD-specific intracellular response profile to BC I332, likely due to a small sample size and high inter-patient heterogeneity. Thus, work continues to expand the patient cohort, and to provide assessment of inhibition in immunophenotypically distinct leukemic cell subsets.

EP384 CIRCULATING EXTRACELLULAR VESICLES FROM ACUTE MYELOID LEUKEMIA PATIENTS REVEAL SPHINGOLIPID DEPLETION AND REDOX METABOLIC FUNCTION

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Background: Extracellular vesicles (EVs) have emerged as a powerful reservoir of biomarkers for liquid biopsy in hematological malignancies. Indeed, EVs are small vesicles released by various blood cells and contain tumor-derived materials such as nucleic acids, proteins, and lipids. Interestingly, cell metabolism could be influenced by EVs through the regulation of redox processes. Of interest, redox metabolism plays a critical role in normal and leukemic hematopoiesis. Thus, although the role of EVs and their lipid cargo as disease biomarkers have been recently acknowledged in various diseases, the lipidomic profile of circulating EVs and their function on redox metabolism are still elusive in acute myeloid leukemia (AML).
Aims: We aimed to explore the lipidomic profile of EVs as a metabolic biomarker for AML and the effects of EVs on redox metabolism of hematopoietic stem/progenitor cells (HSPCs).
Methods: Peripheral blood was collected from AML patients at diagnosis (n=20) and healthy donors (HD, n=20). Immunomagnetically isolated $CD34^+$ cells from umbilical cord blood or AML patients were characterized by analyzing the HSPC-specific cluster of differentiation marker expression, redox profiling (using CellROX, glutathione detection, and MitoTracker) after co-culture with circulating EVs from HD/AML. EVs were purified from platelet-poor plasma by size exclusion chromatography (SEC) and quantified using the NanoSight technology. Quantitative lipidomic profiling was performed by Liquid Chromatography coupled with High-Resolution Mass Spectrometry (LC/HRMS).
Results: In this study, we observed a significant increase in the size of AML EVs compared to HD counterparts ($p= 0,008$). Interestingly, more than 200 molecular lipid species were quantitatively identified in circulating EVs with a total of 25 (out of 200) independent lipid species significantly different between AML-derived EVs and HD. Notably, we reported the abundance of both glycerolipid and fatty acids (FA) species in AML EVs. Within bioactive lipid markedly increased in AML-derived EVs, fatty acid esters of hydroxy fatty acids (FAHFA-18:0_30) were inversely correlated to the percentage of leukemic blasts in the bone marrow ($r= -0,72$, $p=0,009$) suggesting the role as a putative biomarker of disease severity. Through a multivariate statistical analysis of EV lipid profile, we also revealed that AML EVs are depleted in sphingomyelin classes (SMs), a class of lipids that are interconnected to the modulation of oxidative stress. Moreover, after co-cultures of EVs with umbilical cord blood HSPCs, we observed that only EVs isolated from HD increased the granulocyte-macrophage progenitors ($p=0.02$). Conversely, both HD- ($p=0.03$) and AML-derived EVs ($p=0.003$) reduced the megakaryocyte erythroid progenitors. Next, we explored redox metabolism function driven by EVs and we demonstrated a reduction in AML HSPC fraction with high ROS levels in the presence of AML EVs ($p=0.03$). In parallel, AML EVs increased the proportion of AML HSPCs with both high glutathione and mitochondrial potential (p=0.03). Finally, according to the 2017 ELN risk stratification system, we found that EVs from patients with adverse risk were depleted in specific ether-linked phosphatidylethanolamine (EtherPE) and phosphatidylethanolamine (PE) species that are important modulators of EV release and formation.
Summary/Conclusion: This work provides a unique lipid signature of circulating EVs from AML patients and identifies prognostic biomarkers for patients' risk stratification that might reveal novel metabolic vulnerabilities driven by microenvironmental signals.

EP385 FILT3R: AN NGS-BASED ALGORITHM FOR ROBUST DETECTION AND QUANTIFICATION OF FLT3-ITD IN CLINICAL PRACTICE

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Background: *Fms-like tyrosine kinase 3* internal tandem duplications (*FLT3*-ITD) occur in 20-30% of acute myeloid leukemia (AML) cases. These mutations represent both strong prognostic biomarkers and therapeutic targets. Hence, *FLT3*-ITD are systematically sought and quantified using quantitative fragment analysis, as per European LeukemiaNet guidelines. This method estimates the mutant allele fraction as the ratio of the area under the mutant allele (M) peak divided by the area under the wild type (WT) allele peak. Although robust, this technique has several limitations (high limit of quantification 1%, determination of the size of the ITD, limited application). Next generation sequencing (NGS) may represent an alternative method to detect these mutations with high detection sensitivity and the possibility of sequencing several other genes simultaneously.
However, the use of NGS technologies to detect *FLT3*-ITD mutations remains challenging because these mutations are heterogeneous in terms of size and/or insertion site, and the perfect or near perfect duplication of the wild-type sequence. These specificities raise new concerns about bio-informatic processes, and several algorithms have been created to detect this duplication (GetITD, km, ScanITD...). However, most of them fail to detect and annotate the broad variety of ITDs. Others are more efficient but must be used in conjunction with manual analysis which is subjective and thus incompatible with routine activity.
Aims: This work aims to develop a kmer-based algorithm named FiLT3r to detect and quantify ITDs and to compare it with existing algorithms to the reference method.
Methods: The different algorithms were tested and compared to the reference method using patients from a multicenter prospective randomized study BIG1 (NCT02416388). This clinical trial included 500 patients aged 18 to 60 years with de novo AML at diagnosis (Acute promyelocytic leukemia and core binding factor AML were excluded from these protocols). Peripheral blood or bone marrow samples from AML patients were screened with our standard NGS routine with a capture method targeting 81 genes (SSQXT Agilent®) and sequenced with Illumina® technology.
Results: A total of 147 ITDs from 114 *FLT3*-ITD positive patients (23%) and 71 randomized *FLT3*-ITD negative patients (14%), determined according to the fragment method, were sequenced (with an average coverage of 2000 paired-end reads on exon 14-15 *FLT3*). FiLT3r provided results mostly comparable to those obtained by the validated technique, with a sensitivity of 1 and no false positive above a threshold

of 1% (limit of quantification of the reference method). All the ITDs detected with fragment analysis of the 114 patients were confirmed using our NGS-based algorithm even in patients with multiple ITDs. The ratios (M/WT) calculated with our algorithm showed a correlation with the reference method estimated at 0.92 (Figure 1) which appears as the highest correlation coefficient of all the algorithms tested (range: 0.42 – 0.92). Among the patients considered negative using fragment analysis, FiLT3r detected five positive cases but these were found at ratios below the quantification threshold of the reference method. Indeed, this algorithm could detect ITD ratios of about 10^{-4}.

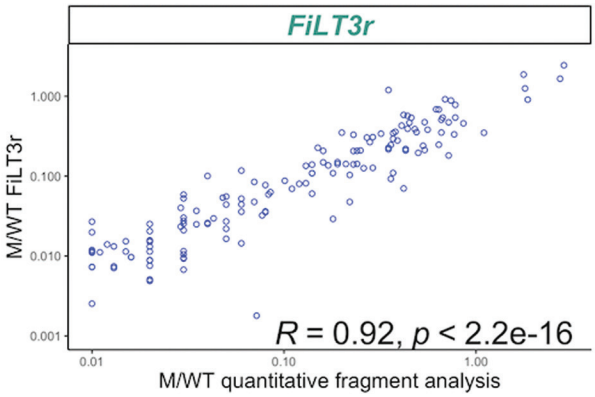


Figure 1: Comparison of FLT3-ITD ratio (M/WT) estimates by fragment analysis versus FiLT3r algorithm

Summary/Conclusion: FiLT3r can accurately and quickly identify *FLT3*-ITDs with a robust estimation. These results need further confirmation on a larger cohort but this algorithm represents a promising NGS-based approach to detect *FLT3*-ITD mutations.

EP386 FREQUENCY AND STIMULATION OF NPM1-SPECIFIC IMMUNE RESPONSES BY ANTI-PD1 ANTI-BODIES IN NPM1-MUTATED AML

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Background: In AML Nucelophosmin1 (NPM1) is one of the most frequently mutated genes and, according to the WHO classification, represents a separate entity that is often associated with a favorable prognosis. Other groups and ours described specific immune responses against immunogenic epitopes derived from the mutational region of NPM1 in AML patients (pts), as well as specific immune responses against leukemic progenitor and stem cells (LPC/LSC).
In a further step, we added the immune checkpoint inhibitor anti programmed death 1 (anti-PD-1), an inhibitory receptor expressed on T cells, to colony forming immunoassays (CFI), to discover whether the immune responses intensify against LSC/LPC comparing $NPM1^{mut}$ and $NPM1^{wt}$ pts.
Aims: In a larger cohort of 15 $NPM1^{mut}$ and 15 $NPM1^{wt}$ AML pts, we investigated immune responses against the mutational epitope NPM1 but also other LAA like PRAME (P300), Wilms' Tumor 1 (WT1) and RHAMM (R3), and compared $NPM1^{mut}$ to $NPM1^{wt}$ pts in CFI to detect CTL mediated immune responses against LSC/LPC.
Methods: We analysed the influence of anti-PD-1 on antigen-specific immune responses by allogeneic cytotoxic T lymphocytes (CTL) against LPC/LSC in functional T cell assays using ELISpot, FACS analysis and colony forming immunoassays (CFI) in $NPM1^{mut}$ vs. $NPM1^{wt}$ pts.
Results: We set out by detecting the reduction of colonies in CFI with the epitope NPM1 and several LAA. In $NPM1^{mut}$ AML pts 9/15 (60%) showed immune responses against all four epitopes. Mean colony reduction for LAA were 32% for P300, 45% for WT-1 and 43% for R3. In $NPM1^{WT}$ AML patient's inhibitory potential of all LAA was seen in 8/15 (53%) samples. Mean colony reduction for LAA was 33% for P300, 34% for WT-1 and 46% for R3. Against the NPM1 epitope $NPM1^{mut}$ patients showed 35% reduction and, as expected, in $NPM1^{WT}$ patients no responses were found, the responses against the other antigens were comparable to the NPM1 mutated patients.
With the addition of anti-PD-1 to CTL before starting CFI, for AML $NPM1^{mut}$ pts the inhibition in CFI using the LAA P300 as target ranged from 0-81% (mean: 32%), for WT1 from 0-74% (mean: 22%), and for R3 from 0-75% (mean: 21%). For AML $NPM1^{WT}$ pts the reduction with P300 with anti-PD-1 as target ranged from 0-59% (mean: 25%), for WT1 from 0-81% (mean: 34%), and for R3 from 0-60% (mean: 23%). Results for LAA were again comparable in both cohorts.
Remarkably, the immune effect in $NPM1^{mut}$ patients increased markedly with the epitope NPM1 and even more when anti-PD-1 was added to CFI, with a mean reduction of 47%. All 15 showed a reduction with anti-PD1, even those that did not show any reduction with the epitope NPM1 alone. A particularly strong additional reduction with the anti-PD1 antibody in CFI of 50% or more was observed in 7/15 $NPM1^{mut}$ pts. 4 of 15 pts showed a slightly lower additional reduction with anti-PD1 in the range of 44-28%.
Summary/Conclusion: We investigated the immune responses of AML pts to LPC/LSC with NPM1/LAA-specific T cells in a larger cohort. With the addition of anti-PD-1 to CFI, the immune resistance could be overcome. In conclusion, the immune checkpoint inhibitor anti-PD-1 increases the cytotoxic effect of T cells against LPC/LSC. The effect was strongest in $NPM1^{mut}$ pts with the epitope NPM1 and even stronger when adding anti-PD-1 to CFI. These data suggest that immunotherapy with a PD-1 antibody, for instance in combination with a NPM1-specific vaccine, possibly in the context of minimal residual disease or maintenance therapy, could be an interesting option for NPM1-mutated patients.

EP387 TARGETING THE IRE1A-XBP1 PATHWAY INDUCES APOPTOSIS IN FLT3-ITD+ AML AND ENHANCES THE EFFECT OF TKI INDUCED FLT3-ITD INHIBITION

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Background: The unfolded protein response (UPR) is a stress sensing signaling network that allows cells to deal with endoplasmic reticulum (ER) stress, a condition characterized by an accumulation of mis- and unfolded proteins in the ER. Acute myeloid leukemia (AML) stem cells reside in the bone marrow niche, where they face stressful conditions, such as hypoxia, low pH and nutrient fluctuations. Together with their oncogene-driven metabolism, they are prone to develop ER stress. Elevated UPR gene expression levels, particularly of IRE1α and XBP1, were found in FLT3-ITD$^+$ AML patient cells. Patients with high XBP1 mRNA expression showed an inferior overall survival compared to those with low XBP1 mRNA expression.
Aims: In this study, we aimed to uncover the potential of pharmacological IRE1α-XBP1 inhibition as a new therapeutic strategy in FLT3-ITD$^+$ AML in combination with a 2nd generation FLT3 tyrosine kinase inhibitor (TKI; quizartinib, AC220). We further wanted to elucidate whether this approach is efficient under hypoxia, the physiological condition in the bone marrow niche that potentially counteracts the TKI response.
Methods: Human FLT3-ITD$^+$ MV4-11, FLT3 wildtype (WT) RS4-11 and murine 32D cells transduced with FLT3-ITD or FLT3 WT were analyzed via Western blot and qRT-PCR. Cell viability was assessed by MTT assay, cell death and apoptosis were measured with propidium iodide (PI) or AnnexinV staining using FACS analysis. The clonogenic potential was determined in CFU assays, using primary patient-derived cells. Hypoxic cell culture conditions were applied (2-3% O_2). Analysis of phosphoproteomics was performed by mass spectrometry.
Results: Pharmacological inhibition of the IRE1α RNase activity using STF-083010 blocked XBP1 splicing and reduced the cell viability of human AML cell lines in a dose dependent way. Interestingly, FLT3 inhibition strongly enhanced the IRE1α mRNA level in 32D FLT3-ITD cells (9.3-fold $p<0.05$) but only weak in 32D FLT3 WT cells (1.5-fold $p<0.01$). 32D FLT3-ITD also showed a 3-fold higher number of PI$^+$ cells after IRE1α inhibition compared to 32D FLT3 WT cells ($p<0.01$). While single treatment of human FLT3-ITD$^+$ MV4-11 cells with either the IRE1α inhibitor or AC220 significantly induced apoptosis, the combinatorial treatment strongly enhanced

this effect (by 3-fold p<0.001). This potent induction of cell death was only observed in FLT3-ITD$^+$ MV4-11 cells, but not in FLT3 WT expressing RS4-11 cells. Likewise, the combination significantly decreased the clonogenic potential of FLT3-ITD$^+$ AML cell lines and AML mononuclear patient cells, but not of healthy donor cells. Cultivation of MV4-11 cells under hypoxia further induced IRE1α signaling and revealed that the effect of AC220 was largely abolished under hypoxia (normoxia: 58.4-fold induction of dead cells p<0.01 hypoxia: 2.2-fold induction p>0.05). Western blot and phosphoproteomic analysis revealed that FLT3 signaling was reduced under hypoxia. Intriguingly, combined targeting of IRE1α and FLT3 overcame this hypoxia-induced AC220 resistance and strongly induced cell death.
Summary/Conclusion: IRE1α-XBP1 signaling is activated in FLT3-ITD$^+$ AML and further enhanced by hypoxic conditions in the bone marrow niche. Targeting IRE1α in FLT3-ITD$^+$ cells is effective to decrease proliferation, clonogenic potential and induces apoptosis. Our data demonstrate that hypoxia-conferred resistance against AC220 can be overcome by simultaneous IRE1α inhibition, making this pathway an interesting novel therapeutic target.

EP388 SWATH-MS PROTEOMIC ANALYSIS IDENTIFIES C/EBPB SUPPRESSION BY RUNX1-ETO AS A POTENTIAL MEDIATOR OF BLOCK IN DIFFERENTIATION

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Background: Acute myeloid leukemia (AML) is a heterogenous disease with multiple morphological, immunophenotypic and genetic features. The t(8;21), which results in the expression of RUNX1-ETO (aka AML1-ETO), is accountable for 12% of AML cases. Even though several studies have determined the transcriptomic changes observed in cells expressing RUNX1-ETO, there is a paucity of studies quantitating proteomic changes.
Aims: To analyze the proteomic profile of RUNX1-ETO expressing cord blood-derived human hematopoietic stem progenitor cells (HSPC) using mass spectrometry techniques.
Methods: We performed quantitative proteomics by SWATH-MS to determine the impact of RUNX1-ETO expression on the proteome using HSPC. Further, to determine changes in subcellular localization induced by RUNX1-ETO, cytosolic or nuclear fractions from these cells were separately analyzed.
Results: We quantified 4,635 proteins of which 2,787 were detected in the cytoplasm, and 1,848 in the nucleus. Statistical analysis identified 257 significantly differentially expressed proteins in RUNX1-ETO HSPC compared to controls, of which 71% were detected in cytoplasm and 29% in the nucleus. We also identified 29 proteins that were seen only in the cytosol and 24 that were seen only in nuclear preparations of RUNX1-ETO cells. Pathway analysis demonstrated significant changes to 'myeloid differentiation' ($p=2.5x10^{-6}$) pathway. Thus, we focused our analysis on identifying the transcription factors potentially responsible for differential expression in RUNX1-ETO cells. Using Metacore™'s transcription factor overconnectivity algorithm we identified C/EBPβ as a novel significant regulator ($p=1.4x10^{-4}$) of the observed 257 proteomic changes. C/EBPβ is a transcription factor belonging to the C/EBP family and related to C/EBPBα, which is mutated in approximately 5-10% of AML patients. In our data, RUNX1-ETO significantly downregulated the expression of C/EBPβ protein *vs* control (2-fold; p=0.01). Analysis of parallel transcriptomic data from the same model showed a 1.4-fold reduction in *C/EBPβ* mRNA level compared to controls suggesting transcriptional suppression by RUNX1-ETO. Further, *C/EBPβ* mRNA is significantly downregulated in t(8;21) patients compared to non-t(8;21) AML FAB M2 patients (2.7-fold; p<0.05). Since *C/EBPβ* is normally upregulated during myeloid development, these data suggest that RUNX1-ETO may inhibit myeloid differentiation by suppressing *C/EBPβ* expression. In support of this, *C/EBPβ* knockdown (KD) in the RUNX1-ETO-expressing cell line, SKNO-1, completely suppressed myeloid cell surface marker expression (CD13, CD33 and CD38) and gave a concomitant 4-fold increase in cell proliferation (p<0.001; n=3). Interestingly, in non-t(8;21) cells lines (HEL and U937) KD of C/EBPβ ablated cell growth (p<0.001) and increased the frequency of apoptotic cells (Annexin V$^+$ 7-AAD$^-$ cells increased by 6-fold in HEL, p<0.01; n=3 and 2-fold in U937 cells, p<0.01; n=3), suggesting that the effects of *C/EBPβ* KD are context dependent.
Summary/Conclusion: In conclusion, proteomics identified hundreds of significantly differentially expressed proteins arising from RUNX1-ETO expression in the cytoplasmic and nuclear compartments. Importantly, we identified C/EBPβ as significantly downregulated mimicking the reduced expression of this transcription factor seen in t(8;21) patients compared AML FAB M2 patients without t(8;21). Functional studies suggest that reduced C/EBPβ expression inhibits myeloid differentiation in a RUNX1-ETO-dependant manner. Currently, we are determining the effect of C/EBPβ KD on normal HSPC growth and differentiation.

EP389 GLUTATHIONE HOMEOSTASIS AND ABCC1 (MRP1) MODULATE THE RESPONSE OF ACUTE MYELOID LEUKEMIA (AML) CELLS TO BCL2 INHIBITION

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Background: The BCL2 inhibitor Venetoclax is a promising targeted anti-cancer agent for the treatment of AML. Despite its overall success, the understanding of molecular mechanisms that modulate Venetoclax efficacy is of utmost importance for successful personalized therapy. It is well established that ATP-binding cassette (ABC-) transporters are important mediators of cancer chemotherapy resistance, but it was unknown if ABC-transporters can modulate the efficiency of BCL2-inhibitors in AML.
Aims: We aim to understand the complex interplay of ABC-transporters and BCL2-inhibitors by systematically evaluating their essentiality in untreated versus BCL2-inhibitor treated AML cell lines.
Methods: We used CRISPR/Cas9-enabled functional genomics, pharmacological and cell biological approaches in human AML cell lines to systematically evaluate the genetic requirements for ABC-transporters in drug-naïve AML. Furthermore, we analyzed how particular ABC-transporters affect the sensitivity of AML cells towards BCL2-inhibitors.
Results: Using CRISPR/Cas9-mediated knockout of all 48 genes encoding ABC-transporters in human AML cells, we show that only *ABCE1, TAP2, ABCA3 and ABCF1* were essential for cell growth of drug-naïve cells. However, we found that knockout of *ABCC1* (*MRP1*) strongly increased the sensitivity of AML cells to the BCL-2 inhibitor Venetoclax. Genetic and pharmacological inhibition of ABCC1 also sensitized AML cells to the BCL2-inhibitors ABT-737, navitoclax and AZD-4320, but not to other drugs that are used to treat AML, such as cytarabine, midostaurine or IDH inhibitors. ABCC1 overexpression induced Venetoclax resistance in leukemia cells. Importantly, MCL1-overexpressing Venetoclax-resistant AML cells could be re-sensitized to BCL2 inhibition by knockout or inhibition of ABCC1. It has been shown that ABCC1-mediated export of molecules requires their conjugation to oxidized glutathione (GSSG). To test whether the ABCC1-mediated effect on BCL2-inhibition requires this pathway, we used buthionine sulfoximine (BSO). As an inhibitor of the glutamate cysteine ligase (GCL), BSO reduces intracellular glutathione (GSH) levels. While BSO treatment alone did not affect the viability of AML cells, it strongly synergized with BCL2 inhibition, improving the efficacy of Venetoclax and AZD-4320.
Summary/Conclusion: Currently, we are investigating the molecular mechanisms underlying the synergy between glutathione homeostasis, ABCC1 and BCL2-inhibition *in vitro* and *in vivo*. In addition to novel molecular insights, our findings could help to establish ABCC1 as a biomarker that helps to predict the efficiency of Venetoclax in the treatment of AML.

EP390 IRAK4 INHIBITOR CA-4948 POTENTIATES ANTITUMOR EFFECTS OF AZACITIDINE AND VENETOCLAX IN HUMAN ACUTE MYELOID LEUKEMIA

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Background: Acute myeloid leukemia (AML) is known to be associated with high lethality despite intensive treatment. Recently published study demonstrated that expression of IRAK4-L is mediated by mutant splicing factor U2AF1 and is associated with oncogenic signaling in human AML and myelodysplastic syndromes (MDS). Preliminary data from our ongoing Phase 1 dose escalation study demonstrated that treatment with IRAK4 inhibitor CA-4948 has shown early signs of clinical activity in patients with relapsed/refractory AML and high-risk MDS.

Aims: Our goal was to identify an effective combination of CA-4948 with standard-of-care (SOC) drugs for the treatment of FLT3-WT AML.
Methods: We used CellTiter Glo cell viability assay to evaluate the anti-tumor effects of CA-4948 in combination with AML SOC drugs daunorubicin, Ara-C, decitabine, azacitidine and venetoclax in FLT3-WT AML cell lines THP-1, F-36P, OCl-AML2 and GDM-1. GI50 (the concentration for 50% of maximal inhibition of cell proliferation) was determined for each drug in AML cell lines. Either GI50 (below peak plasma concentration) or peak plasma concentration (if GI50 was higher than peak plasma concentration) of each drug was used as clinically relevant concentration for combination experiments.
Results: We identified THP-1 and F-36P cell lines as resistant to clinically relevant concentrations of venetoclax, whereas OCl-AML2 cell line was resistant to the treatment with azacitidine. Synergistic effect of combining CA-4948 with Ara-C was observed in THP-1 cell line. We found that CA-4948 potentiated antitumor effects of azacitidine in 3 of 4 FLT3-WT AML cell lines whereas we did not observe any additive or synergistic effect of combining CA-4948 with decitabine. The combination of venetoclax and CA-4948 inhibited the cell growth in 2 of 4 AML FLT3-WT cell lines more effectively than either of the two agents alone. Moreover, we found that CA-4948 significantly potentiated antitumor effects of azacitidine+venetoclax in all AML FLT3-WT cell lines.
Summary/Conclusion: Our results demonstrate that combination of CA-4948, azacitidine and venetoclax exhibits synergistic activity in FLT3-WT leukemia cells providing a rationale for clinical testing of this combination in FLT3-WT AML patients.

EP391 RECURRENT DELETIONS IN CLONAL HEMATOPOIESIS ARE DRIVEN BY MICROHOMOLOGY-MEDIATED END JOINING

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Background: Human aged hematopoietic stem and progenitor cells (HSPCs) are prone to clonal expansion due to the acquisition of recurrent somatic mutations. This phenomenon is known as age-related clonal hematopoiesis (ARCH). While somatic pre-leukemic mutations (pLMs) which define ARCH are mostly nonsynonymous single nucleotide variants (SNVs), insertions and deletions (indels) are less common and the mutational mechanisms underlying indels are less understood.
Aims: In the current study we aim to characterize mutational processes leading to recurrent deletions in clonal hematopoiesis.
Methods: We used CRISPR/Cas9 system to introduce targeted DSBs into the hotspot region of *ASXL1* and *SRSF2* genes to recapitulate recurrent deletions in these genes. We further studied the mutational mechanisms leading to these deletions by in vitro knock out models and PARP1 inhibitor treatments.
Results: In the current study we inspected the genomic regions around recurrent deletions in myeloid malignancies, and identified microhomology (MH)-based signatures in *CALR*, *ASXL1* and *SRSF2 loci*. We demonstrate that these deletions are the result of double stand break (DSB) repair by a PARP1 mediated Microhomology-mediated end joining (MMEJ) pathway. Importantly, we provide evidence that recurrent MH-based deletions originate in pre-leukemic HSCs, suggesting an MMEJ predominance in clonal hematopoiesis. While polymerase theta (POLQ) is considered a key component in MMEJ repair, we provide evidence that pre-leukemic MMEJ (preL-MMEJ) deletions can be generated in *POLQ* knock out cells. In contrast, inhibition of the replicative polymerases (which are co-expressed with *PARP1* in human HSCs) resulted in a significant reduction in preL-MMEJ.
Summary/Conclusion: Our data indicate an association between polymerase theta independent MMEJ and clonal hematopoiesis and elucidate mutational mechanisms involved in the very first steps of leukemia evolution.

EP392 TARGETING THE RUNX1-RUNX1T1 FUSION GENE USING CRISPR-CAS9 TECHNOLOGY EFFECTIVELY INHIBITS PROLIFERATION AND DECREASES TUMOR VOLUME IN VITRO AND IN VIVO

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Background: Acute myeloid leukemia (AML) with translocation 8;21 (AML8;21) is a core-binding factor AML characterized by the oncogenic fusion protein RUNX1-RUNXT1. AML8;21 is one of the most common types of AML and is associated with a favourable prognosis with an estimated 5-year overall survival of 60-70%. However, 30% of patients relapse following first line treatment, leaving these patients with very limited treatment options. Patients older than 65 years represent a particular challenge as many are not candidates for treatment with cytarabine and daunorubicin. The RUNX1-RUNX1T1 fusion protein impairs differentiation and maturation of hematopoietic cells and is unique to the malignant clone, thus constituting a potential target for treatment. In recent years, CRISPR-Cas9 technology has shown great promise in various gene therapy applications. In cancers with known oncogenic drivers, such as AML8;21, there is further potential for novel treatment strategy development utilizing CRISPR-Cas9.
Aims: In this study, we aimed to utilize a novel CRISPR-based treatment strategy to target the *RUNX1-RUNX1T1* fusion gene.
Methods: The oncogenic fusion gene *RUNX1-RUNX1T1*, was targeted with CRISPR-Cas9 in the human AML cell line, Kasumi-1, and in archival cells obtained from *RUNX1-RUNX1T1*-positive AML patients treated at the Department of Hematology at Aarhus University Hospital, Denmark. CRISPR-Cas9-based disruption of the *RUNX1-RUNX1T1* fusion gene was validated using targeted polymerase chain reaction (PCR) and Sanger sequencing. Kasumi-1 cell population growth and cell population proliferation was investigated following CRISPR-CAS9-based disruption of *RUNX1-RUNX1T1*. Six nude mice were injected with CRISPR-Cas9 *RUNX1-RUNX1T1* disrupted Kasumi-1 cells or non-treated Kasumi-1 cells in the right and left flank, respectively. Animals were sacrificed after four weeks and tumor volume was evaluated.
Results: We show CRISPR-Cas9-based disruption of *RUNX1-RUNX1T1* in Kasumi-1 cell line and AML-patient-derived cells. *In vitro* cell growth rate and proliferation were decreased by 58 % and 74 %, respectively, in CRISPR-Cas9 *RUNX1-RUNX1T1* disrupted Kasumi-1 cells compared to controls. Four out of 6 mice had tumor growth following injection with *RUNX1-RUNX1T1* disrupted or control Kasumi-1 cells an thus allowed for analysis of *RUNX1-RUNX1T1* disruption effect on tumor volume. Two mice developed a tumor in only the control flank while the two other mice developed tumors in both flanks. In the two mice with tumor development in both flanks, tumor volumes were decreased by 69 % and 91 % in the CRISPR-Cas9 *RUNX1-RUNX1T1* disrupted flank, as compared to the control flank.
Summary/Conclusion: In this proof of principle study, we demonstrate a novel CRISPR-based technology that effectively inhibits proliferation and decreases tumor volume *in vitro* and *in vivo*. Our results suggest that targeting the *RUNX1-RUNX1T1* fusion gene can potentially be a future treatment strategy for patients with AML8;21.

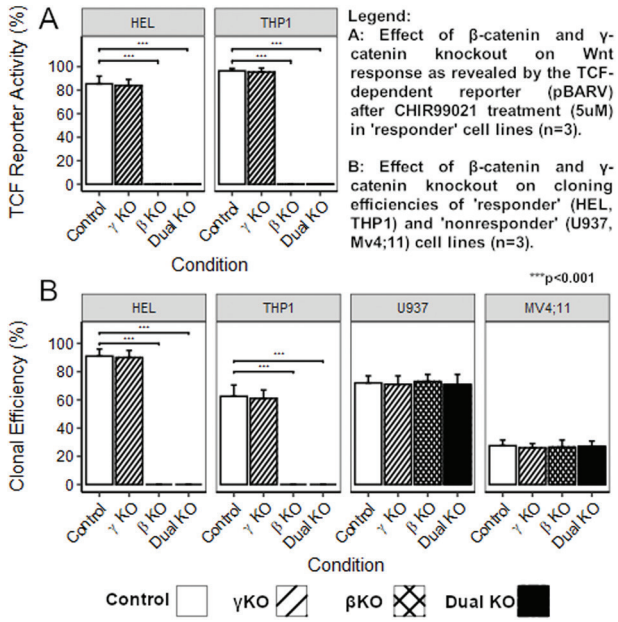
EP393 CANONICAL WNT SIGNALING-RESPONSIVE ACUTE MYELOID LEUKEMIA CELLS ARE DEPENDENT ON BETA-CATENIN BUT NOT GAMMA-CATENIN FOR CLONAL GROWTH

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Background: Canonical WNT signaling is a critical pathway for normal development. β-catenin, the central mediator, is constitutively degraded in the absence of an agonist. Following activation, stabilized β-catenin localizes to the nucleus and associates with TCF/LEF factors to create a transcription complex that targets genes involved in survival, proliferation, cell fate determination and stemness. WNT signaling has been identified as one of the most frequently dysregulated pathways in acute myeloid leukemia (AML), with β-catenin prominently overexpressed at mRNA and protein levels in patients where it is associated with poor clinical outcomes. In addition, overexpression of β-catenin in human hematopoietic stem cells (HSC) blocks multilineage differentiation, mimicking the AML phenotype. However, whether canonical WNT signaling has an essential role in AML remains contentious due to leakiness in gene targeting and RNAi approaches and failure to exclude possible redundancy in respect of its close homologue, γ-catenin. Furthermore, only a subset of patients and cell lines demonstrate nuclear translocation of β-catenin, suggesting dependency is unlikely to be universal in AML.
Aims: To establish whether AML cells are dependent on β-catenin and/or γ-catenin expression for their growth and survival using CRISPR-Cas9 to genetically edit cells.
Methods: We employed CRISPR-Cas9 lentivirus to generate single and dual knockout of β-catenin (βKO) and γ-catenin (γKO) to study the

functional impact of complete knockout of canonical WNT signalling in AML cell lines. All KO cultures were validated by sequencing alongside ablation of protein expression and TCF reporter response. Equivalent non-targeted CRISPR-Cas9 lines were used as controls.
Results: As previously shown, we found that AML cell lines are heterogeneous in their response to β-catenin agonists with "responders" (such as HEL and THP1) showing strong nuclear localization of β-catenin and TCF-dependent transcriptional responses to agonist, whilst "non-responders" (such as U937 and Mv4;11) failed to localize β-catenin to the nucleus and generated no transcriptional response. We generated complete knockouts of β-catenin and γ-catenin (singly and in combination) in all these lines starting with clonal populations co-expressing a TCF-dependent YFP reporter. βKO resulted in ablation of TCF reporter signal in responder lines, whilst γKO had no effect (Fig.1A), showing that β-catenin is essential for canonical WNT signaling and its role was not redundant in respect of γ-catenin. We found βKO was incompatible with clonal growth in responder lines whereas γKO had no effect. Predictably, colony forming efficiency of non-responder lines was unaffected by any KO condition (Fig.1B). Clonal growth of βKO lines could be rescued by co-cultivation with WT cells (but not with WT conditioned medium, supplementary cytokines, or stromal support) suggesting rescue by a short-range/labile autocrine factor or engagement with a cell surface molecule. Rescued clonal βKO cultures grew autonomously in bulk culture when purified by FACS, but could not be re-cloned, demonstrating stable and continuing dependence on β-catenin for clonal growth.



Summary/Conclusion: Together these data show that β-catenin has functional relevance for clonal growth in WNT-responsive AML lines but not in lines that are unresponsive to WNT agonist. We saw no dependency on γ-catenin in any context. We are currently performing RNAseq to identify candidate genes mediating β-catenin-dependent survival under clonal conditions.

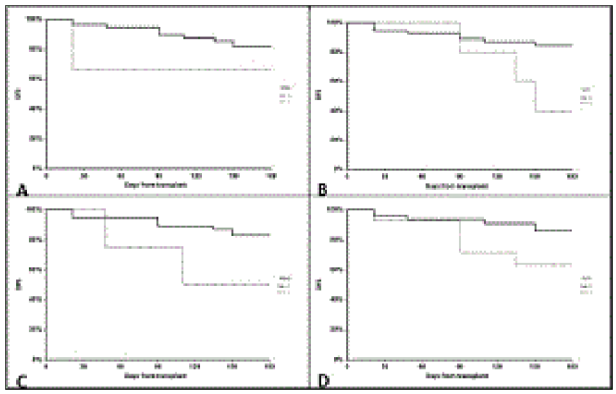
EP394 BASELINE SOMATIC MUTATIONS PREDICT DISEASE FREE SURVIVAL AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA: A RETROSPECTIVE MONOCENTRIC REPORT

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Background: In the last years the advent of Next Generation Sequencing (NGS) contributed to the identification of new somatic mutations involved in the leukemogenesis process, allowing a revised stratification of the biological risk for acute myeloid leukemia (AML) and providing a new tool for minimal residual disease evaluation.
Aims: We evaluated the impact between NGS profile and post transplant outcome, with particular interent on relapse occurrence.
Methods: We enrolled 64 patients with AML submitted to allogeneic stem cell transplantation (HSCT) in our department between November 2015 and September 2020. NGS panel performed at diagnosis included 18 genes: CBL, SF3B1, U2AF1, ZRSR2, KRAS, ASXL1, CEBPA, KIT, DNMT3A, EZH2, IDH1, IDH2, RUNX1, SRSF2, TET2, TP53, WT1, NRAS.
Results: Mutation distribution was as follows: CBL (n=1), SF3B1 (n=1), U2AF1 (n=1), ZRSR2 (n=1), KRAS (n=1), ASXL1 (n=9), CEBPA (n=9), KIT (n=15), DNMT3A (n=22), EZH2 (n=17), IDH1 (n=10), IDH2 (n=10), RUNX1 (n=6), SRSF2 (n=2), TET2 (n=30), TP53 (n=3), WT1 (n=6), NRAS (n=4). Median age was 55.5 years (17-73). Risk group according to European Leukemia Net was as follows: favourable (n=8), intermediate (n=42), adverse (n=14). Thirty-nine patients achieved a first complete remission before transplant, 8 were in second remission, 14 had relapsed disease and 3 received HSCT upfront. A significant difference in terms of DFS was found accordingly to some mutations. Patients mutated for TP53 (n=3) showed a 6 months DFS of 66.7% as compared to 81.4% in non mutated (n=61) (p=0.02, Fig.1A). Mutated WT1 patients (n=6) had a 6 months DFS of 40% as compared to 84.8% in non mutated (n=58) (p=0.047, Fig.1B). Six-months DFS was of 63.5% and 83% in patients with (n=4) and without (n=60) NRAS mutation, respectively (p=0.005, Fig1C). Accordingly to FLT3 mutation, 6 months DFS was of 63.5% in mutated patients (n=14) as compared to 83% for non mutated (n=49) (p=0.048, Fig1D). Multivariate analysis for DFS confirmed TP53 (HR 12.96, 95% CI 4.16-39.61, p=0.0009), WT1 (HR 5.03, 95% CI 1.08-23.37, p=0.04), FLT3 (HR 4.63, 95% CI 1.22-17.50, p=0.02) and NRAS (HR 8.17, 95% CI 4.42-39.62, p=0.0004) together with absence of complete remission at the time of transplant (HR 7.89, 95% CI 2.23-27.92, p=0.001) as independent factors for relapse after transplant. Moreover, we found a detrimental impact of triple mutation FLT3+NPM1+DNMT3A on DFS. Patients with any of these mutations (n=30) had 6 months DFS of 85.2% as compared to 89.8% for patients with one or two mutations (n=23) and 50% in patients triple mutated (n=8) (p=0.04). We then evaluated if a difference might be in young (<60 years) and old patients in terms of mutations influence. TP53, WT1, FLT3 and triple mutation DNMT3A, FLT3 and NPM1 were confirmed in young whereas only NRAS was confirmed in old patients.

Figure 1:6-months DFS according to TP53 (A), WT1 (B) NRAS (C) and FLT3 (D) mutations.



Summary/Conclusion: The presence of some mutations like as WT1, TP53, NRAS, FLT3 or concomitant mutated status for FLT3, NPM1 and DNMT3A worsened post transplant outcome in terms of disease free survival, independently from transplant features. Certainly, these finding need to be confirmed in a larger study population.

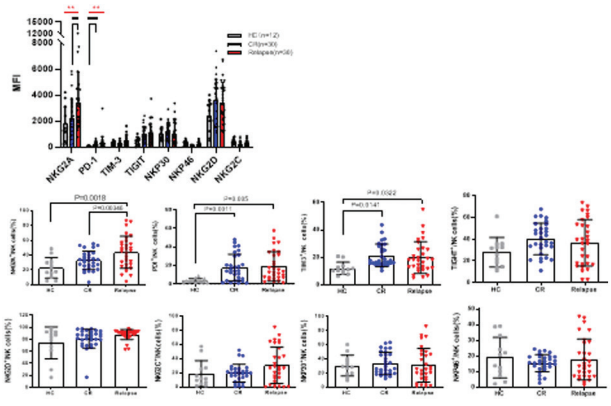
EP395 NK-CELLS EXHAUSTION WHICH DUE TO NKG2A OVER-EXPRESSION IS ASSOCIATE WITH RELAPSED IN ACUTE MYELOID LEUKEMIA PATIENTS

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Background: Leukemia relapse is the main cause of treatment failure in leukemia.Natural killer (NK) cell is effective lymphocytes and play irreplaceable role in anti-leukemia procession. However,whether the status of NK cells affects recurrence is rarely discussed.
Aims: To evaluate the prognostic impact of NK-cells exhaustion in relapsed patients, and explore its impact due to NKG2A over expression
Methods: We perform analyses on 72 bone marrow samples, enrolled from 12 health donors (HC) and 30 AML patients who had experienced first hematological relapse after HSCT (Relapse) as well as 30 matched AML patients in remission (CR), to detect NK-cells phenotype,cytotoxicity, proliferation as well as RNA-sequences in the above group. The cytotoxicity and cytokine secretion of NK cells was determined using CD107a expression and IFN-γ production against K562 or THP-1 cell line as targets. In each of the above groups, NK cells were sorted for killing AML blasts to detect NK lysis function.
NK cells or blocking the NKG2A receptor NK cells were xenografted into NPG mice with or without leukemia to detect NK cells survival in vivo. NK cells sorted from spleen were used for cytotoxicity assessment of anti-leukemia in vitro. And tumor burden in NPG mice was monitored by using in vivo imaging system.
Results: The results declared that exhausted NK-cells expansion showed with naïve phenotype which $CD56^{bright}$ (P=0.0002) and NKG2A receptor (P=0.00346) overexpression in AML relapsed patients. Although there existed NK-cells expansion in AML relapsed patients with the frequency of $KI67^{+}$NK cells significantly higher(P=0.002),the cell cycle of NK cells was stagnated in G1 stage in AML relapse patients(P<0.0001) compared to those patients in CR group. After 48 hours of co-incubation, NK-cells sorted from relapsed patients resulted in significantly less leukemia blasts apoptosis(P=0.0245) in vitro. Further-more, NK cells display compromised cytotoxicity of CD107a degranulation (P=0.0008) and IFN-γproduction (P=0.0167) in the presence of K562 target cells ex vivo. The RNA-seq data show NK-cells exhaustion is followed up down-regulation of the transcription factors T-bet(P=0.0122)and up-regulation of the cyclin D2(P=0.0035).
Among the 30 AML relapsed patients, only 21 patients received chemotherapy and/or DLI treatment, of which 13 patients were treated effectively and the rest were ineffective.Surprisingly, in these patients with curative effects after treatment, the proportion of $NKG2A^{+}$NK cells sharp dipped(P=0.0075), and the IFN-γproduction (P=0.0263) also improved, comparing with their data on relapsed time one by one. Whatever, in patients who have failed treatment, the expression of NKG2A is further up-regulated(P=0.0075), and the function of NK cells remains unchanged, corresponding to their data on first relapsed time one by one.
In immunodeficiency mice model with adoptive NK cells infusion, we found that NK-cells exhausted with elevated NKG2A expression(P<0.005)and limited anti-leukemia function(P<0.05)and shorter persistent time in leukemia-infiltration mice compared with those mice without leukemia(P<0.05).Meanwhile, in immunodeficient mice with leukemia-burden, infusion of NK cells blocking NKG2A receptor can significantly reduce tumor burden(P<0.001)and improve the long-term survival rate of mice compared to those xenografted with untreated NK cells(P<0.001).



Summary/Conclusion: NK-cells exhaustion is associated with relapse in AML patients. NKG2A receptor blocking could rescue NK cells exhaustion and may be considered as a penitential effective therapy to improve the therapy efficacy for relapsed AML patients.

EP396 LONGITUDINAL PATIENT-DERIVED XENOGRAFT MODELS REVEAL CONVERGENT MOLECULAR EVOLUTION IN ACUTE MYELOID LEUKAEMIA

C. Engen [1], M. Hellesoy [2], T. H. Dowling [1,3,*], S. Eldfors [4], B. Ferrel [5], S.-E. Gullaksen [1,6], M. Popa [7], A. Brendehaug [8], R. Karjalainen [4], M. M. Majunder [4], K. Porkka [9], R. Hovland [10,11], Ø. Bruserud [6], J. Irish [12], C. Heckman [4], E. McCormack [1,3], B. T. Gjertsen [13,14]

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Background: Acute myeloid leukaemia (AML) is considered a highly heterogeneous disease. Novel therapeutic approaches in AML aim to target the molecular mechanisms thought to drive leukemogenesis, but emergent evidence suggests that intra-leukemic composition may be more diverse than previously appreciated. To improve AML outcome, the representation of leukaemic composition in patient derived xenografts and their potential in precision oncology has to be elucidated.
Aims: Interpreting the intra-leukaemic heterogeneity and hierarchy may be challenging in large patient cohorts. Here, we decipher the temporal disease composition of an AML patient through longitudinal sampling and explore the inherent leukaemogenic potential of the primary samples through establishment of serial patient-derived xenograft (PDX) models.
Methods: Primary and PDX-derived samples were analysed in parallell by high-resolution genetic and phenotypic approaches, including sequencing, immunophenotyping and *ex vivo* drug sensitivity testing.
Results: Comparison of the genetic composition revealed that all PDX samples bore a closer resemblance to other PDX samples than to the distinct primary samples from which they originated, indicating a pattern of convergent molecular evolution likely resulting from the selective force of the murine environment.
Across the primary and PDX samples, we identified at least six discrete leukaemia-initiating cell populations, of which five were characterised by known recurrent mutations in AML, including mutations in *ASXL1*, *FLT3* and two independent NRAS mutations. These populations correlated with immunophenotypically defined cell subsets displaying distinct drug sensitivity profiles, suggestive of distinct functional properties.
Summary/Conclusion: Our results indicate that the genetic and phenotypic development are closely intertwined, and that diversity in the leukaemic gene-environment likely influences disease trajectories.

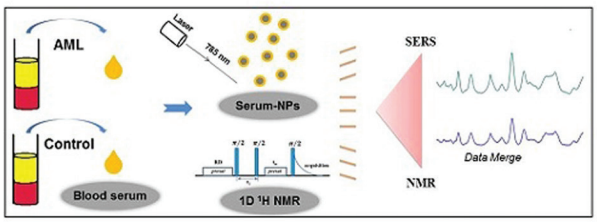
EP397 DIFFERENTIATION OF ACUTE MYELOID LEUKEMIA SUBTYPES BY SERUM-BASED SPECTROSCOPY COUPLING WITH NON-TARGETED METABOLIC FINGERPRINTS

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Background: The proportion of adult non-M3 AML patients with poor prognosis is relatively large, which is mainly restricted by the current clinical detection limits and sensitivity. To explore new markers that can realize rapid screening and sensitive diagnosis of de novo non-M3 diagnosis of AML subtypes has important clinical significance.
Aims: The aim of this study is to explore serum-based markers in non-M3 AML patients after developing a synthetic approach on Ag nanoparticles-based surface-enhanced Raman spectroscopy (SERS) and non-targeted proton NMR metabolomics.
Methods: According to FAB classification, the serum samples were prepared from five types of non-M3 AML patients (including M0~M2, M4, and M5, n=50 for each type) and healthy controls (n=50, age and gender matched). The Ag substrate nanoparticle-serum complex was first prepared for SERS measurement. The serum metabolites were identified by 1D ^{1}H NMR method. Statistical methods were utilized in unsupervised and supervised analyses. Both SERS band-intensity data and the metabolite-concentration data were set to merge in classification model for determination of relative diagnostic markers. The receiver operating characteristic (ROC) curves were used to assess the performance of these markers.
Results: We found significant changes in non-M3 AML patients with different subtypes. These appeared in tryptophan, serine, phenylalanine, proline and valine, as well as a variety of nucleic acid bases, phospholipids, D-mannose and collagen. These components were specifically characterized according to vibration mode due to their secondary structure. Several amino acids including tryptophan, serine, phenylalanine, proline and valine, as well as D-mannose were shared in serum metabolites analysis. These metabolites/components were shown to be the key to identify different AML subtypes. Further metabolic pathway analysis suggested disorders in multiple pathways, among which all five types can be separated when SERS and NMR data were set to merge for classification. Typically, the M5 AML was found to be abnormally active in glutathione metabolism, which may show some specificity for diagnosis, but its underlying mechanism still need to be addressed.



Summary/Conclusion: We have proposed the combined analysis of serum-based optics and metabolomics to provide rapid screening markers for AML patients with non-M3 diagnosis. It was also demonstrated that this method was of great value in clinical application with acceptable accuracy and good reproducibility.

EP398 MEGAKARYOCYTIC TRANSCRIPTION FACTOR ARID3A SUPPRESSES GATA1S-INDUCED MALIGNANT TRANSFORMATION

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Background: Down syndrome-associated myeloid leukemia (ML-DS) is characterized by the triad of trisomy 21, fetal origin and mutations in *GATA1* (*GATA1s* mutations). We previously described that miR-125b synergized with mutated GATA1s via downregulation of the transcription factor ARID3A. However, the mechanisms of this synergy remained to be understood.
Aims: We aimed to understand the function of ARID3A in normal hematopoiesis and unravel its role in the pathogenesis of Down syndrome (trisomy21)-associated leukemia in cooperation with oncogenic GATA1s.
Methods: We combined CRISPR-Cas9 genome editing with lentiviral gain- and loss-of-function studies in hematopoietic stem/progenitor cells (HSPCs) and primary patient blasts. We integrated gene expression profiling after *Arid3a* modulation in *GATA1s* fetal cells with CUT&RUN and mass spectrometry analyses to identify key ARID3A-regulated pathways involved in leukemic transformation.
Results: RNA-Seq data of sorted blood cells indicated increased *ARID3A* expression in megakaryocytes compared to erythroid cells. Accordingly, *Arid3a* overexpression in fetal and adult HSPCs promoted megakaryocytic differentiation (1.73x and 2.89x fold increased CD41a^{+}CD42d^{+} megakaryocytes, p=0.0.17 and p=0.018, respectively), while shRNA-mediated *Arid3a* knockdown in fetal HSPCs caused a 40% reduction (p=0.04). Interestingly, while *Gata1s* perturbs erythroid differentiation and induces hyperproliferation of fetal HSPCs, *Arid3a* knockdown blocks their otherwise unperturbed megakaryocytic differentiation, leading to the expansion (3.6x fold) of CD117^{+}CD41^{+} megakaryocytic progenitors *in vitro* and development of ML-DS-like leukemia (CD41^{+}CD117^{+}) upon transplantation into syngeneic C57BL/6J recipients *in vivo* (71 days median disease-free survival and 100% penetrance).
To understand the ARID3A molecular network and its role in leukemia progression, we leveraged gene expression data (RNA-Seq), chromatin occupancy (CUT&RUN) and mass spectrometry (LC-MS/MS). Integrated analysis uncovered that ARID3A promotes terminal differentiation by occupying and inducing megakaryocytic genes in concert with GATA1. In parallel, ARID3A binds SMAD2/3, forming a complex that mediates TGFβ-induced cell cycle arrest and apoptosis. In line with a role as tumor suppressor, low expression in pediatric AML patients (NCI-TARGET) associates with poorer overall survival (53.9% vs. 67.7%; P-log-rank = 0.025). Importantly, restoring expression of *ARID3A* in ML-DS patient-derived xenografts suppressed leukemic growth and promoted megakaryocytic differentiation *in vitro* and *in vivo*.
Summary/Conclusion: We uncovered a novel function of ARID3A in promoting megakaryocytic differentiation in concert with GATA1 and mediating TGFβ-induced cell cycle arrest and apoptosis in complex with SMAD2/3. Inversely, ARID3A repression is a key event in the pathogenesis of ML-DS as *Arid3a* knockdown blocks the otherwise unperturbed megakaryocytic differentiation of hyperproliferative *Gata1s* megakaryocytic progenitors arresting them in an undetermined differentiation status and causing leukemia. Our work provides a basis to develop refined treatment approaches by restoring the ARID3A-induced differentiation program.

EP399 SIGNALLING INTERACTIONS OF MEGAKARYOCYTE-ERYTHROID PROGENITOR CELLS AT TIME OF DIAGNOSIS PREDICT SURVIVAL IN ACUTE MYELOID LEUKAEMIA

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Background: Although high rates of initial responders to cancer therapies are observed, relapse and metastasis are the most frequent causes of cancer-related death. Providing insights into cancer cell populations, and elucidating biological mechanisms of relapse is necessary for tailoring more effective treatment options. This is also apparent in Acute Myeloid Leukaemia (AML), a highly heterogeneous aggressive blood cancer with poor overall survival. Hence, there is a major challenge that could be addressed using high-throughput single-cell technologies combined with effective bioinformatics tools.

Aims: We hypothesised that characterizing hematopoietic cells in AML, and investigating the strength of signalling interactions between proteins at time of diagnosis, could identify predictors of survival.
Methods: To investigate our hypothesis, we performed CyTOF analysis on peripheral blood samples collected from 45 AML patients. The samples were stained with an antibody panel consisting of 21 surface and 15 intracellular markers, allowing for deep phenotypic profiling as well as monitoring of signalling pathways. To improve phenotypic characterisation of hematopoietic cells, a gating strategy was implemented using data from seven healthy donors. Next, Linear Discriminant Analysis allowed us to align cancer cells to their closest healthy cell phenotypes, resulting in a single-cell hematopoietic classifier. To alleviate the challenge of modelling complex single-cell data, Conditional Density Resampled Estimate of Mutual Information (DREMI) was utilised. DREMI quantifies the information transfer between pairs of proteins measured with single-cell resolution. Application of Machine Learning (ML) on DREMI-derived features combined with Feature Selection, allowed us to develop cell type specific models for survival, and to rank the most informative signalling interactions.
Results: By applying ML to DREMI-derived features extracted from different hematopoietic cell populations, we constructed cell type specific models for survival that were validated twice, with repeated cross-validation (n=38) and an independent validation cohort (n=7). Our analysis suggested that signalling interactions of cancer cells aligned to Megakaryocyte-Erythroid Progenitor (MEP) cells defined on the basis of CD45-low/CD34+/CD38+/CD123-low markers at time of diagnosis, predicted clinical outcome with an average performance of 0.83 Area Under the Curve, 0.78 Balanced Accuracy, 0.86 Positive Predictive Value and 0.82 F1 score. Our analysis also suggested that three signalling interactions of MEP cells between, pCREB-pSTAT5, pSTAT1-pSTAT5 and pHistone3-pSTAT5 were the most informative predictors. Retrospective analysis of both training/testing and validations cohorts (n=45), using Cox proportional-hazards modelling and Kaplan-Meier survival analysis, re-confirmed the potentials of the identified interactions to predict clinical outcome. Finally, our framework allowed us to investigate the dynamics of the identified interactions, using paired CyTOF samples collected 4 and 24 hours after chemotherapy initiation.
Summary/Conclusion: We presented a novel data-drive approach that leverages hematopoietic single-cell classification with ML modelling of signalling interactions to predict survival. In this way, our work provides direct associations between cell phenotypes, signalling states and clinical outcome. Although, the developed computational framework, has been specifically designed and applied for the analysis of signalling dynamics in AML, it can be applied to other cancer types as well.

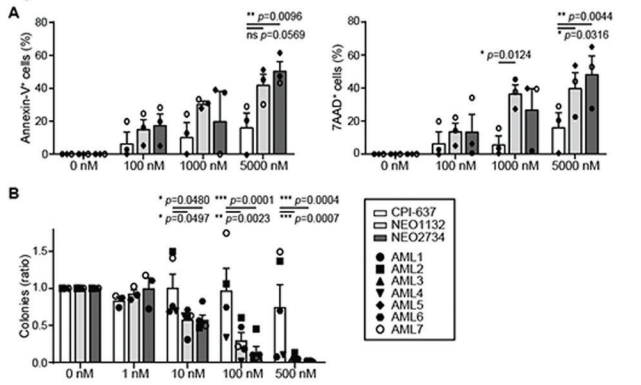
EP400 THE NOVEL ORAL BET-CBP/P300 DUAL INHIBITOR NEO2734 IS HIGHLY EFFECTIVE IN ERADICATING ACUTE MYELOID LEUKEMIA BLASTS AND STEM/PROGENITOR CELLS

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Background: Acute myeloid leukemia (AML) is a disease characterized by transcriptional dysregulation, that results in a block in differentiation and aberrant self-renewal. Inhibitors directed to epigenetic modifiers, aiming at transcriptional reprogramming of AML cells, are currently in clinical trials for AML patients. Several of these inhibitors target bromodomain and extra-terminal domain (BET) proteins, cyclic AMP response binding protein-binding protein (CBP), and the E1A-interacting protein of 300 kDa (p300), affecting histone acetylation. Unfortunately, single epigenetic inhibitors showed limited efficacy due to appearance of resistance and lack of effective eradication of leukemic stem cells.
Aims: To evaluate the efficacy of the novel dual BET and CBP/p300 inhibitors NEO2734 and NEO1132 in the elimination of AML (stem/progenitor) cells.
Methods: We investigated the efficacy of NEO2734, NEO1132 and the CBP/p300 inhibitor CPI637 to induce cell death in AML cell lines and primary AML (stem/progenitor) cells. Moreover, we studied the effect of treatment with the NEO drugs on myeloid blast proliferation, apoptosis, clonogenic capacity of long- and short-term surviving AML cells *ex vivo*, on engraftment potential in a patient-derived xenograft AML mouse model (NSG mice injected with primary AML), and we determined the toxicity of the NEO drugs on normal hematopoietic cells.
Results: The two novel, orally available inhibitors NEO1132 and NEO2734 targeting both the BET and CBP/p300 proteins inhibited proliferation of a panel of AML cell lines, NEO2734 being the most potent, with IC50 values ranging from 27 nM to 125 nM. Both NEO1132 and NEO2734 induced apoptosis by downregulating c-Myc and Bcl2. Moreover, incubation of primary AML samples with the NEO drugs eliminated leukemic CD45dim blasts, myeloid CD45dimCD33+ leukemia cells, and CD45dimCD34+ immature blasts, while the lymphocytes were unaffected. Both NEO2734 and NEO1132 induced apoptosis in primary CD45dim leukemic blasts (Figure 1A). Importantly, treatment with NEO1132 and NEO2734 resulted in a significant reduction in clonogenic capacity of leukemic stem/progenitor cells from AML patient samples. Already after treatment with 10 nM a significant reduction in the number of colonies was observed in all tested primary AML cases (Figure 1B). To evaluate the potential of the NEO drugs to reduce human AML burden *in vivo*, primary AML cells were injected into NSG mice and the mice were orally treated with NEO2734 or NEO1132 (10 mg/kg for 11 times). A significant reduction in leukemic burden in the bone marrows of the mice was observed after treatment with NEO2734. Finally, we demonstrated that NEO2734 increased effectiveness of combination chemotherapy treatment *in vivo*.
To restore normal hematopoiesis after therapy, therapeutic approaches targeting leukemia cells should spare normal hematopoietic cells. Both NEO2734 and NEO1132 reduced the survival of normal human bone marrow cells only at high concentrations (1 μM), and with a 3.4-fold and 2.0-fold lower efficiency than the drugs affected primary AML cells. Oral treatment with NEO2734 or NEO1132 did not significantly reduce the weight of the mice, and did not affect the survival of normal mouse hematopoietic cells.

Figure 1



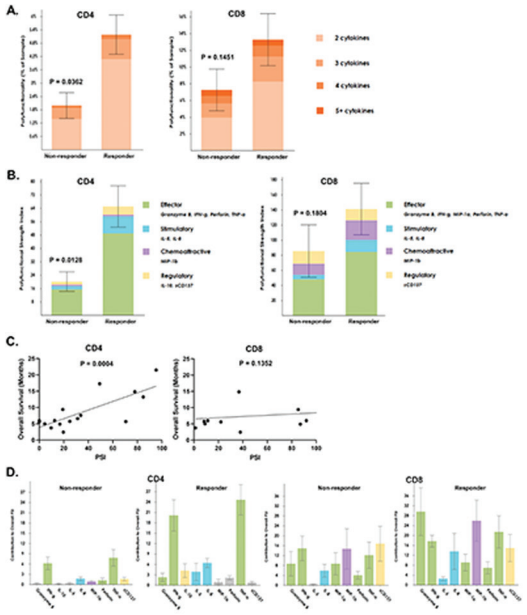
Summary/Conclusion: The dual BET-CBP/P300 inhibitor NEO2734 eliminates AML blasts and LSCs/progenitors in a nanomolar concentration, implicating that dual inhibition of BET and CBP/p300 using NEO2734 is a promising therapeutic strategy for AML patients, making it a focus for clinical translation.

EP401 POLYFUNCTIONALITY DETERMINED BY SINGLE-CELL PROTEOMICS OF BONE MARROW-DERIVED CD4 T-CELLS FROM PATIENTS WITH ACUTE MYELOID LEUKEMIA PREDICTS PATIENTS RESPONDING TO ANTI-PD-1-BASED THERAPY

H. Abbas [1,*], S. Mackay [2], M. Cyr [2], J. Zhou [2], G. Issa [3], M. Alfayez [3], S. Kornblau [1], E. Jabbour [3], G. Garcia-Manero [3], M. Konopleva [3], M. Andreef [3], N. Daver [3]

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Background: In a phase 2 clinical trial in patients with relapsed/refractory AML, combining azacitidine with nivolumab demonstrated encouraging response rates (33%), median event-free and overall survival, compared with a historical cohort of contemporary patients treated with azacitidine-based therapies. Biomarkers of response are yet to be determined.
Aims: In this sudy, we aimed to identify biomarkers of response to nivolumab-based therapy using single cell polyfunctional proteomic assays.
Methods: Eleven non-responders and 5 responders to treatment based on ELN2017 response criteria had available samples and were analyzed. Bone marrow samples were collected prior to and at end of second treatment cycle. A total Polyfunctional T cells co-secreting 2+ cytokines were assessed with the 32-plex proteomics. The polyfunctional strength Index (PSI) of single T cells was computed as the percentage of polyfunctional cells, multiplied by mean fluorescence intensity of the proteins secreted by those cells.
Results: A total of 16 patients (5 CR/CRi and 11 non-responders) with R/R AML who received a median of 3 (range 2-17) cycles and a median of 11 (range 3-33) doses of nivolumab were analyzed (Table 1). The pretreatment bone marrow CD4+ but not CD8+ T cells had significantly higher frequency of polyfunctional cells (p=0.04 and 0.15, respectively) and significantly higher PSI (p=0.01 and 0.18, respectively) in responders compared with non-responders (**Figure 1A-B**). Also, pretreatment bone marrow PSI of CD4+ (P<0.001) but not CD8+ (P=0.14) subsets demonstrated a significant positive association with overall survival (OS) across all patients, likely partly driven by response enrichment, suggesting that the degree of polyfunctional state of CD4+ cells may potentially also predict outcomes in AML patients treated with azacitidine/nivolumab (**Figure 1C**). Further evaluation of the PSI composition across cell types revealed that IFN-g and TNF-a were the major drivers of enhanced PSI of pretherapy CD4+ subset, whereas Granzyme B, IFN-g, MIP-1b and TNF-a drove the non-significantly enhanced pretreatment PSI of CD8+ subset in the responders (**Figure 1D**). Using t-SNE dimension reduction, CD4+ and CD8+ cells from responders and non-responders had distinct clustering patterns. Highly polyfunctional groups clustered together in both CD4+ and CD8+ T cells. The most dominant functional group across CD4+ and CD8+ cells was the effector protein pattern, which was more notable in the pretreatment bone marrows of responders compared to non-responders and also corresponded to the highly polyfunctional group. Compared to non-responders, the pretherapy CD4+ T cells of responders had more distinct and unique polyfunctional groups (green rectangles) such as co-expression of TNF-a/IFN-g/IL-8, TNF-a/IFN-g/Granzyme B or TNF-a/IFN-g/Perforin/IL-8 proteins.



Summary/Conclusion: The single-cell multiplexed functional proteomics precision profiling demonstrated that the pretreatment PSI of CD4+ cells was significantly associated with response and OS in relapsed patients treated with azacitidine/nivolumab and should be evaluated prospectively to ascertain whether this could be an effective biomarker to select AML patients for PD-1 based therapies. Pretreatment PSI may have a potential role as a biomarker in the wider sphere of immunotherapy in AML. Such analyses are warranted and encouraged.

EP402 RAPID GENOMIC PROFILING IN ACUTE MYELOID LEUKEMIA WITH MYELODYSPLASIA-RELATED CYTOGENETIC ABERRATIONS

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Background: Despite recent advances in the understanding of the molecular biology of acute myeloid leukemia (AML), the outcome of patients in the high risk subgroup, especially of AML with myelodysplasia-related changes (AML-MRC), remains poor. Newly developed therapeutic options such as CPX-351 offer the possibility to more refined treatment approaches. However, this requires fast detection of cytogenetic abnormalities that define AML-MRC. Conventional karyotyping is still the golden standard in routine AML diagnostics, but this analysis is labor and time consuming. To select the best available therapeutic option, it is crucial to determine copy number and structural variations in the shortest time possible.
Aims: To establish and validate karyotyping based on low coverage whole genome sequencing (WGS) of AML patients using long read Oxford Nanopore technology (ONTseq) that offers the possibility for diagnostic testing within a short timeframe of 48-72 hours.
Methods: Cytogenetically characterized diagnostic samples from peripheral blood or bone marrow of AML patients with MRC, such as complex karyotype or monosomal karyotype, were sequenced on a GridION sequencer within a ~20 hours sequencing run. Sequencing was performed using SQK-LSK109 kits according to the manufacturer's instructions. Analysis of sequencing reads and generation of profiles was performed using an 'in house' bioinformatics pipeline based on publicly available tools, such as nglmr aligner, samtools, IGVTools, R package ACE, and a custom script for transforming graphical genome profiles to karyotype formula. For the current analysis copy number variations by ONTseq were only considered if ≥30% of a chromosome arm was aberrant.
Results: Sequencing of the first 47 cases achieved a 3.1-fold genome coverage (range: 1.9-5.0) and established copy number profiles of all samples at a high resolution of ≤0.1 Mbp. To check reproducibility, n=10 AML cases were sequenced and profiled at two medical centers. All 83 aberrations of these cases with gain or loss >10 Mbs were identified by both laboratories, and the fraction gained/lost was highly concordant (R^2=0.998). Considering all 47 cases, the median number of unbalanced aberrations found by cytogenetics were 4 (range 1-11) and by ONT-profiling were 3 (0-14) per patient. Additional 59 and 49 aberrations were identified by ONTseq that affected 10-30% and 5-10% of the chromosome arm, respectively, that were not considered here. Comparing the copy number status of all chromosome arms for all patients we found a 91% concordance, while 5% of chromosome arms were aberrant by ONT and 4% by cytogenetics only. Those discrepancies were expected and could be explained on the one hand by a higher resolution of ONT profiling, and on the other hand by the fact that 'marker chromosomes' often contain the genomic material that is classified as lost in conventional cytogenetics. Of note, ONT profiles captured also very complex rearrangements, such as chromothripsis and focal amplifications, at high resolution.
Summary/Conclusion: Our retrospective analysis of a well characterized cohort of cytogenetically aberrant AML patients demonstrates the feasibility of ONTseq-based low-coverage WGS with excellent reproducibility and resolution. Thus, ONTseq provides an opportunity to rapidly

and reliably delineate AML-MRC within 48-72 hours and thereby advance genotype-based treatment strategies.
AD and CL, LB and MH contributed equally to this work.

EP403 ENHANCED EFFICACY OF THE DCP-001 RELAPSE VACCINE WHEN COMBINED WITH VENETOCLAX AND 5-AZACITIDINE IN A HUMANISED IMMUNOCOMPETENT MOUSE MODEL OF AML

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Background: The allogeneic, leukemia-derived dendritic cell vaccine, DCP-001, is a relapse vaccine capable of generating cellular and humoral immune responses in acute myeloid leukemia patients (AML). In an ongoing phase II study (Clintrials.gov: NCT03697707), DCP-001 is observed to induce immune response specifically against tumour associated antigens relevant for AML. Preclinical efficacy studies have previously shown DCP-001 vaccination to significantly repress subcutaneous tumour growth in a humanised immunocompetent mouse model of AML. The reproducibility of the preclinical model provides a platform for optimizing vaccination strategies and evaluating DCP-001 efficacy in combination with established AML treatment agents.
Aims: To determine, in a preclinical setting, whether DCP-001 vaccination was compatible with the approved AML drug therapy comprised of 5-Azacitidine (5-AZA) and Venetoclax (VEN).
Methods: 25 female NSGS mice were inoculated with 1 x 10^5 human CD34$^+$ cells. A 12-week maturation period was permitted for engraftment and human immune cell development during which blood was sampled to track chimerism by FACS (hCD45, mCD45, hCD3 and hCD19) and complete blood count (CBC) analysis. Subsequently, the leukemia cell line DCOne^{LUC} was engrafted subcutaneously (5 x 10^6 cells/mouse) and animals were randomized by weight and chimerism and assigned to the following groups: untreated control (n = 6), vaccination (DCP-001, QWx2., n = 7), treatment (AZA 1mg/kg and VEN 50 mg/kg, QDx5, n = 6) and combination (DCP-001, QWx2 + AZA 1mg/kg and VEN 50 mg/kg, QDx5, n = 6). Disease progression and therapy response were monitored by calliper-based measurement of tumour volumes and optical imaging of the bioluminescent cell line, DCOne^{LUC}.
Results: Tumour volumes indicated that all therapy groups were capable of slowing DCOne^{LUC} tumour growth as compared with control group. Importantly, mean tumour volume (± SEM) 6 weeks after therapy initiation was significantly reduced in the combination group (181.8 ± 29 mm^3) as compared to control (522 ± 97.5 mm^3), but also vaccination (326.9 ± 54.6 mm^3) or drug treatment alone (293.8.8 ± 29 mm^3). Bioluminescence imaging and quantification corroborated tumour volume data indicating combination therapy to be the most efficient. AZA-VEN treatment was associated with transient but reversible weight loss and also a reduction in chimerism as determined by the fraction of peripheral blood cells expressing hCD45 at endpoint.
Summary/Conclusion: Preclinical modelling of AML in a humanized mouse model reproduced evidence that DCP-001 vaccination is capable of slowing AML cell line derived tumour growth. Furthermore, vaccination efficacy was significantly enhanced when combined with AZA-VEN drug treatment. Off target effects of drug treatment reduced circulating human immune cells, suggesting optimization of treatment and vaccination scheduling may further enhance the anti-leukemic effect of the combination therapy. These preclinical results support use of DCP-001 as add-on to treatment with AZA-VEN in clinical trials in AML patients.

EP404 TARGETING DOWN SYNDROME-ASSOCIATED LEUKEMIA AT ITS CORE: LSD1 INHIBITION IN COMBINATION WITH DISRUPTION OF JAK-STAT SIGNALING

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Background: Children with Down syndrome are predisposed to develop acute megakaryoblastic leukemia (ML-DS). Thereby, ML-DS leukemogenesis is a stepwise process evolving from pre-leukemic transient abnormal myelopoiesis (TAM). Previously, we showed that the transition from TAM to ML-DS is characterized by the activation of target genes of the histone demethylase LSD1 and acquisition of mutations in signaling pathway genes, *e.g.* JAK-STAT signaling. As children with Down syndrome often suffer from severe toxicities upon intensive chemotherapy, targeted approaches for the treatment of ML-DS are desirable.
Aims: Here we set out to investigate pharmacological LSD1 inhibition (LSD1i) – also in combination with the JAK1/2 inhibitor Ruxolitinib – as therapeutic strategy in ML-DS.
Methods: *In vitro* drug efficacy screens for LSD1 inhibitors as monotherapy or in combination with Ruxolitinib were performed in pediatric AML cell lines as well as different patient-derived xenografts (PDX) calculating EC50 and Bliss synergy score. This drug combination of LSD1i and Ruxolitinib was further investigated *in vivo* in a PDX-based ML-DS mouse model. To identify molecular mechanisms of drug synergy between LSD1i and inhibition of JAK-STAT signaling we performed RNAseq in two different PDX.
Results: In line with the activation of genes positively regulated by LSD1, we observed particularly high LSD1 protein expression in ML-DS primary samples. LSD1i in the ML-DS cell line CMK as well as in five different PDX induced myeloid differentiation displayed by increased expression of CD86 and CD11b. However, LSD1i only led to proliferation arrest without increasing the rate of apoptotic cells. Thus, we tried various drugs in combination with LSD1i (*e.g.* Azacytidine, Venetoclax) to enhance the antileukemic effect, and identified the JAK1/2 inhibitor Ruxolitinib as the most effective. The combination of LSD1i and Ruxolitinib caused a synergistic as opposed to a merely additive antileukemic effect in ML-DS samples measured by the Bliss synergy score. Consequently, we tested LSD1i and Ruxolitinib in a PDX-based murine ML-DS model, where the combination led to a significant reduction in blast count compared to monotherapies and control group. Concerning molecular mechanisms of drug synergy, RNAseq data revealed that LSD1i and Ruxolitinib synergistically inhibited pathways involved in cell division, such as DNA replication or transition from G1 to S phase during cell cycle. On the contrary, LSD1i induced interleukin signaling in mono- and combination therapy, which was repressed by Ruxolitinib. Western blot analysis confirmed increased STAT phosphorylation upon LSD1i that was abrogated in combination with Ruxolitinib. Hence, our data point towards increased interleukin signaling after LSD1i as potential mechanism to sensitize cells to additional Ruxolitinib treatment.
Summary/Conclusion: We identified LSD1i in combination with disruption of JAK-STAT signaling by Ruxolitinib as potential new treatment strategy in ML-DS with efficacy *in vitro* and *in vivo*. Thereby, both drugs synergized in inducing proliferation arrest and differentiation. The regulation of interleukin signaling by LSD1i might be a potential mechanism of sensitizing ML-DS blasts to Ruxolitinib.

EP405 MESENCHYMAL STROMAL CELLS PROTECT ACUTE MYELOID LEUKEMIA CELLS FROM VENETOCLAX-INDUCED APOPTOSIS THROUGH CONTACT-DEPENDENT MECHANISMS

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Background: Acute myeloid leukemia (AML) is a heterogeneous clonal disorder characterized by immature myeloid cell proliferation. Leukemic cells reside in highly specialized bone marrow (BM) niches composed of distinct cell populations, including mesenchymal stromal cells (MSCs). AML cells depend for survival on B-cell lymphoma 2 (BCL-2) family members, which regulate the intrinsic pathway of programmed cell death. Venetoclax (VEN) was the first BCL-2-selective agent to enter the clinic and it showed breaking through effect in combination with demethylating agents in older patients with treatment-naïve AML. Despite the encouraging clinical results of VEN, mechanisms of resistance were also described. Of note, the high rate of relapse may in part be explained by the inability of treatments to efficiently overcome the protection of the BM niche. Indeed, recent evidence demonstrated that BM-derived MSCs provide a protective microenvironment, which modulates drug sensitivity in several hematological disorders, including AML. However, the role of MSCs in modulating the response to VEN treatment has been poorly elucidated.

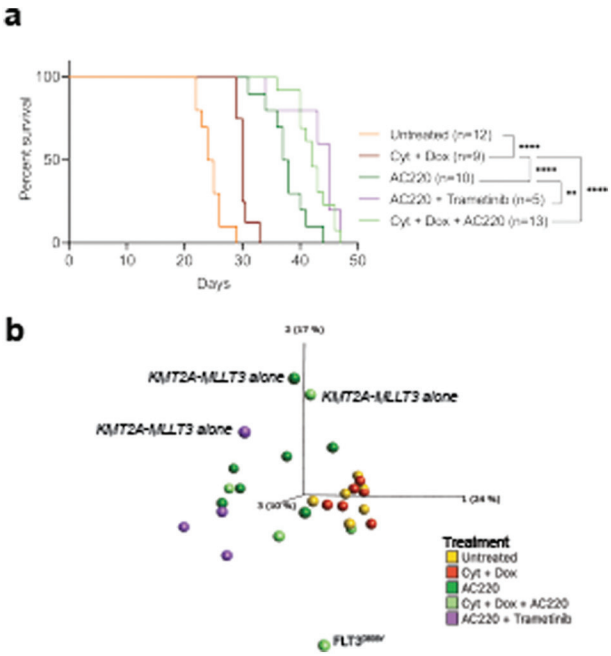
Aims: The aim of this study is to investigate the mechanisms of MSC-mediated VEN resistance in AML, to unravel new MSC–dependent mechanisms promoting leukaemia progression.
Methods: We isolated BM-derived mononuclear cells from healthy donors (HDs, undergoing stem cell transplant) and AML patients to generate HD/AML-MSCs. Next, we set up co-cultures with HD/AML-MSCs and the AML cell line (MV4-11) or primary AML cells. Before and after co-culture, we investigated the viability of AML cells treated with different doses of VEN.
Results: First, we studied the effects of single-agent therapy with VEN on the AML cell line, MV4-11. We evaluated cell apoptosis and we confirmed that VEN reduced significantly the viability of MV4-11 in a dose-dependent manner, with an enhanced effect at higher concentration. Next, we performed co-culture experiments between MV4-11 and HD-/AML-MSCs. We set up the co-cultures with and without trans-wells to unearth if the MSC-mediated protection is contact-dependent or is based on the release of soluble factors. We found that both HD- and AML-MSCs, significantly reduced the apoptosis of MV4-11 after VEN exposure, regardless VEN dose, supporting the fundamental role of MSCs in drug resistance. Interestingly, we clarified that the mechanisms involved in MSC-mediated protection were contact-dependent. Indeed, the addiction of trans-wells to the co-culture system almost abrogated the MSC-protective effect on VEN-induced apoptosis, suggesting a complex interplay between AML cells and adhesion molecules in our setting (a set of experiments to identify the signaling pathway involved is ongoing). Finally, we performed the co-culture experiments with primary AML cells, isolated at diagnosis. We found that AML cells, treated with VEN, showed different apoptotic rates, suggesting that AML cells have intrinsic factors making them more resistant or sensitive to the treatment. Furthermore, we found that both HD- and AML-MSCs protected AML cells from apoptosis induced by VEN, confirming the key role of MSCs in drug resistance.
Summary/Conclusion: For the first time, our data clarify that both primary HD- and AML-MSCs protect AML cells, including primary samples, from VEN-induced apoptosis, through contact-dependent mechanisms. Overall, our results indicate that the BM microenvironment, in particular MSCs, can promote leukemia progression, favoring drug resistance to VEN treatment.

EP406 TREATMENT IS SHAPING CLONAL EVOLUTION AND RESISTANCE PATTERNS IN MURINE KMT2A-REARRANGED LEUKEMIA WITH SUBCLONAL FLT3N676K

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Background: Our understanding of how individual mutations, whether present in all or just a fraction of the leukemia cells, affect cellular responses to therapy is limited. Leukemia mouse models provide a unique possibility to explore how therapy affects the evolution of genetically distinct clones and identify mechanisms of resistance allowing transfer to human disease.
Aims: Herein, we studied how different therapies influenced survival, clonal evolution, and resistance patterns in mouse *KMT2A-MLLT3* leukemia with subclonal $FLT3^{N676K}$.
Methods: Bone marrow (BM) from a leukemia expressing *KMT2A-MLLT3*-mCherry in all cells and a $FLT3^{N676K}$-GFP in 40% of cells, were re-transplanted to sublethally irradiated recipients. Upon engraftment, treatment was started with either chemotherapy (cytarabine for 5 days (d)+doxorubicin for 3 d), the FLT3 inhibitor AC220, chemotherapy followed by AC220, or AC220+Trametinib, a MEK inhibitor. Targeted treatment was given for 28d; controls received vehicle. The leukemias were analyzed by flow-cytometry, RNA-sequencing and targeted gene re-sequencing.
Results: Each treatment prolonged survival with a median latency of 30d for chemotherapy, 37.5d for AC220, 42d for chemotheraphy+AC220, and 45d for AC220+Trametenib, versus 25.5d for the control (**Fig 1a**). Most cells expressed our marker genes and mice displayed splenomegaly and leukocytosis.
We next determined how treatment impacted evolution of the *KMT2A-MLLT3+*$FLT3^{N676K}$ cells and while they constituted all cells in control and chemotherapy-treated mice, the other treatments impacted their evolution. Three distinct patterns were discerned with either >80% of *KMT2A-MLLT3+*$FLT3^{N676K}$ cells, >80% of cells expressing *KMT2A-MLLT3* alone, or dual similar sized clones of cells expressing *KMT2A-MLLT3* alone or *KMT2A-MLLT3+*$FLT3^{N676K}$. Eradication of the FLT3-leukemia cells was rare, but most common in mice receiving AC220+Trametinib and the frequency of dual clones increased when mice received chemotherapy followed by AC220, in line with treatment selectively affecting evolution.
To find clues to treatment resistance, RNA-sequencing (N=44) revealed segregation into three major clusters: 1) leukemias expressing *KMT2A-MLLT3* alone, 2) control and chemotherapy-treated leukemias and 3) AC220 treated leukemias. Notably, a set of AC220-treated mice clustered close to the control and chemotherapy-treated mice (**Fig 1b**). Flow-cytometry data showed that the clustering correlated with the fraction of a myeloid cell population aberrantly expressing B220, which constituted most cells in the control and chemotherapy treated leukemias. Gene set enrichment analysis revealed enrichment of gene sets correlating with stem cells and oxidative phosphorylation, suggesting a switch in cellular phenotype and metabolic state upon resistance in those AC220 treated leukemias. By contrast, the AC220 leukemias in cluster 3, instead showed enrichment of gene sets correlating with granulocyte/macrophage progenitors and immune regulatory pathways, indicating selective dependence of distinct cellular pathways upon resistance. Finally, acquisition of AC220 resistance mutations was rare with a $FLT3^{D835Y}$ and a $Ptpn11^{G503V}$ in two leukemias.



Summary/Conclusion: The specific treatment given affected survival and impacted the evolution of genetically distinct cells. The general lack of acquired mutations upon targeted treatment suggests that target-independent mechanisms that result in alternate activation of survival/proliferation explains acquired resistance in a majority of mice.

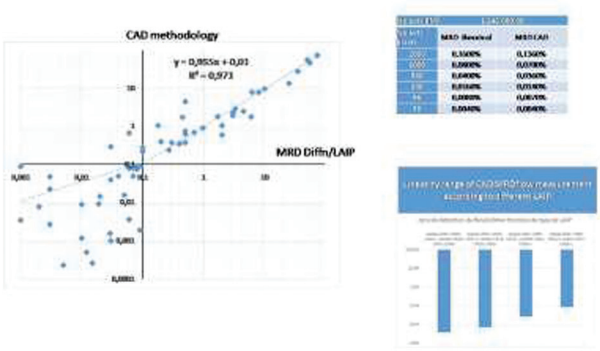
EP407 COMPUTER AIDED DESIGN (CAD) FLOW IN ASSESSMENT OF AML MRD FLOW -ALFA FRENCH FLOW AML MRD INTERGROUP

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Background: MRD monitoring is now mandatory for treatment response evaluation in AML clinical trials (ELN-2017 guidelines). In this setting, beside to molecular biology methods, multiparameter flow cytometry assay represents the most reliable approach.
Aims: The aim of this study was to compare conventional MRD flow analysis (LAIP/diff normal) versus computer aided design (CAD) flow in assessment of AML MRD flow using panel and settings of -ALFA French Flow AML MRD.

Methods: 120 Bone marrow AML samples issued from 60 patients (between 2018-2020) who received conventional chemotherapy regimen (3+7) or Vyxeos, 30 diagnosis and 30 follow-up MRD1 after induction.
Results: The CAD method is based on the use of an R script that compares the MRD sample to a panel of 20 reference BM and the diagnostic sample using the unsupervised clusterisantion method flowsom. It is applied following a basic cytometry analytical strategy of cleaning up confounding events (debris, aggregates...). It can be used with any software that can extract data from cytometry files (FCS, LMD) in the form of text files of type csv (comma separated values). The script then combines the files extracted from the follow-up diagnosis and the reference samples.
The extracted data are limited to blast populations (SSlow CD45+ CD117+ and or CD34+) that have been perfectly cleaned of cell debris or doublets or contamination by mature cells.
Carries out an unsupervised clustering on all the data with the FlowSOM algorithm, then produces an FCS file that integrates the results of this unsupervised clustering into additional parameters (FlowSOM mapping, metacluster among others). It is then easy to reuse this new FCS file in a cytometry software and to condition the populations on the results of this clustering in order to quantify the residual population and compare it to the reference bone marrows.Finally, our script performs a pre-analysis: it identifies and quantifies the SOM flow metaclusters in the CD34+ CD117+ space for all samples (diagnosis, followup and references). It then extracts the metacluster whose proportion of events at the monitoring point is significantly different from that observed for the reference pith (> mean+6sd) and displays the combination(s). It calculates the mrd in % of WBC CD45+ of the owup sample. The limits of sensitivity of the CAD method shows that a MRD remains evaluable by CAD up to 0.004% (50 events in 1 000 000). We compared the results between the conventional method and the CAD method on 60 MRD sample half from BDplatform and half from navios platform, the slope of the correlation line was 0.95 with an R2 of 0.97 and the coeficient as shown in Figure 1.Using the definition threshold of a positive MRD at 0.1%, the agreement of the results between the two methods was evaluated by the cohen kappa coeficient of 0.87, which reflects an almost perfect agreement between the two methods.



Summary/Conclusion: The advantage of this way of proceeding lies on the one hand in the rapidity of the detection of abnormal populations: the calculations performed by the PC being relatively fast <1min, but also in the absence of subjectivity of the observer: the metaclusters are determined by the algorithm and clearly identified in the file resulting from the script and finally a major advance: the comparison of the follow-up sample to the reference samples is independent of the diagnostic sample allowing detection of phenotypic shift. Finally, this method shows a very strong correlation with the conventional method.

EP408 THE IMPACT OF MUTATIONAL LOAD (VAF) DETECTED IN THE TP53, EZH2, U2AF1, WT1, FLT3 AND SF3B1 GENES WAS IDENTIFIED AS AN INDEPENDENT PROGNOSTIC MARKER FOR OS OR RFS IN A COHORT OF 497 CASES WITH AML

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Background: The prognostic classification of acute myeloid leukemia (AML) proposed by the European Leukemia Net (2017) is based on the presence of mutations in FLT3 (ITD), NPM1, CEBPA, RUNX1, ASXL1 and TP53. However, there is little information about the role of mutational load in the genes involved in AML. The impact of mutant ASXL1, DNMT3A, JAK2, TET2, TP53, and NPM1 variant allelic frequency (VAF) in newly diagnosed acute myeloid leukemia has been previously described (Short NJ, Blood advances 2020; Sasaki K, Cancer 2020), but not in other genes involved in AML.
Aims: The objective of the current study was to evaluate the prognostic impact of the VAF, detected by NGS in a custom panel of genes associated to myeloid pathology in a cohort of AML patients, who have been treated in the healthcare practice at the Hospital 12 de Octubre in Madrid, according to the type of treatment received (intensive treatment, hypomethylating agents or low-dose cytarabine).
Methods: The study was conducted in a series of 535 patients diagnosed with AML, whose median age is 67 years. Patients evaluated for Overall Survival (OS) and Relapse-Free Survival (RFS) were 497 cases: 238 cases had received intensive treatment (3+7 schemes or similar), 113 had received hypomethylating agents (azacitidine or decitabine) and 146 with low-dose cytarabine schemes. 38 patients received supportive care and were excluded from the analyses. The mutational profile at diagnosis was identified by NGS (Ion Torrent System), using a panel of 41 genes involved in myeloid pathologies: ASXL1, BCOR, BCORL1, CALR, CBL, CEBPA, DNMT3A, EPAS1, EPOR, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KDM6A, KIT, KMT2A, KRAS, MPL, NF1, NPM1, NRAS, PHF6, PRPF40B, RAD21, RUNX1, SETBP1, SF3A1, SF3B1, SH2B3, SMC1A, SRSF2, STAG2, TET2, THPO, TP53, U2AF1, VHL, WT1 and ZRSR2.
Pathogenic or likely pathogenic variants with >1% VAF were considered. Mutational load (VAF) was assessed as a continuous variable.
Results: The percentage of mutations in older and younger patients was 97.7% and 89.8% respectively.
Younger AML patients have more frequently mutated NPM1 (34.4% vs 18.6%; P=0.004) and patients over 60 years old have more frequently mutated RUNX1 (18.4% vs 8.6%; p=0.005) and ASXL1 ((16.6% vs 3.9%; p<0.001) genes.
In the Cox multivariate analysis, the variables associated with worse OS in patients with intensive treatment were older age or higher TP53_VAF, U2AF1_VAF and EZH2_VAF; and higher TP53_VAF or the presence of EZH2-mutated were found as adverse factors for RFS. In patients who received hypomethylating agents, the variables associated with lower OS were higher TP53_VAF and WT1_VAF; and the presence of mutations in the BCOR, KIT or ETV6 genes was associated to worse RFS. Finally, in patients treated with low-dose cytarabine, TP53 is associated with worse OS and a higher mutational load of TP53 or mutations in the BCOR gene are associated with a worse RFS.

A. Group 1: Intensive treatment (3+7 scheme or similar) (n=238)				
	OS		RFS	
	HR (95% IC)	p-value	HR (95% IC)	p-value
Age	1,026 (1,010 - 1,04)	0,001	-	-
EZH2_VAF	4,97 (1,48 - 16,71)	0,009	-	-
TP53_VAF	13,79 (4,86 - 39,13)	p < 0,001	12,45 (2,9 - 52,97)	p < 0,001
U2AF1_VAF	598 (57 - 8.6273)	p < 0,001	-	-
EZH2	-	-	3,54 (1,76 - 7,12)	0,002
SF3B1_VAF	-	-	54,46 (4,6 - 647,6)	0,001

B. Group 2: Treatment with hypomethylating agents (azacitidine, decitabine...) (n=113)				
	OS		RFS	
	HR (95% IC)	p-value	HR (95% IC)	p-value
TP53_VAF	3,48 (1,89 - 6,38)	p < 0,001	-	-
WT1_VAF	17,9 (1,5 - 203,4)	0,02	-	-
BCOR	-	-	4,58 (1,56 - 13,41)	0,005
BCORL1	-	-	6,15 (1,7 - 21,9)	0,005
ETV6	-	-	3,19 (1,3 - 7,6)	0,009
KIT	-	-	3,94 (1,49 - 10,45)	0,006
FLT3_VAF	-	-	5,97 (1,3 - 26,9)	0,02
NF1_VAF	-	-	16,49 (4,1 - 65,9)	p < 0,001

C. Group 3: Treatments with schemes that include low-dose cytarabine (n=146)				
	OS		RFS	
	HR (95% IC)	p-value	HR (95% IC)	p-value
TP53	3,024 (1,89 - 4,8)	p < 0,001	-	-
TP53_VAF	-	-	2,63 (1,36 - 5,10)	0,004
BCOR	-	-	3,4 (1,6 - 7,2)	0,001

Table 1. Cox multivariate analysis for OS and RFS in the three treatment groups. The variables included are: age (continuous variable), high-risk score, mutational load (VAF) and mutated panel genes (No/Yes).

Summary/Conclusion: The impact of TP53 mutational load has prognostic influence on the 3 treatment groups. There are other genes where the impact of their mutational load depends on the treatment received: Variants-VAF of splicing genes such as U2AF1 and SF3B1 and chromatin modifying genes such as EZH2 only has an influence on the intensive treatment group.

EP409 LONG NON-CODING RNA FAM30A AS A NOVEL REGULATOR OF LEUKEMIC STEM CELL FATE IN ACUTE MYELOID LEUKEMIA

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Background: High long-term relapse after induction chemotherapy is frequently observed among acute myeloid leukemia (AML) patients largely due to the presence of a heterogenous population of leukemic stem cells (LSC) with uncontrolled self-renewal ability and capable of maintaining an undifferentiated state. Based on a 17-gene stemness signature for high-risk AML (Ng SW, *Nature*. 2016), we identified FAM30 as a novel long non-coding RNA (lncRNA) highly expressed in the most primitive hematopoietic lineage. Nonetheless, the role of FAM30A in hematopoiesis as well as its clinical significance in AML remain unknown.
Aims: We aimed to characterize FAM30A at a molecular level and unravel the functional roles of this lncRNA in differentiation and chemoresistance processes in AML.
Methods: Colony-forming unit (CFU) methylcellulose assays were performed to assess the role of FAM30A in differentiation. FAM30A gain- or loss-of function studies were used to monitor RNA expression levels of LSC- and myeloid markers. Protein and RNA immunoprecipitation and RNA pulldown (biotinylated-tagged RNA) assays were performed in order to demonstrate RNA-protein specific interactions. To determine whether FAM30A has any protein-coding potential, we used sucrose gradient-based fractionation and performed targeted polysome profiling. Localization of FAM30A was revealed by cell fractionation.
Results: FAM30A expression levels were compared between AML patients and healthy donors based on a RNAseq dataset of a TCGA cohort (PanCancerAtlas) and revealed a significantly higher expression of FAM30A in AML samples compared to healthy donors ($p<0.001$, n=186). Importantly, high levels of FAM30 significantly correlated with unfavourable karyotypes and refractory disease. AML cell lines expressing high levels of FAM30A were used as a mechanistic model to study the molecular mechanisms in AML LSC residing in the CD34+ CD38- fraction as these cells have been shown to be most therapy-resistant and least immunogenic. Polysome profiling showed that FAM30A is indeed a long multi-exonic non-coding protein transcript, predominantly not found in polysomal fractions. However, we observed that FAM30A is mainly cytoplasmic at steady state. *In silico* prediction of potential binding sites of RNA-binding proteins (RBP) binding sites showed several putative conserved binding motifs for Musashi-2 (MSI2), a well-characterised oncoRBP known to play a critical role in regulating chemoresistance and LSC fate. Accordingly, detailed analysis of FAM30A sequence revealed MSI2-binding sites organized in tandem repeats. CFU-assays showed that exogenous expression of the MSI2-interacting region of FAM30A massively enhanced the potential of colony-formation ($p<0.001$) and promoted a monocyte-like differentiation status in AML LSC-like cell lines. Reversely, FAM30A knockdown in FAM30A^{high} cell lines was able to impair differentiation. Nonetheless, rescue experiments of the MSI2-binding region of FAM30A could not restore the original stem cell-like phenotype, suggesting a MSI2-dependent regulation of LSC stemness by FAM30A.
Summary/Conclusion: We identified the novel lncRNA FAM30A and its binding partner MSI2 as a potential novel regulatory axis of leukemic stem cell phenotypes which mediates differentiation and chemoresistance in AML. Moreover, we suggest that modulation of FAM30A expression could be exploited as a new therapeutic avenue in refractory and relapse AML.

EP410 COMBINATORIAL INHIBITION OF TIGIT AND CD39 INCREASE T-CELL MEDIATED KILLING IN AML

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Background: The inhibitory receptor TIGIT, as well as the ectonucleotidases CD39 and CD73 constitute potential exhaustion markers for T cells. Detailed analysis of these markers may shed light into dysregulation of the T-cell response in acute myeloid leukemia (AML) and help to identify potential therapeutic targets.
Aims: In the current study we analyzed multiple inhibitory receptors and members of the purinergic system which have also been involved into downregulation of T-cell effector function aiming to identify relevant new pathways of T-cell mediated immune failure in AML.
Methods: The differentiation state, phenotype and expression of transcription factors was assessed on T cells derived from peripheral blood (PB n=38) and bone marrow (BM n=43). PB and BM collected from patients with newly diagnosed primary AML, at relapse after intensive chemotherapy and in remission were compared to healthy volunteers (HD n=12). The surface expression of PD-1, TIGIT, CD73, and CD39, as well as of the differentiation markers CD45RO, CCR7, CD25 and CD127 were determined on CD8$^+$and conventional and regulatory CD4$^+$T (CD4$^+$CD127$^-$CD25^{hi})cells using multiparameter flow cytometry.
Results: An increased frequency of terminally differentiated (CD45R$^-$CCR7$^-$) CD8$^+$ T cells was confirmed in the PB and BM regardless of the AML disease status ($p<0,05$). Moreover, CD39 was aberrantly expressed on this population: we observed an increased frequency of CD39$^+$TIGIT$^+$CD73$^-$CD8$^+$ T cells in PB from patients with newly diagnosed AML and relapsed AML compared to PB from HDs (13,47 ± 4,03 vs. 15,8 ± 3,04 vs. 3,03 ± 1,21; $p<0.05$; $p<0.01$). For analysis of the functional relevance of the CD39$^+$TIGIT$^+$CD73$^-$CD8$^+$ T cells mononuclear cells of the PB (PBMC) from HDs were pre-incubated with inhibitors against TIGIT (50µg/ml) and CD39 (50µg/ml) and co-cultured with either AML OCI-3 or OCI-5 cells (E:T Ratio 6:1, n=3). After 24 hours of co-culture lysis of AML cells was assessed by flow cytometry. Treatment of anti-TIGIT, anti-CD39 or the combinatorial inhibition significantly increased T-cell mediated lysis of AML cells (lysis of AML OCI-3 cells measured by fold change: anti-CD39 1,53; anti-TIGIT 2,22; anti-CD39 + anti-TIGIT 2,67 and lysis of AML OCI-5 cells: anti-CD39 2,21; anti-TIGIT 1,63; anti-CD39 + anti-TIGIT 2,81).
Summary/Conclusion: CD8$^+$ T cells in the PB and BM from patients with AML exhibit a key signature of CD39$^+$TIGIT$^+$CD73$^-$CD8$^+$ T cells that were specifically increased at different stages of the disease. Through inhibition of CD39 in combination with TIGIT T-cell mediated lysis could be increased in AML. These results provide a rationale to further evaluate the TIGIT checkpoint blockade in combination with inhibition of the purinergic signaling to improve T-cell mediated cytotoxicity in AML.

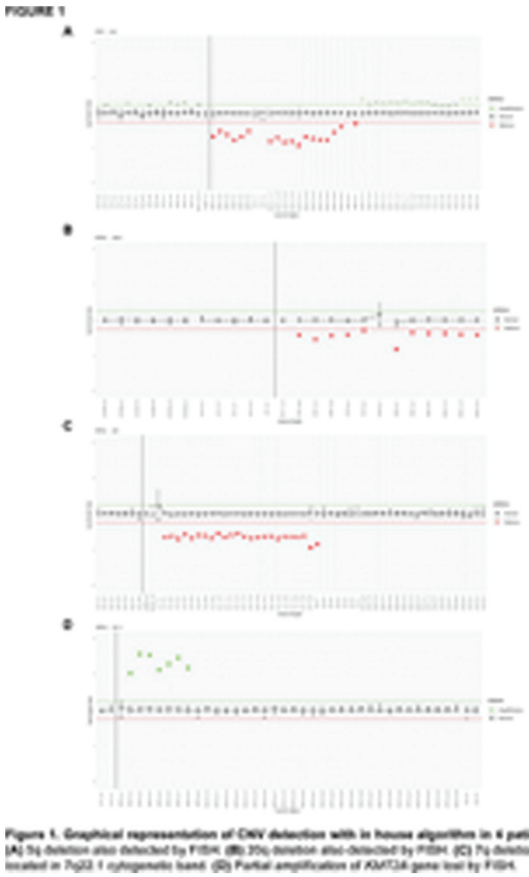
EP411 NEW CUSTOM ALGORITHM FOR COPY NUMBER DETECTION IN MYELOID MALIGNANCIES USING A TARGETED NGS PANEL

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Background: Diagnosis of myeloid malignancies requires multiple testing strategies to characterize the genetic makeup of these pathologies. Single nucleotide variants (SNVs), short insertions and deletions (INDELs), copy number variants (CNVs) and other structural variants (inversions and translocations) are the critical genetic abnormalities that dictate therapeutic decisions. While, Next Generation Sequencing (NGS) allows for the detection of all those alterations, only SNV and INDELs detection has been implemented in clinical diagnostic laboratories, limiting the potential of NGS. In fact, CNV detection still relies on karyotype and fluorescence in situ hybridization (FISH) for their detection.
Aims: To develop an algorithm that confidently identifies copy number alterations using a capture-based NGS custom panel currently used only for SNV and INDELs detection.
Methods: We designed a capture-based NGS panel with SOPHiA GENETICS that includes 72 genes with clinical relevance in myeloid neoplasms. The panel includes genes in chromosomes 5, 7, 8, 11, 17 and 20.

The algorithm is based in depth of coverage of the samples, taking into account a unique sample, and comparing it to the whole batch of samples. To generate a batch of normal samples we use 114 samples that have not any previous myeloid neoplasm diagnosis. For the analysis group, we selected a cohort of 19 patients with myeloid malignancies with available NGS data and FISH data for any of the 6 following markers: del(5q), del(7q), +8, amp(11q), del(17p) and del(20q).
Libraries were built according to the SOPHiA GENETICS protocol and sequenced on 600 cycles V3 flow cells in a MiSeq sequencer (Illumina) in batches of 8 samples. The runs were demultiplexed using MiSeq Reporter, and alignment was done by SOPHiA DDM software. Finally, SAMTools was used for depth of coverage calculation and R for custom CNV analysis.
Results: A median of 6.03M reads per sample was obtained, in which 70.13% were on target aligned. We calculated the depth of coverage of those samples and a median of 2835X was obtained. We called every exon on the panel for the copy number.
For the 47 FISH results, the concordance was 95.74% (45/47). We detected 8 alterations in 7 patients using NGS approach. We confirmed by NGS the two positive results detected by FISH, a 5q deletion and a 20q deletion (Figure 1A, Figure 1B). In two patients, we detected two alterations in the relevant markers that were not tested by FISH. Additionally, we detected two more alterations in other regions no analyzed by FISH (del(20p) and amp(21q)) in two patients. The two discordant results could be explained taking into account the two different approaches for the analysis.
In UPN12 we detected a 7q deletion by NGS approach (Figure 1C), while it was negative by FISH. This 7q deletion is located in *CUX1* gene (7q22.1 cytogenetic band) while our FISH probe is located in 7q31 cytogenetic band.
In UPN14 we detected a partial amplification of *KMT2A* gene (11q23.3 cytogenetic band) by NGS (Figure 1D), whereas FISH probe was negative. The amplification detected affects exon 2 to exon 8 of the gene, potentially making it undetectable by routine FISH approaches.



Summary/Conclusion: Our new designed algorithm allows for the accurate and diagnostic detection of CNV using NGS data. The high concordance between data obtained with our new algorithm and the current gold standard (FISH) demonstrate the feasibility of using NGS data for the detection of CNV in myeloid malignancies. Most importantly, data obtained from NGS offers additional genetic information often overlooked by FISH due to its limitations.

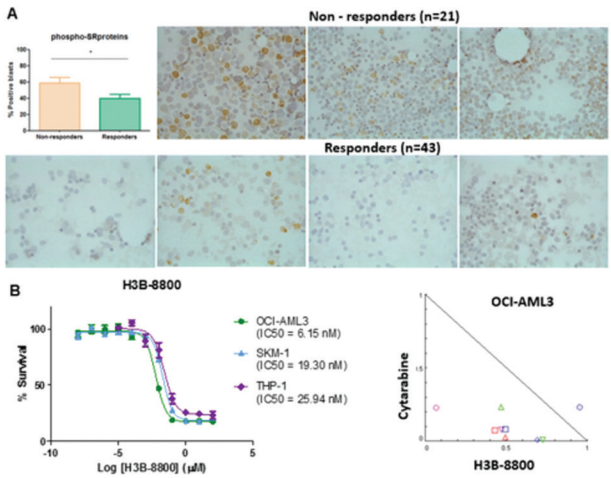
EP412 STUDY OF THE ROLE OF SR PROTEINS IN CYTARABINE TREATMENT RESISTANCE IN ACUTE MYELOID LEUKEMIA

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Background: In recent years, several targeted therapies have received the approval for treating AML. Nevertheless, for many patients 7 + 3 chemotherapy regimens remain as the treatment of choice, and so, their lack of efficacy are the main cause of death in the disease. Therefore, there is still a necessity of more appropriate and personalized treatments, which try to avoid resistance development.
Aims: In this study, we elucidate the implication of splicing factor SR proteins in cytarabine resistance and propose new combinational therapies.
Methods: The public database GEPIA was used to compare the expression levels of genes codifying SR proteins from the LAML (TGCA) repository versus the GTEx repository (controls). Expression levels of *SRRM2* and *SRSF12* in controls, AML patients, and other myeloid disorders (MPNs and MDS) were studied by qPCR (n=54). The analysis of the proteomic profile associated to cytarabine treatment resistance was performed by LC-MSMS after IMAC enrichment (n=3). Expression levels of SR proteins and phospho-SR proteins were assayed by immunohistochemistry of paired bone marrow smears from 7 AML patients, and at the diagnosis moment of different cytarabine-response groups (n=64). The efficacy of different spliceosome inhibitors (H3B-8800, Madrasin, SPHINX31, and SRPKIN-1) and their combination with cytarabine were studied in AML cell lines.
Results: Public data showed differences in the expression levels of 4 SR proteins (*SRRM2*, *SRSF12*, *SRSF9*, and *U2AF1L5*). *SRRM2* and *SRSF12* genes exhibited overexpression in bone marrow of AML patients compared to controls, MPNs and MDS. Likewise, proteomic analysis identified an increase in the phosphorylation of SRRM2, among other SR proteins comparing paired samples before and after cytarabine resistance development. These data were validated by immunohistochemistry in which the levels of phospho-SR proteins were significantly lower in cytarabine-responders AML patients compared to non-responders (figure 1A). Finally, different spliceosome inhibitors demonstrated *in vitro* efficacy in the nanomolar (H3B-8800) or micromolar range (Madrasin, SPHINX31, and SRPKIN-1). The combination of cytarabine plus H3B-8800 showed synergism activity in OCI-AML3 cells (figure 1B).

Figure 1. (A) Immunohistochemistry of bone marrow smears of AML patients at diagnosis with anti-phospho - SR proteins antibody. (B) IC50 of H3B-8800 and its combination with cytarabine in AML cells.



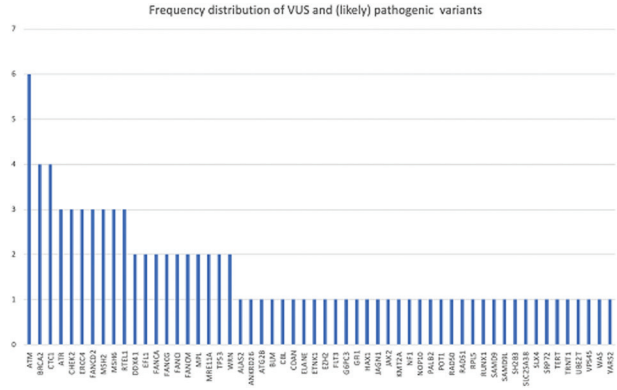
Summary/Conclusion: The spliceosome pathway seems to be involved in cytarabine resistance in AML patients. The levels of *SRRM2* and *SRSF12* are higher in AML compared to controls and other myeloid disorders. The levels of phospho-SR proteins increase after cytarabine treatment in AML patients that relapse, and are especially higher at diagnosis in refractory patients. Certainly, the study of phospho-SR proteins at diagnosis could serve as a possible predictive biomarker of cytarabine response. The combination of cytarabine plus spliceosome inhibitors as H3B-8800, a small molecule that binds to the SF3b spliceosome complex, could improve the response in AML patients.

EP413 ANALYSIS OF GERMLINE PREDISPOSITION IN PATIENTS WITH MYELOID NEOPLASMS: ASSOCIATION BETWEEN MOLECULAR ALTERATIONS AND CLINICAL HISTORY

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Background: Hereditary myeloid malignancies syndromes (HMMSs) are rare but increasingly important clinical entities. These affect ~5-10% of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In the 2016 revision, the WHO distinguished them from sporadic myeloid neoplasms, by proposing a specific category: myeloid neoplasms with germline predisposition.
Aims: We prospectively studied the prevalence of HMMSs in a cohort of consecutive patients diagnosed at our institution and explored if there was any association with patients´ medical history.
Methods: So far, we have examined 56 paired somatic/germline samples from 21 MDS and 35 AML consecutive patients (16-80 years). Fifteen (27%) of them were considered secondary neoplasms. The germinal samples included 31 fibroblasts culture from skin biopsy, 22 $CD3^+$ lymphocytes isolated from peripheral blood (PB) and 3 PB in remission. We analyzed them, through targeted Next-Generation sequencing (NGS) using a custom gene panel of >170 genes including all those previously associated to HMMSs. Besides, we conducted a thorough interview with patients to learn about their personal and family history of cancer and signs related to HMMSs.
Results: In 10 patients, we did not identify any clinically relevant germinal variant. We found 91 germline variants in 82% (46/56) of patients categorized as variants of uncertain significance (VUS) or (likely) pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria. Their frequency is shown in figure 1. Mean number of variants per patient was 1.62. In total, 13 (14%) variants were considered as (likely) pathogenic and were present in 12 (21%) patients. Six of them (11% patients) have been associated to HMMSs with an autosomal dominant (AD) inheritance pattern (*ANKRD26, CHEK2, ELANE, SAMD9, and TP53* in 2 patients), indicating a potential molecular cause of the disease. Two variants (*EZH2, SH2B3*) have been related to sporadic myeloid neoplasms but not to a germline origin. Although other heterozygous variants (in genes *CTC1, FANCM, SLC25A38, SLX4*) have been related to HMMSs, their inheritance pattern is autosomal recessive. Considering those 6 patients with AD (likely) pathogenic variants, mean age was 54 (47-67years). Four of them (67%) presented a personal history of cancer and their myeloid neoplasms were considered secondary to it. In contrast, we noted that only 33% of them exhibited at least one 1st grade relative with cancer and that none of them showed >1 family history of cancer. Patient with *CHEK2* and one of those with *TP53* mutations presented with typical described phenotype (gynecological cancer history and Li Fraumeni related neoplasms, respectively). However, in the other patients with AD (likely) pathogenic variants, we did not find any sign related to hereditary predisposition syndromes.



Summary/Conclusion: In agreement with previous studies, 11% of patients in our series had a potential hereditary myeloid malignancy syndrome, although only 33% of them presented typical phenotypes. Some patients with HMMSs may not initially have suspicious personal or family history due to lack of knowledge about their own or relatives past blood test results, unexplained causes of death in the family, incomplete penetrance, variable expressiveness, or *de novo* mutations. On the other hand, it is necessary to expand this series to obtain more information on these entities in order to be able to select appropriately those patients who require a germline study and a different clinical management.

EP414 THE MOLECULAR BASIS AND CLINICAL OUTCOMES OF CALM-MLLT10 FUSION POSITIVE ACUTE LEUKEMIA

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Background: CALM-MLLT10 is a recurrent but rare fusion gene in leukemia and lacks relevant reports.
Aims: To investigate the cytogenetic and molecular characteristics of t(10;11)(p13;q21)/CALM-MLLT10 positive acute leukemia (AL), and to observe the clinical outcome with chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) of this molecular entity leukemia.
Methods: The G-biding karyotype and reverse transcriptase PCR results of 9627 AL cases admitted to Hebei Yanda Ludaopei Hospital from Jan. 1, 2015 to Dec. 31, 2020 were retrieved and analyzed to determine the cases positive for t(10;11)(p13;q21)/CALM-MLLT10. Eighty-six gene panel mutation screening results, RNA sequencing (RNA-seq), and clinical records of the positive cases were further analyzed.
Results: A total of 21 CALM-MLLT10 positive cases were enrolled in this cohort, including 16 males and five females, with the male-to-female ratio=3.2:1. There were 12 adults and nine children, with a median age of 24 (4-37) years. According to the lineage of leukemia, there were 12 cases of acute myeloid leukemia (AML), five T-cell acute lymphoblastic leukemia (T-ALL), one B-ALL, one mixed-phenotype AL (MPAL) with T/B antigen expressed, one MPAL with T/M antigen expressed, and one B lymphoblastic lymphoma. 91.6% (11/12) of CALM-MLLT10 positive AML cases had complex abnormal karyotypes or had additional abnormalities. PHF6 gene mutations frequently accompanied in CALM-MLLT10 positive AML cases, with an incidence of 87.5% (7/8), which is significantly higher than 3% in the CALM-MLLT10 negative AML cases, and the other frequently mutated genes include TET2, EZH2, and TP53. In CALM-MLLT10 positive T-ALL cases, JAK1/3 mutation incidence is 80%, and PHF6 mutation incidence is 40%. RNA-seq analysis showed that HOXA family genes were extensively overexpressed in CALM-MLLT10-positive AL cases. MYCN, MEIS1, SOX4, BAALC, and FLT3, which relate to poor prognosis in hematological malignancies, were also significantly overexpressed. The overall response to induction chemotherapy of these cases was poor, and 13 of them underwent allo- HSCT. Two of them underwent the second HSCT and the third HSCT, respectively, due to relapse. There were 8 cases that underwent allo-HSCT died

from relapse (5 cases), infection (2 cases), and severe graft verse host disease (1 case), respectively.
Summary/Conclusion: The total incidence of CALM-MLLT10 in AL is about 0.2%, with the majority were male cases, and it can clinically manifest with AML, T-ALL, B-ALL, and MPAL. This suggests that the founder CALM-MLLT10-positive leukemia cells are at an early stage of the hematopoietic stem and progenitor cells. The accompanying PHF6, JAK1/3, and other gene mutations may synthetically determine the lineage of the leukemias. Early hematopoietic differentiation stage, complex or additional aberrant karyotypes, extensive HOXA family genes and other poor prognostic gene overexpression, high-frequency PHF6 and JAK1/3 mutations, together contributed to the poor response to chemotherapy and even poor prognosis of allo-HSCT. There is an urgent demand to find molecular targets and targeted therapy to improve this molecular entity leukemia's clinical outcome.

EP415 PRL-PRLR AXIS IMPLICATION IN CHEMORESISTANCE AND PROLIFERATION IN ACUTE MYELOID LEUKEMIA

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Background: Current cytotoxic treatments for acute myeloid leukemia (AML) eliminate the bulk of proliferating cells, but leave the majority of quiescent leukemic stem cells (LSC) and chemoresistant cells unaffected. The latter, might be able to generate a subpopulation of cells with the same characteristics, promoting chemotherapy resistance. A previous *in silico* study performed in our laboratory identified the prolactin receptor (PRLR) as one of the main pathways implicated in AML progression and the study of its signalling pathways lead us to investigate its role in chemoresistance and AML progression.
Aims: The main objective was the identification of the role of the prolactin (PRL):PRLR axis in the transformation events associated with the initiation and maintenance of AML and its druggable potential.
Methods: The surface expression of PRLR was assessed by flow cytometry. The effect in cell viability of the natural ligand prolactin (hPRL) and its antagonist (hPRL-G129R) was studied by flow cytometry. Experiments using wildtype (PRLRwt) and a dominant negative (PRLRsh) receptor ectopically expressed and an active (PRLwt) and a dominant negative (PRLmut) ligand expressed on AML cells were performed to assess their effect on chemotherapy resistance. Gene expression analyses were done by real time quantitative PCR. To determine the role of PRLR-PRL axis *in vivo,* conditioned NSG mice were transplanted with RLuc-AML cells and mice were treated with hPRL or hPRL-G129R and monitored during the experiment. Next, conditioned NSG mice were transplanted with PRLwt- and PRLmut-transduced AML cells and the engraftment was analysed by flow cytometry.
Results: PRLR surface expression correlated positively with a higher resistance to Cytarabine, but not Azacytidine or Daunorubicine. The same results were observed when PRLRwt isoform was overexpressed. Nevertheless, changes in genes related to Cytarabine resistance were not observed and no differences were observed on PRLR surface expression in refractory vs non-refractory AML primary samples. On the other hand, cells transduced to secrete active PRL did not possess such resistance.
PRLRwt overexpression promoted a higher proliferative rate in comparison to parental and PRLRsh transduced cells. In addition, hPRL treatment, but not hPRL-G129R, induced proliferation only due to ectopic PRLRwt expression. hPRL treatment increased the proliferation of AML cells in comparison to hPRL-G129R treatment *in vivo*. What is more, mice injected with PRLmut transduced cells had a lower engraftment capacity in comparison to PRLwt injected ones *in vivo* and a lower clonogenicity capacity *in vitro*.
Summary/Conclusion: PRLR expression, but not increased levels of its ligand PRL, confers resistance to Cytarabine *in vitro*, but genes implicated in this process were not affected, suggesting that other mechanism should be involved.
PRL-PRLR signalling promotes proliferation signals in AML, both *in vivo* and *in vitro*. An overexpression of PRLR generates a worse AML prognosis due to its effect in proliferation, while antagonizing the receptor decreases proliferation. Interestingly, the inactive form of hPRL confers a lower clonogenicity *in* vitro and engraftment capacity *in vivo*.
In summary, PRLR and PRL have an important role in AML proliferation and prognosis, so targeting PRLR and using inactive forms of its ligand may be a useful treatment against AML.

EP416 MAIT CELLS NUMBERS AND FREQUENCIES IN PATIENTS WITH ACUTE MYELOID LEUKEMIA AT DIAGNOSIS: ASSOCIATION WITH CYTOGENETIC PROFILE AND GENE MUTATIONS.

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Background: Intensive chemotherapy (iCT) remains the main therapeutic option for a majority of patients with acute myeloid leukemia (AML). However, relapses are frequent and cause a high fatality rate, prompting the need for new therapeutic strategies, as well as a better stratification of patients to guide treatment choice. Multiple ongoing pre-clinical and clinical studies aim at harnessing the immune system against AML. Mucosal-Associated Invariant T cells (MAIT) constitute one of the largest subset of innate-like, cytotoxic T cell subsets in humans. A small but increasing number of papers suggest a role for MAIT cells in cancer but their functionality show different trends according to different studies.
Aims: In this study, we quantified circulating MAIT cells at diagnosis in a prospective cohort of newly diagnosed AML patients. We also monitored MAIT cells during intensive chemotherapy in a subset of these patients.
Methods: This study included patients with a newly diagnosed AML admitted at the Hematology department of Toulouse University Hospital-IUCT-O from 1st January 2015 to 31st October 2019. A written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. All cytometry analyses were performed on fresh whole-blood lymphocytes and data were acquired on the Navios cytometer, and analyzed with the Kaluza software. Statistical analyses were performed with the Graphpad Prism software.
Results: We included 216 patients in this study. We observed a dramatic decrease of MAIT cell, compared to Healthy donors ($p<0.0001$). Whereas the relative proportions of CD4+ and CD8+ T cells were conserved in disease, the frequency of MAIT cells decreased importantly in AML patients ($p<0.0001$). In stark contrast, the percentage of activated MAIT was significantly higher in patients than controls ($p=0.0065$). We evaluated whether MAIT cells dynamics during this induction phase would differ, as compared with conventional CD4+ and CD8+ T cells. In our cohort, 25 patients were monitored at D15 post-induction, at the nadir of circulating lymphocyte numbers. The drop in MAIT cell numbers was more pronounced than for CD4+ ($p<0.0001$) and CD8+ T cells ($p<0.001$). We also obtained samples from 78 patients at D35 post-induction, which is the time point at which remission is evaluated, and leucopoiesis usually resumes. Indeed, at D35, CD4+ and CD8+ concentrations raised back to baseline levels, although CD4+ concentrations remained slightly lower than their D0 levels. MAIT cells showed the same trend, with no significant difference between pre- and post-treatment levels. We could obtain cytogenetic parameters in 207 (90.4%)patients and MAIT cells numbers dropped significantly according to the cytogenetic profile. Finally, we obtained at least partial mutation data for a total of 119/123 patients (96,7%) FLT3-ITD mutation were associated with higher numbers of CD4+, CD8+ and MAIT cells. IDH1/2 mutations were found in 29/118 patients (24.6%), and were associated with higher MAIT cell numbers only.
Summary/Conclusion: In this study we observed a significant MAIT cell deficiency in AML patients, which is differently associated with the cytogenetic and molecular profile of the patients, and the occurrence of complete remission after iCT.

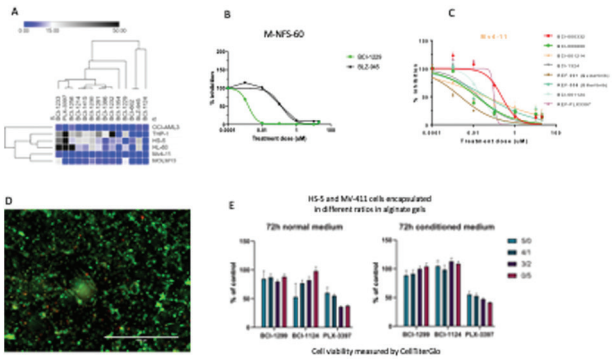
EP417 PRECLINICAL DEVELOPMENT OF NOVEL COMBINED CSF1R/FLT3 INHIBITORS IN ACUTE MYELOID LEUKEMIA

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Background: Despite emerging insight into the molecular pathogenesis of acute myeloid leukaemia (AML), few new therapeutic drugs have been approved and overall survival in elderly patients remains poor. Tumor-stromal interactions in AML are important for disease development and therapy resistance, and bone marrow stroma seem like an attractive therapeutic target. Inhibition of colony stimulating factor 1 receptor (CSF1R) is proposed to be an effective target to block

infiltrating monocytes and tumor-associated macrophages that support tumor growth. Our laboratory is currently developing a novel class of small molecule kinase inhibitors towards FLT3 and CSF1R through a collaboration with BCI Pharma to target high-risk mutations. We propose an increased beneficial effect of conventional and novel therapeutics by targeting the supportive microenvironment in addition to direct leukemic cell death. Experimental evidence positioning inhibitors of CSF1R as treatment should, together with data from preclinical and early phase clinical trials, facilitate translation and clinical development of CSF1R-targeted therapy in AML.
Aims: We propose the potential of CSF1R/FLT3-targeted therapy as well as to elucidate the supportive mechanisms of the tumor microenvironment in AML.
Methods: We have established IC-50 values of various CSF1R and FLT3 inhibitors on multiple leukemic and stromal cell lines by high-throughput dose-response WST-1 assay. To further investigate the interactions of leukemic cells with the stromal compartment of the bone marrow in AML, a 3D co-culture model using alginate gel was established. The leukemic cell line MV-4-11, and the stromal cell line HS-5 were incapsulated in different ratios in 5% alginate gel and exposed to a few selected CSF1R and FLT3 inhibitors, as well as stromal-conditioned media. An *in vivo* maximum tolerable dose (MTD) experiment was performed for the selected FLT3 and CSF1R inhibitors. We are currently running an orthotopic MV-4-11 experiment were FLT3 and CSF1R inhibitors are given in sequence and as monotherapies. Malignancy and effect of treatment are assessed through bioluminescent imaging.
Results: Dose-response assays of several CSF1R and FLT3 inhibitors on leukemic and stromal cell lines showed significant inhibition and reduced viability by several compounds (Figure 1A),where the most potent inhibitors were selected for further *in vitro* and *in vivo* experiments. CSF1R inhibitor BCI-1229 is more potent than the commercially available inhibitor BLZ-945 in the CSF1R-dependent cell line M-NFS-60 (Figure 1B). Several FLT3 inhibitors show inhibitory effect on the cell line MV-4-11 that is comparable to commercially available reference compounds (Figure 1C). Further, the co-culture alginate gel is compatible withthe leukemic and stromal cells illustrated by live/dead imaging (Figure 1D). Interestingly, FLT3-inhibitors has significantly reduced effect on leukemic and stromal cells cultured in stromal-conditioned media after 72 hours (Figure 1E).



Summary/Conclusion: In summary, we employ a novel approach to develop combined CSF1R/FLT3 targeted therapy for AML to assess the protective tumor microenvironment and by direct leukemic cell death. Ultimately, our goal is to facilitate translational medicine by performing rigorous preclinical experiments and to select compounds to be tested in a clinical trial setting combined with conventional and other novel therapeutics.

EP418 CHECKPOINT KINASE 1 IS OVEREXPRESSED, BY POST-TRANSCRIPTIONAL REGULATION, IN IMMATURE AND MONOBLASTIC / MONOCYTIC ACUTE MYELOID LEUKEMIA

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Background: Checkpoint kinase 1 (CHK1), encoded by *CHEK1*, supports tumor cell survival by restraining replication stress (RS), either induced, endogenously, by oncogenic transformation or, exogenously, by chemotherapy. CHK1 upregulation in cancer cells has been associated with decreased proteasomal degradation, challenging a direct correlation between CHK1 transcript and protein levels. CHK1 inhibition appears to be an attractive strategy for acute myeloid leukemia (AML) treatment (NCT02649764; NCT03735446). However, CHK1 protein expression in AML patients (pts) remains uncharacterized, precluding the identification of AML subgroups that may benefit the most from CHK1 targeted therapy.
Aims: We sought to measure CHK1 expression and activity in AML and assess whether it associates with specific clinical or biological AML features.
Methods: Bone marrow aspirate and peripheral blood cells from *de novo* diagnosed AML pts (n=29) were processed for RNA and protein extraction. Normal bone marrow (NBM) aspirates (n=8) were used as controls. *CHEK1* transcript was quantified by qRT-PCR. CHK1 protein was quantified by total CHK1 immunoblot and its kinase activity was detected by immunoblotting Serine 296-phosphorylated CHK1. AML pts were then divided according to low or high *CHEK1* mRNA levels, low or high protein expression, or detectable *versus* undetectable CHK1 activity and the various subgroups were tested for differences in the frequency of clinically relevant characteristics.
Results: We found no correlation between *CHEK1* mRNA and CHK1 protein levels or activity in our AML cohort. Furthermore, AML pts expressed similar *CHEK1* transcript levels to those observed in healthy controls. In contrast, CHK1 protein was significantly upregulated in AML when compared to NBM. This led us to hypothesize that CHK1 protein may be biologically and clinically more relevant than the transcript levels in AML. Indeed, there were no significant differences between *CHEK1* mRNA-low and -high pts in any of the features analysed (age, sex, WBC, morphologic classification and ELN genetic risk). In contrast, AML pts with high CHK1 protein were significantly enriched in monocytic/monoblastic morphology (90% of all monocytic AML, n=10), and also included all immature AML cases (n=5). Notably, CHK1-high pts were significantly enriched in ELN intermediate-risk cases. Finally, we observed that constitutive CHK1 activation was associated with hyperleukocytosis, with a 10-fold higher median of WBC at presentation.
Summary/Conclusion: Our data show that CHK1 upregulation takes place during AML development in a post-transcriptional manner. We propose that highly proliferative AML activate CHK1, affording protection against proliferation-associated RS. CHK1 upregulation occurs preferentially in immature and monocytic lineage committed AML, suggesting these subgroups may be optimal candidates for therapeutic intervention with CHK1 inhibitors.

EP419 DEEP HYPOXIA REDUCES SENSITIVITY OF ACUTE MYELOID LEUKEMIA CELL LINES TO THE PAN-AURORA INHIBITOR TOZASERTIB

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Background: The pivotal role of hypoxic bone marrow microenvironment (BMM) has been demonstrated in acute myeloid leukemia (AML) development and maintenance, however whether it influences the fitness of leukemic stem cells (LSCs) and their susceptibility to drug treatment still remains to be clarified. Increasing evidences suggest that hypoxic BMM represents a key regulator of transcriptomic and metabolomic profiles of LSCs, influencing their proliferation capacity and leading resistance to chemotherapeutic treatments. Aurora kinases A and B are crucial actors during mitosis and their over-expression has been described in AML, making them a promising therapeutic target. Phase II studies of Aurora kinase inhibitors combined with induction chemotherapy have demonstrated good tolerability and efficacy in patients with high-risk AML (Brunner, Lancet Haematol 2020).
Aims: The present study aim to explore the effects of Aurora kinases inhibitor Tozasertib in AML cell lines cultured either under normoxic or hypoxic conditions.
Methods: AML cell lines (NOMO-1: t(9;11); MOLM-13: FLT3-ITD; MV-4-11: t(4;11), +8, +19; KASUMI-1 t(8;21), c-KIT and p53 mutated)

were treated under either normoxia or hypoxia (1%O_2) with the pan Aurora inhibitor Tozasertib (100 and 2500nM). After 24 and 48h of treatment, Annexin V and PI staining were performed to evaluate the induction of apoptosis and proliferation capacity. Protein level alterations were analyzed by Western blotting (WB).
Results: Tozasertib strongly inhibited growth and proliferation in AML models, but it was less effective in a low oxygen environment. In particular, all tested AML cell lines showed increased cell death in a dose-dependent manner, however under hypoxic conditions the apoptotic cell death was significantly reduced compared to the normoxic counterpart (AnnexinV$^+$ cells were 32-60% under hypoxia *vs* 47-70% under normoxia after 48h treatment; $p<0.05$). Of note, inhibition of Aurora kinases induced mitotic arrest; therefore, we evaluated the effect of tozasertib on cellular proliferation demonstrating a reduced ability of the drug to induce the accumulation of cells in G2/M phase under hypoxic culture conditions. The reduced anti-leukemic activity of tozasertib in hypoxic AML cell lines was confirmed also at the protein level. WB analysis demonstrated that inhibition of Aurora kinases was associated with activation of the *TP53* pathway, inducing the expression of p-p53(ser15), p21 and γH2AX as well as the cleavage of CASPASE 3 and PARP in all tested cell lines. However, the upregulation of the above proteins was less pronounced under hypoxic conditions. Interestingly, the drug treatment correlated, in an O_2 independent manner, with a strong increase of trimethylation levels at lysine 36 of histone H3 (H3K36me3), that is involved in regulation of the DNA damage response (DDR) network.
Summary/Conclusion: Cytostatic and cytotoxic effects after treatment with Tozasertib were observed in MLL-AF9 translocated, FLT3-ITD, and both *wt* and mutant TP53 AML models, which represent an important goal in AML therapy. Nevertheless, the hypoxic microenvironment strongly influenced the efficacy of Aurora kinase inhibition in AML cell lines, highlighting the crucial role of environment in AML treatment. In conclusion, our study confirmed the pivotal role of low oxygen environment in regulating cellular response to Aurora kinase inhibition and sets the *rationale* for further investigations aimed to identify new combination therapies against AML LSCs.
This study was supported in part by AILBologna.

EP420 METABOLIC PECULIARITY OF PML/RARA EXPRESSING CELLS AND ARSENIC TRIOXIDE RESISTANCE

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Background: Central in the pathogenesis of APL, the PML/RARa fusion protein rewires metabolic pathways to feed anabolic cell growth. ATRA and ATO-based therapies render APL the most curable subtype of AML, yet approximately 5% of cases are resistant and 5 to 10% relapse.
Aims: To characterize the metabolic peculiarity and the energy requirements of PML-RARa expressing cells, to identify new therapeutic targets and strategies.
Methods: we analyzed primary samples from 5 APL with PMLRARa, normal CD34+ cells differentiated to promyelocytes and granulocyte, the U937-PR9 (PML-RARa inducible system), the NB4 APL cell line, and two NB4-ATO-resistant clones. We measured cell's metabolism using a Seahorse Bioscience XFe96 analyzer, the rate of oxidation of each fuel was measured by means of mitochondrial respiration using the XF Mito Fuel Flex Test. We assessed expression of carnitine transporter CT2 (SLC22A16), PRDX, p-AMPK, MCL-1 and Glut 1 by western blot; *SLC22A16* by q-RTPCR; cellular viability by ATP Glow Assay and ROS by mytosox assay.
Results: APL samples showed reduced respiratory and glycolytic capacity compared with normal promyelocytes (Fig. 1a). Expression of PML-RARa in U937-PR9 cell lines increases mitochondrial respiration rate (OXPHOS) and inhibits glycolysis. We evaluated dependency (cells' reliance on a particular fuel source), flexibility (difference between fuel capacity and dependency, the oxidation of an alternative fuel) and capacity (the ability of a cell's mitochondria to oxidize a fuel when other fuel pathways are inhibited). Primary APL blast cells depends mainly on fatty acids (FA), (FA: 63±20 % vs glucose: 5 ± 7 % and glutamine: 5 ± 7 %) ($p<0.0005$); they display a great flexibility, switching to glucose, glutamine or FAO to meet their energetic need (FA: 35±21 % vs glucose: 51± 30 % and glutamine: 36 ± 17 %) (Fig. 1b), consistent with the high adaptability of APL cells. Normal promyelocytes depend on FA and glucose for mitochondrial respiration, conversely APL blasts show enhanced FAO, increase in the carnitine transporter CT2, and lose pyruvate dependence, featuring flexibility for glucose utilization, and high lactate production when mitochondrial respiration is inhibited (Fig. 1c). The enhanced FAO and CT2 over-expression observed in APL blast was confirmed in the PR9 system after PML/RARa induction. ATO resistance involves a switch towards glycolysis, reduced viability at low glucose cc (p= 0.0008) and 1.5 times increase of the glucose transporter Glut1, increase in glycolytic and in mitochondrial ATP production; an increase in FAO confirmed by a higher sensitivity to Perexilin, inhibitor of CPTA1 (p=0.003), and a 1.7 fold increase in the expression of CT2. One clone shows also high level of ROS (p=0.0001), the cellular integrity is protected by increased levels of Periredoxin in both, and a 1.5 fold increase in pAMPK that induces FAO and glycolysis. The apoptosis escape in ATO resistant cells has been related to a concomitant increase (1.7 folds) in the expression of Mcl1.

Figure 1

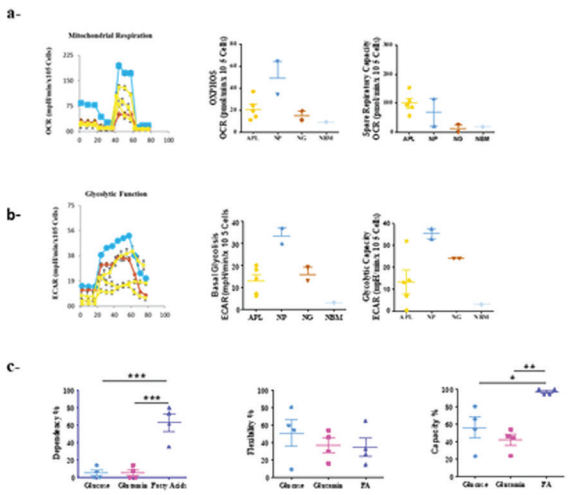


Figure 1 a) Mitochondrial respiration measured by Seahorse assay in normal promyelocyte (NP), Normal granulocyte (NG) and APL primary blasts b) Glycolytic respiration measured by Seahorse assay in NP, NG and APL primary blasts c) Evaluation of the mitochondrial fuel used by primary blast obtained from APL patients using the XF Myto Fuel Flex Test. The graphs shown dependency, capacity, and flexibility of the cells to oxidize three mitochondrial fuels: glucose (pyruvate), glutamine (glutamate) and long-chain fatty acids.

Summary/Conclusion: FA is the principal fuel used by APL blasts and PML/RARa induces FAO. Metabolic shift from respiration to glycolysis and FAO in NB4-ATO resistant cells is mediated by pAMPK, the increase of glycolytic flux contributes to NADPH production and cell survival under oxidative stress. The increase in Mcl1 contributes to apoptotic resistance. ATO resistant patients could benefit from treatment with ATO in combination with glycolysis' and FAO inhibitors.

EP421 ZINC IN THE MODULATION OF THE DNA DAMAGE RESPONSE – PREVENTIVE, GENOTOXIC AND CYTOTOXIC ROLES IN ACUTE MYELOID LEUKEMIA

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Background: Genome integrity is maintained by the DNA damage response (DDR). DDR defects are described to contribute to leukemogenesis, namely to Acute myeloid leukemia (AML) development and progression. Micronutrients are DDR cofactors, critical for optimal DDR functioning. Zinc (Zn) is particularly relevant in apoptosis, cell cycle and DNA repair. AML patients commonly present decreased serum Zn levels, but its biological significance and impact in the DDR is not understood.
Aims: We explored the role of Zn in DDR modulation in AML cells and its therapeutic potential in combination with conventional chemotherapy and with a DDR inhibitor.
Methods: The AML cell line HEL was incubated for 15 days in three culture conditions: standard Zn concentration (Std), Zn depletion (ZnD) and supplementation with 40µM of $ZnSO_4$ (ZnS). After 2, 7 and 15 days, cells were exposed to genotoxic stimuli: 10µM of H_2O_2 for 30 minutes or 1 minute of UV radiation (E_e=2.9841 $W.cm^{-2}$). Chromosomal damage, cell death and division rates were studied by cytokinesis-block micronucleus assay. To monitor repair kinetics, levels of γH2AX were evaluated 0h, 1h and 24h after exposure. Expression of 14 DDR genes (*PARP1*, *XRCC1*, *MSH2*, *MSH6*, *MLH1*, *XPA*, *ERCC1, RAD23B*, *RAD51, PRKDC*, *XRCC6*, *PALB2*, *FANCD2*, and *MGMT*) was analysed by qRT-PCR. An immortalized cell line of normal lymphocytes (IMC) was submitted to the same experiments. Lastly, HEL cells were incubated with the DDR inhibitor olaparib and the chemotherapeutic compound cytarabine in monotherapy and combination with 40µM of $ZnSO_4$. Cell viability was analysed by trypan blue assay and cell death by annexin V/7-AAD staining by flow cytometry. Data was analysed considering a confidence level of 95% ($p<0.05$).
Results: ZnS lymphocytes displayed lower basal damage than those in Std conditions. Lymphocytes in ZnD shown increased damage biomarkers through time (1.3-fold, p=0.0234). Cell death was lower in ZnS lymphocytes and division rates slightly increased, whereas in ZnD an increase in cell death and lowered division rates were observed. Oppositely, in AML cells, basal damage through time of Zn supplementation increased (1.2-fold, p=0.0470), cell death slightly increased and division rates decreased (1.1-fold, p=0.0117). After genotoxic stimuli, ZnS lymphocytes shown less damage levels, particularly after 7 and 15 days of supplementation. ZnD lymphocytes presented more damage biomarkers. AML cells cultured in ZnS had considerably higher damage levels after exposure than in Std conditions and the lowest damage scores were found in ZnD. γH2AX monitorization shown a repair response in ZnS lymphocytes that was not achieved in Zn absence. In AML cells, γH2AX activation persisted 24h after exposure, but ZnD cells shown a more evident repair kinetics. No significant differences were observed in DDR genes expression among all conditions. Olaparib and cytarabine reduced cell proliferation and viability in a dose and time-dependent manner, inducing cell death by apoptosis. Further, $ZnSO_4$ improved cytotoxic effects as a marked decrease of the IC_{50} of each compound comparatively to monotherapy was observed (2.8-fold and 5.4-fold, respectively).
Summary/Conclusion: ZnS improved the DDR in normal cells while ZnD favoured genomic instability, confirming the importance of Zn in genome integrity. In AML cells, Zn increased the genotoxicity of H_2O_2 and UV radiation and the therapeutic effects of olaparib and cytarabine. These results suggest that Zn supplementation is a potential co-adjuvant strategy improving genotoxic or DDR-targeting therapies in AML.

EP422 LINKING CDK6 TO THE EPIGENOME

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Background: Cyclin-dependent kinase (CDK) 4 and CDK6 are key players mediating G1 progression. In addition, CDK6 - but not CDK4 - has been implicated in gene transcription. High CDK6 levels are frequently observed in human malignancies and CDK4/6 inhibitors show promising efficacy against different types of tumors, including hematopoietic malignancies. One hallmark of leukemia is aberrant DNA methylation patterns. The molecular mechanisms underlying these aberrant genomic methylation patterns are poorly understood. We here provide evidence for a role of CDK6 in epigenetic alterations in leukemia.
Aims: We aim at understanding how CDK6 interferes with the epigenetic landscape and which leukemic subtypes will have an advantage from combinatorial drug treatment with CDK6 inhibitors and drugs interfering with epigenetic players.
Methods: To study the interplay between CDK6 and the epigenome, we use a murine Bcr/Abl p185 ALL model and murine hematopoietic progenitor cells (HPC^{LSK}) transformed with different AML oncogenes generated from wildtype and Cdk6 knockout mice and/or treated with CDK4/6 inhibitors. We performed RNA-Seq, Chip-Seq, Phosphoproteomics and RRBS as well as in vitro assays to investigate proliferation, apoptosis and differentiation.
Results: CDK6 activity is associated with specific changes in CpG methylation. ChIP-seq revealed that CDK6 binds to genomic regions of DNMTs. Phosphoproteomic studies and RNA-Seq analysis uncover the regulation of several epigenetic factors by CDK6 at different levels. RNA-seq data from human ALL and AML samples assessed the correlation between CDK6 and DNMT expression. Reduced representation bisulfite sequencing analysis uncovers reversible and cell line-specific changes in DNA methylation patterns upon CDK6 loss. As a consequence, CDK6 interferes with the response to epigenetic agents.
Summary/Conclusion: We show that CDK6 affects the methylation pattern by altered expression and phosphorylation of several epigenetic modifiers, such as DNMTs and EZH2, in leukemia and therefore enhances the sensitivity towards specific epigenetic agents.

EP423 GENOMIC LANDSCAPE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA OLDER THAN 70 YEARS

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Background: Acute myeloid leukemia (AML) is mainly a disease of older patients (pts) with median age of 70 years (yrs) at diagnosis. Age and age-related unfavorable prognostic factors, like adverse genetic changes, impact management and outcome. While large cohorts of younger AML have been extensively studied at the molecular level, genomic aberrations underlying elderly AML have by far been less well characterized.
Aims: To evaluate the mutational landscape of 294 elderly AML (median age 76 yrs; range, 70-90 yrs) entered into the AMLSG BiO Registry (NCT01252485). Primary treatment was intensive chemotherapy (IC, n=33), hypomethylating agents (HMA, n=164) or best supportive care (BSC, n=97).
Methods: Custom Haloplex HS target enrichment system (Agilent) for resequencing of the entire coding regions of 94 myeloid disease related genes (Illumina MiSeq).
Results: Based on an average gene coverage of 300x(fold) for consensus reads and a defined variant allele frequency (VAF) ≥5%, we identified 1095 mutations (mut) in 83 genes in 286 of the 294 pts with a median of 4 mut/pt (range 0-9). The vast majority were missense mut (n=743, 67.9%) followed by indels (n=214, 19.5%), nonsense (n=112, 10.2%) and splice site mut (n=26, 2.4%). Within our cohort of older pts most frequently mutated genes were *TET2* (23.2%), *TP53* (22.8%), *FLT3* (ITD and TKD, 24.5%), *SRSF2* (22.8%), *DNMT3A* (21.8%), *RUNX1* (18.0%), *NRAS* (13.3%), *NPM1* (12.6%), *IDH2* (10.5%), *ASXL1* (9.5%), *SF3B1* (8.5%) and *U2AF1* (7.8%). Observing a broad variance for VAF most pts displayed a dominant clone with a VAF in ~50% range. For mut affecting the functional gene classes methylation, chromatin-spliceosome, signaling, transcription, tumor suppressors, and others, VAF differed significantly ($P<.001$).
According to ELN 2017 risk classification 34 (12.2%) had favorable, 76 (27.3%) intermediate and 168 (60.4%) adverse risk. Risk groups did not correlate with age, categorized as 70-74 yrs, 75-80 yrs, and

≥80 yrs, but with functional classes. Within the favorable, intermediate and adverse risk groups 68%, 67% and 49% of pts (*P*=.002) had methylation mut and 74%, 57%, and 68% (*P*=.002) signaling mut, respectively. Methylation mut were correlated with higher white blood cell counts (*P*<.001), lactate dehydrogenase, and bone marrow blasts (*P*=.002 each).
Genomic classification based on cytogenetics and patterns of comutations (Papaemmanuil et al, NEJM 2016) revealed chromatin-spliceosome (n=101), *TP53*-aneuploidy (n=86), not classifiable (n=36), *NPM1* (n=33), other classes (n=17), and no class (n=21).
Median follow-up was 3.1 years (95% CI: 2.1-4.1). Due to the different treatment regimens, outcome analyses were restricted to overall survival (OS). Median OS was 0.5 years (0.3-0.7 yrs) with no difference for ELN risk groups (*P*=.302). According to treatment median OS was 0.97 yrs for IC, 0.76 yrs for HMA and 0.15 yrs for BSC (*P*<.001) with no significant difference between IC and HMA (*P*=.475). The general beneficial effect for HMA compared to BSC, decreased with age (70-74 yrs, *P*<.001; 75-80 yrs, *P*=.029; ≥80 yrs, *P*=.889). The *TP53*-aneuploidy group had the worst and the spliceosome group the best OS (*P*=.046). A significant benefit for HMA compared to BSC was seen for the *TP53*-aneuploidy group (*P*<.001), but not the spliceosome group (*P*=.394).
Summary/Conclusion: The mutational landscapes of elderly AML differs significantly from that of younger AML. Adapting genomic classification of younger AML, distinct subgroups of prognostic relevance were also observed in elderly AML.
FGR and MH, KD and LB contributed equally.

EP424 MELFLUFEN DEMONSTRATES HIGH EFFICACY IN CYTARABINE AND VENETOCLAX RESISTANT AML MODELS

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Background: Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by the accumulation of immature myeloid cells resulting in hematopoietic insufficiency such as cytopenia or anemia. SOC consists of cytarabine (ara-C) and anthracyclines or combinations of hypomethylating agents or low dose ara-C with BCL-2 protein inhibitor venetoclax. These strategies provide high initial response rates, yet only a fraction of patients achieve cure. Up-front resistance as well as relapse following initial therapy underlines the need for novel therapeutic approaches. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that leverages aminopeptidases and thereby rapidly delivers and releases alkylating agents in tumor cells. Increased expression of aminopeptidase N (ANPEP) has been associated with the malignant AML phenotype and is detected on stem cells and leukemic blasts. APN has been shown to hydrolyze melflufen providing a rational to evaluate melflufen efficacy in the relapsed/refractory (RR) AML setting.
Aims: To investigate the therapeutic potential of melflufen in cytarabine and venetoclax resistant AML cell lines *in vitro* and *in vivo* as well as in cells from relapsed AML patients ex vivo. A secondary aim was to investigate the expression profile of aminopeptidases and their relation to clinical parameters in AML patients.
Methods: The parental AML cell line MV4-11 and its venetoclax (MV4-11_VXR) and ara-C (MV4-11_aCR) resistant sublines were obtained from the RCCI collection of the University of Kent. *In vitro* drug toxicity was assessed using the CellTiter-Glo (CTG) viability assay. The expression of aminopeptidase was analyzed on previously sequenced/published AML samples. *In vivo* assessment of melflufen efficacy using chicken embryo chorioallantoic membrane (CAM) assay and *ex vivo* drug sensitivity assessment of melflufen in AML patient samples using high throughput multi-color flow cytometry are ongoing.
Results: Expression analysis of aminopeptidase in AML patient samples showed that multiple aminopeptidases, previously shown to hydrolyze melflufen including DPP7, LTA4H, RNPEP, ANPEP, are abundantly expressed in AML. *In vitro* drug efficacy evaluation showed that in parental MV4-11 cells 72h melflufen treatment results in high cell viability reduction similar to venetoclax (IC50 range 2-10 nM), while somewhat lower efficacy is seen for ara-C (IC50 400nM). Interestingly, MV4-11_VXR also displayed increased resistance to ara-C (IC50 2.5µM) indicating overlapping resistance mechanisms for the two drugs. Importantly, in both MV4-11_VXR and MV4-11_aCR sublines melflufen efficacy was retained, suggesting that melflufen could target both resistant cell populations.
Summary/Conclusion: In summary, melflufen demonstrates high efficacy in venetoclax and ara-C resistant AML models *in vitro*. In addition, abundant expression of aminopeptidases in the AML patient samples provides rational for further clinical evaluation of melflufen in the RR AML setting.

EP425 ASSOCIATION OF ATG10 FUNCTIONAL GENETIC VARIANTS IN ACUTE MYELOID LEUKEMIA

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Background: Acute myeloid leukemia (AML) is the most common type of acute leukemia with higher incidence among the elderly population. Furthermore, individuals with genetic predisposition, previous cancer and with an age-related genetic condition, named Clonal Hematopoiesis of Indeterminate Potential (CHIP) are also at a higher risk of developing AML. Thus, finding new tools for monitoring these risk groups would be of great interest for the field. AML is characterized by altered autophagy, a vital mechanism to remove and recycle unnecessary or dysfunctional cellular components. *ATG10* is one of the autophagy core genes, involved in the autophagosome formation, a crucial step in the autophagy process.
Aims: We hypothesize that single nucleotide polymorphisms (SNPs) located in regulatory regions of the *ATG10* gene might contribute to the development of this hematological neoplasm. In this study, we examined the association of three potentially functional genetic polymorphisms in the *ATG10* gene: rs1864182T>G, rs1864183C>T and rs3734114T>C, with AML.
Methods: A multicenter cohort involving 309 AML patients and 356 healthy subjects for three *ATG10* SNPs were screened. The allele frequencies and their association to AML were obtained for the dominant and recessive models adjusted for age and gender. For the three SNPs the Hardy-Weinberg equilibrium was verified. The functional consequences of the *ATG10* SNPs in its canonical function were investigated in vitro using peripheral blood mononuclear cells (PBMCs) from a cohort of 46 healthy individuals. Autophagy flux for the most interesting SNPs was performed using gold standard protocols. Informed consent was obtained from all subjects involved in the study.
Results: Logistic regression analysis adjusted for age and gender revealed that patients carrying the $ATG10_{rs1864182G}$ allele showed a significantly decreased risk of developing AML under the dominant model (OR[odds ratio]=0.58, p=0.006), whereas patients carrying the homozygous $ATG10_{rs3734114C}$ allele had a significantly increased risk of AML in the recessive model (OR=of 2.70, p=0.024). We did not find any association between $ATG10_{rs18641823}$ with AML. Functional analysis showed that individuals carrying the $ATG10_{rs1864182G}$ allele had both decreased levels of ATG10 protein, as well as autophagy flux when compared to homozygous major allele carriers. In particularly, we found a reduced degradation step in the autophagy process when compared with the homozygous major allele group. The correlation between the $ATG10_{rs3734114}$ SNP and autophagy flux could not be determined due to the low proportion of subjects carrying the homozygous $ATG10_{rs3734114C/C}$ in the healthy cohort, which in agreement with the observed frequency in the European population.
Summary/Conclusion: Our results indicate that *ATG10* genetic variants show potential clinical implications in AML. Elderly and patients at higher risk could be screened for $ATG10_{rs3734114}$ to define further monitoring, while our results regarding $ATG10_{rs1864182}$ suggest a new target that is worth to be further explored in the context of AML.
This research was funded by FEDER and Foundation for Science and Technology (FCT), grant number POCI-01-0145-FEDER-028159 and POCI-01-0145-FEDER-030782); by Fondo de Investigaciones

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EP426 IL-3 RESCUES MUTANT FLT3 AND KIT-POSITIVE AML CELLS FROM TARGETED THERAPY

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Background: Receptor tyrosine kinases *FLT3* and *KIT* are mutated in up to 40% of AML patients. Mutant receptor tyrosine kinases (RTK) are promising targets for cancer treatment. Especially, selective FLT3 inhibitors (quizartinib, sorafenib, midostaurin, etc) show significant clinical activity in AML patients. However, relapses associated with the acquired drug resistance by leukemia cells remain major limitation of the monotherapy with RTK inhibitors.
Aims: We aimed at identifying cytokines and growth factors mediating response of leukemia cells to RTK inhibitors to better understand the mechanisms of therapy escape by leukemia cells.
Methods: We used a panel of human leukemia cells lines - Kasumi-1, MV4;11, HL-60, Kg1a, THP-1 and stroma-derived cell line - HS-5. qPCR was used to measure cytokine and growth-factor receptors expression at the mRNA level in cells treated with inhibitors. Confocal microscopy and flow cytometry were applied to detect KIT, FLT3, TrkA and IL3-R proteins at the protein level. By the lentiviral transduction we obtained cells with the overexpression of mutant KIT (N822K) and FLT3-iTD based on the murine cytokine-dependent cell line FDC-P1. We also established ERK-KTR reporter cell lines based on the HS-5 and THP-1 cells to study MAPK activity in living stroma and macrophages at the single-cell level when co-cultivated with leukemia cells. THP-1 cells were differentiated into macrophages with phorbol 12-myristate 13-acetate.
Results: Up-regulation of IL-3R and NTRK1 (encoding TrkA) in response to RTK targeted therapy was a unique feature of AML cells with mutant RTK - FLT3 and KIT. Recombinant IL-3 rescued Kasumi-1 and MV4;11 cells from KIT and FLT3 inhibition, respectively, and this effect was enhanced by NGF (ligand of TrkA). Overexpression of mutant *KIT* in IL-3-dependent FDC-P1 resulted in the up-regulation of *IL-3R*, that points to the direct link between mutant RTKs and IL-3R at the transcription level. Combination of RTK inhibitors with SRC (bosutnib and bafetinib) and JAK2 (ruxolitinib), but not MAPK targeting drugs, abrogated IL-3 rescue-effect on AML cells. Moreover, SRC and JAK2 inhibition sensitized Kasumi-1 and MV4;11 cells to several RTK inhibitors. Notably, the toxic effect of RTK inhibition with respect to leukemia cells was attenuated in the presence of HS-5 or THP-1 cells. RTK and downstream kinase inhibitors differently changed ERK activity in stroma cells and model macrophages in the presence or abscence of leukemia cells. Thus, dual targeting of RTK and SRC or JAK2 is promising for the effective suppression of leukemia cells proliferation via abrogation of cytokine-mediated death-escape by leukemia cells.
Summary/Conclusion: IL-3 and NGF play a vital role in the development of therapy-resistant AML cells with mutant RTKs. Studies with patient-derived xenotransplantation models are needed to clarify the findings. All in all, our study provides a rational for the use of RTK inhibitors in combination with agents blocking compensatory cytokine and growth factor signaling.

Acute myeloid leukemia - Clinical

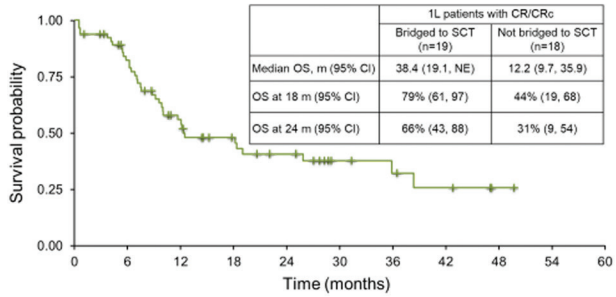
EP427 TAGRAXOFUSP IN PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM: LONG-TERM RESULTS FROM A PIVOTAL TRIAL

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Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy. CD123, the interleukin-3 (IL3) receptor alpha subunit, is overexpressed in BPDCN cells, making it an attractive therapeutic target. Tagraxofusp (TAG, SL-401) is a CD123-directed immunotherapy consisting of recombinant human IL3 and a truncated diphtheria toxin. TAG was FDA approved in 2018 for BPDCN treatment in adult and pediatric (≥2 y) patients (pts) and was recently approved in the EU as monotherapy for first line (1L) treatment in adults. Herein, we show long-term follow-up results from the largest prospective trial (NCT02113982) in pts with BPDCN.
Aims: To study the long-term safety and efficacy of TAG in pts with BPDCN.
Methods: This multicenter, open-label, phase 1/2 study consisted of Stages 1–4 (dose escalation, expansion, confirmatory, and continued access, respectively). Pts received TAG by IV infusion once daily on d 1–5 of a 21-d cycle; the dose was 7 or 12 mcg/kg in Stage 1 and 12 mcg/kg in Stages 2–4. The primary outcome was complete response (CR, defined as CR + clinical CR [CRc, CR with residual skin abnormality not indicative of active disease]). Pts with CR/CRc undergoing allogeneic (allo)/autologous (auto) stem cell transplantation (SCT) discontinued TAG treatment; pts with CR/CRc not undergoing SCT and the remaining pts received TAG until disease progression/unacceptable toxicity. Long-term data were analyzed in all pts for safety and in 1L pts for efficacy.
Results: Of the 89 pts with BPDCN enrolled and treated (3 with TAG 7 mcg/kg and 86 with TAG 12 mcg/kg) over a 4-y period, 65 1L pts who received TAG monotherapy at a 12-mcg/kg dose were assessed for efficacy. The median age of 1L pts was 68 y (range: 22–84) and 80% were male. At study completion in March 2020 (cutoff date), the median follow-up was 34 m. Most common treatment-emergent adverse events (TEAEs; in >40% of pts [N=89]) were increased alanine (64%) or aspartate (60%) aminotransferase, hypoalbuminemia (51%), fatigue (44%), pyrexia (44%), thrombocytopenia (43%), nausea (42%), and peripheral edema (42%). Most TEAEs occurred during cycle 1; 19 (21%) pts had capillary leak syndrome (CLS; grade 2 in 12 [14%], grade 3 in 2 [2%], grade 4 in 2 [2%], grade 5 in 3 [3%]). All but 1 CLS events occurred in cycle 1; the median time (range) to CLS onset from therapy start was 6 d (3–51) and to CLS resolution was 5 d (2–69). CLS was managed by albumin supplementation, diuretics, and steroids, per recommended guidelines. For 1L pts, overall response rate was 75% (49/65) and 37/65 (57%) achieved CR/CRc, with a median time to CR/CRc of 39.0 d. Pts with CR/CRc received a median 4 TAG cycles (range: 1–76) and the median duration of CR/CRc was 24.9 m (95% CI: 3.8, not estimable; range: 1.0–57.4). Nineteen (51%) pts with CR/CRc bridged to SCT (13 allo, 6 auto) after a median time on study of 81 d (range: 27–182). The 18-m survival probability for 1L pts was 50% (95% CI: 36.7, 61.4) and median overall survival was 15.8 m (Figure).

Figure



1L, first-line; CR, complete response; CRc, clinical CR; NE, non-estimable; OS, overall survival; SCT, stem cell transplantation.

Summary/Conclusion: In 1L pts with BPDCN, TAG monotherapy led to high response rates with durable responses. Overall, TAG therapy had a well-characterized and manageable safety profile. CLS management guidelines were developed and implemented during the trial. The high CR rate allowed pts to receive a median 4 cycles of TAG and 51% of responders were bridged to SCT. TAG is the first CD123-targeted therapy and first approved treatment for BPDCN in the US and EU. It is under investigation in other CD123-expressing hematologic malignancies.

EP428 PROGNOSTIC FACTORS OF OVERALL AND RELAPSE-FREE SURVIVAL FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) IN REMISSION: MULTIVARIATE ANALYSES FROM THE QUAZAR AML-001 TRIAL OF ORAL AZACITIDINE (ORAL-AZA)

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Background: Demographic and disease factors influence survival outcomes for patients (pts) with AML. In the phase 3 QUAZAR AML-001 trial, Oral-AZA significantly prolonged overall (OS) and relapse-free (RFS) *vs*. placebo (PBO) for pts with AML in first remission after intensive chemotherapy (IC) (Wei, *NEJM*, 2020). Univariate analyses showed OS and RFS benefits with Oral-AZA *vs*. PBO across pt subgroups defined by baseline characteristics.
Aims: Multivariate analyses were performed to identify baseline characteristics independently predictive of OS and RFS in the QUAZAR AML-001 trial, and to assess Tx effects of Oral-AZA *vs*. PBO on OS and RFS when adjusted for baseline factors.
Methods: Pts were aged ≥ 55 yrs with AML in complete remission (CR) or CR with incomplete blood count recovery (CRi) after induction ± consolidation. Within 4 months of attaining CR/CRi, pts were randomized 1:1 to receive Oral-AZA 300 mg or PBO for 14d of repeated 28d cycles. Cox proportional hazards models were used to estimate the Tx effects of Oral-AZA *vs*. PBO on OS and RFS, adjusting for baseline age, sex, ECOG PS score, cytogenetic risk at diagnosis, prior myelodysplastic syndrome (MDS), geographic region, response after induction (CR or CRi per investigator) and at baseline (per sponsor), measurable residual disease (MRD) status, receipt of consolidation therapy, number of consolidation cycles, baseline platelet count, and baseline ANC. In a stepwise procedure, randomized Tx and baseline variables were selected incrementally into a Cox model if $P \leq 0.25$. After each addition, the contribution of the covariate, adjusted for other covariates in the model, was evaluated and retained in the model if $P \leq 0.15$.
Results: Oral-AZA Tx remained a significant independent predictor of improved OS (hazard ratio [HR] 0.70; $P = 0.0017$) and RFS (HR 0.57; $P < 0.0001$) *vs*. PBO after controlling for baseline characteristics (**Table**). MRD status at baseline, cytogenetic risk at diagnosis, and pt age were each also independently predictive of OS and RFS (**Table**). Response after induction (CR *vs*. CRi) and baseline ANC were predictive of OS but not RFS, whereas prior MDS, non-CR/CRi vs. CRi at baseline, and number of consolidation cycles were predictive only of RFS.

Variable	Overall Survival HR [95%CI]; *P* value	Relapse-free Survival HR [95%CI]; *P* value
Oral-AZA vs PBO	**0.70 [0.56, 0.88]; 0.0017**	**0.57 [0.45, 0.70]; <0.0001**
MRD– *vs*. MRD+ at baseline	0.54 [0.43, 0.67]; <0.0001	0.49 [0.39, 0.61]; <0.0001
Intermediate *vs*. Poor cytogenetic risk at diagnosis	0.57 [0.42, 0.76]; 0.0002	0.49 [0.36, 0.66]; <0.0001
Age (continuous variable)	1.03 [1.01, 1.05]; 0.0046	1.02 [1.00, 1.04]; 0.0468
ANC (continuous variable)	1.25 [1.03, 1.50]; 0.0202	NIFM
Prior MDS (Yes *vs*. No)	NIFM	1.60 [1.11, 2.30]; 0.0116
CR *vs*. CRi response after induction	0.80 [0.60, 1.06]; 0.1138	NIFM
non-CR/CRi *vs*. CRi at baseline	NIFM	0.39 [0.18, 0.87]; 0.0216
0 *vs*. 2 consolidation cycles	NIFM	1.28 [0.92, 1.78]; 0.1355
1 *vs*. 2 consolidation cycles	NIFM	1.35 [1.04, 1.89]; 0.0224

NIFM, not in final multivariate model.

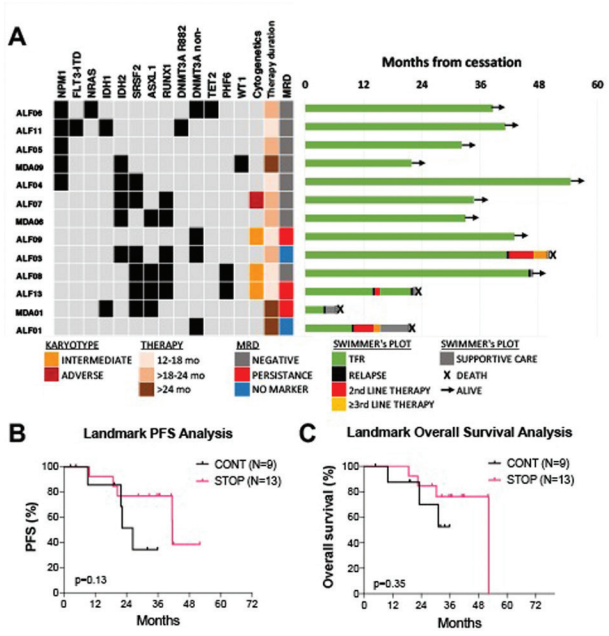
Summary/Conclusion: Tx with Oral-AZA reduced the risk of death by 30% and the risk of relapse by 43% *vs*. PBO, independent of baseline characteristics. Cytogenetic risk at diagnosis, MRD status at baseline, and pt age also independently predicted OS and RFS outcomes. CR vs. CRi response after induction, and no consolidation vs 2 consolidation cycles, did not significantly influence OS or RFS outcomes.

EP429 TREATMENT FREE REMISSION (TFR) AFTER CEASING VENETOCLAX-BASED THERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Phase 3 studies have confirmed the benefit of adding venetoclax (VEN) to azacitidine (AZA) or low dose cytarabine (LDAC) in older/unfit patients (pts) with newly diagnosed AML. For pts responding to VEN-AZA or VEN-LDAC, the median duration of response was 18 and 12 months, respectively. Therefore, remission duration will exceed 12 months in majority of responders. It is currently unknown whether pts should continue therapy until progression and whether elective cessation of therapy could detrimentally impact long-term outcome.
Aims: To compare the natural history of pts receiving ≥12 months of VEN-based therapy in first remission after electively ceasing therapy or continuing treatment until progression.
Methods: Pts with AML receiving VEN combined with either hypomethylating agents (HMA) or LDAC for ≥12 months and in first remission were included in this retrospective analysis. Two treatment approaches were compared: elective cessation of therapy in remission followed by monitoring (STOP cohort) or continued therapy until relapse (CONT cohort). Data cut-off was 31Jan2021.
Results: 25 pts from 2 centres were included: 13 in STOP cohort and 12 in CONT cohort. The median follow-up was 55 months. Median age at AML diagnosis was 74 years (range 65-80). Treatments included VEN-HMA (68%) or VEN-LDAC (32%). Both STOP and CONT cohorts had comparable rates of ELN 2017 adverse risk (50% vs 46%). The median number of cycles received was shorter in the STOP (17; range 12-29) vs CONT (30; range 12-57) cohort. Median time on therapy (TOT) was also shorter in the STOP cohort (19.1 vs 33.2 months). In the STOP group, the reason for treatment cessation was patient request in 46% and medical in 54%. After ceasing therapy in the STOP cohort, the median treatment-free remission (TFR) was 45.8 months (range 3.8-54.5)(Figure 1A). Five pts (38%) subsequently relapsed, of which 3 had concurrent *SRSF2* and *ASXL1*mutations. 2/5 relapses occurred >36 months of TFR. In the CONT cohort, 5 pts were receiving ongoing therapy at data cut-off. Eight (67%) have relapsed, with 5 relapsing >24 months of therapy. More pts had acquisition of cytogenetic abnormalities at relapse in the CONT cohort (6/8; 75%), compared to the STOP group (2/5; 40%).
Overall, 14 pts had *NPM1* and/or *IDH2* mutations (mut): 8 in the STOP and 6 in CONT cohort. 10 achieved undetectable MRD (by flow cytometry and/or qPCR), of which 1 patient (10%) relapsed. In the STOP cohort, 7/8 with *NPM1* and/or *IDH2* mut are still in TFR. We next performed a landmark analysis to compare OS among pts in the STOP and CONT cohorts. The landmark was taken from the median TOT in the STOP group (19 months), in order to exclude lead-time bias in pts relapsing early in the CONT group. This revealed no significant difference in progression free (p=0.13, Figure 1B) or overall survival (p=0.35, Figure 1C) between the two groups. Among relapsed pts, 3/5 in the STOP and 4/8 in CONT cohorts were salvaged. In the STOP group, 2/3 relapsing pts re-challenged with the same VEN-based regimen achieved second CR/CRi. The median time from relapse to death was similar in both groups: median 9.8 vs 6 months in the STOP vs CONT cohorts, respectively (p=0.15).



Summary/Conclusion: In elderly/unfit pts with AML receiving front line VEN-based treatment and in CR/CRi after 12 months therapy, the likelihood of a durable TFR is highest among pts with *NPM1/IDH2* mutation and MRD negativity at the time of therapy cessation. A prospective, randomised, discontinuation study in pts in CR_{MRDneg} after 12 months should be considered.

EP430 QUIZARTINIB WITH DECITABINE AND VENETOCLAX (TRIPLET) IS HIGHLY ACTIVE IN PATIENTS WITH FLT3-ITD MUTATED ACUTE MYELOID LEUKEMIA

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Background: The outcomes in patients (pts) with newly diagnosed FLT3 mutated (m) acute myeloid leukemia (AML) who are ineligible for intensive induction chemotherapy (IC) are poor. Added to a low-intensity chemotherapy backbone, first-generation FLT3 inhibitors (FLT3i), such as midostaurin and sorafenib, result in a median OS of 8 months in the frontline (Gallogly ASH 2017, Ohanian AJH 2018), and 4-8 months in relapsed/refractory (R/R) settings (Yilmaz JHO 2020, Ravandi Blood 2013). Quizartinib, a potent second-generation FLT3i, demonstrated synergy with venetoclax (VEN) in AML cell lines and PDX models (Mali Haematologica 2020). We designed this study to evaluate the safety and efficacy of quizartinib, VEN, and decitabine (DAC) combination in pts with R/R or newly diagnosed *FLT3*m AML.
Aims: To establish recommended phase 2 dose (RP2D) and optimal schedule of DAC + quizartinib + VEN in R/R or newly diagnosed *FLT3*m AML.
Methods: Frontline cohort included pts who are ineligible for IC, and R/R cohort included pts who received ≤ 5 prior treatments. All pts had a performance status of ECOG ≤2, QTcF <450 msec prior to therapy. All pts underwent day 14 bone marrow, and VEN (400 mg/day) was put on hold in patients with bone marrow (BM) blasts ≤ 5% (or marrow aplasia). Pts with day14 BM blast >5% continued venetoclax for 21 days during cycle 1. All pts induced with 10 days of DAC (20 mg/m2). In subsequent cycles, DAC was administered for 5 days. Quizartinib (30 or 40 mg/day) was administered daily continuously.
Results: Overall 21 pts were enrolled and 17 evaluable at the time of this report (4 are still in cycle 1) (Table). Of 13 pts with R/R AML (median 3 [range 1-5] prior therapies, 85% with ≥1 prior FLT3i's), 9 (69%) achieved CRc (2 CR, 7 CRi) with 4/9 and 5/9 evaluable responders FLT3-PCR (sensitivity 10^{-2}) and multicolor flow cytometry (MFC) negativity (sensitivity 10^{-4}), respectively. The median number of cycles to response was 1 [range 1-2]. 30- and 60-day mortality rates were 0% and 8%. Of 4 patients with newly diagnosed AML, all achieved CRc (2 CR, 2 CRi) with 4/4 and 2/3 evaluable responders negative MRD by FLT3-PCR and MFC, respectively. No pts developed a dose-limiting toxicity (DLT) with 30 mg/day quizartinib, however with the 40mg/day quizartinib, the first 2 patients treated developed hematologic DLT (grade ≥3 neutropenia with a <5% cellular bone marrow with no residual AML lasting ≥42 days). Hence, quizartinib 30 mg/day dose was declared RP2D for the triplet. Grade ≥3 non-hematologic toxicities in >2 pts included lung infections (N=9) and neutropenic fever (N=6). No unexpected toxicities were noted. No QTcF prolongations >480 msec were noted. With a median follow-up of 7.2 months, the median OS was not reached in the frontline cohort and was 7.1 months in R/R cohort. 2/4 and 5/9 CRc pts underwent ASCT in frontline and R/R cohorts, respectively. All frontline patients were alive at the last follow-up; 3 in CR and 1 relapsed disease on salvage therapy. Of 9 CRc pts in the R/R cohort, 4 are alive (3 CR, 1 relapse), and 5 died (4 from relapse, 1 death in CR from sepsis). Baseline and longitudinal 36-marker mass cytometry (CYTOF), including FLT3, STAT, RAS-MAPK, and apoptosis pathway markers, is ongoing.

Patient Characteristics	DAC + Quizartinib + Venetoclax (n=21) N (%), Median [Range]	
	Relapse/Refractory (N=17)	Frontline (N=4)
Age-years	51 [23-86]	72 [65-85]
Gender- Male	5 (30)	1 (25)
Diagnosis, AML		
De novo	15 (88)	1 (25)
Secondary	1 (6)	2 (50)
Therapy related	1 (6)	1 (25)
Prior therapies, median	3 [1-5]	n/a
Intensive Rx, yes	15 (88)	n/a
FLT3 inhibitor, yes	14 (82)	n/a
Venetoclax, yes	8 (47)	n/a
ASCT, yes	7 (41)	n/a
Karyotype		
Diploid	8 (47)	1 (25)
Adverse	2 (12)	2 (50)
Other	7 (41)	1 (25)
FLT3 mutations		
ITD	13 (100)	4 (100)
ITD allelic frequency	0.28 [0.04-0.76]	0.32 [0.21-0.41]
TKD	0 (100)	
Other mutations*		
DNMT3A	8 (47)	1 (25)
NPM1	7 (41)	3 (75)
WT1	7 (41)	0(0)
TET2	6 (35)	0(0)
RAS/MAPK	3 (18)	0(0)
RUNX1	3 (18)	0(0)
IDH2	2 (12)	2 (50)
Quizartinib Dose Levels		
30 mg/day	16 (93)	3 (25)
40 mg/day	1 (7)	1 (25)

*Mutation analysis missing in 1 patient, ≥2 mutations included, RAS/MAPK - RAS, PTPN11, CBL, NF1

Summary/Conclusion: DAC + VEN + quizartinib is active in heavily pretreated and prior FLT3i exposed R/R *FLT3*-ITDm pts, with CRc rates of 69% (55% of responders were negative MRD by MFC) and the med OS of 7.1 months. The regimen was well tolerated with no 30-day mortality. Accrual to the triplet continues and updated clinical and correlative data will be presented.

EP431 SECOND ALLOGENEIC STEM CELL TRANSPLANTATION FOR SECONDARY AML RELAPSING AFTER FIRST TRANSPLANTATION-A COMPARISON BETWEEN MYELOABLATIVE AND REDUCED INTENSITY CONDITIONING: FROM THE ALWP OF THE EBMT

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Background: Secondary acute myeloid leukemia (sAML) has been associated with inferior outcomes compared to *de novo* AML. Relapse (rel) is the most frequent cause of transplant failure reaching up to 50% in high-risk AML. Median OS in sAML is 8 months. The available data for patients (pts) with sAML undergoing a second hematopoietic stem cell transplantation (HSCT2) for rel post first transplantation (HSCT1) is limited. Furthermore, no study has compared myeloablative (MAC) versus reduced intensity conditioning (RIC) for HSCT2 in sAML.
Aims: The study aimed to assess HSCT2 outcome for sAML comparing MAC to RIC.
Methods: This was a retrospective analysis based on data from the EBMT registry, including adult pts aged ≥18 years with sAML undergoing HSCT2 during the years 2005-2019 for rel post-HSCT1. Allografts were from a matched sibling donor (MSD), unrelated donor (UD), or haploidentical donor (Haplo) for both HSCT1 and HSCT2. Multivariate analysis (MVA) adjusting for potential confounding factors was performed using a Cox's proportional-hazards regression model for main outcomes.
Results: 215 pts were included: RIC (n=134), MAC (n=81). Median F/U was 41.0 (27.7-69.3) and 28.5 (23.9-75.4) months. Median age was 55.1 (23.9-70.1) and 52.5 (18.2-67.8) years (p=0.10), and 56.0% and 54.3% were male (p=0.81), respectively. Median time from HSCT1 to rel for MAC and RIC was 19 and 24 months (p=0.55). Disease status was CR in 40.3% and 40.8%, and active disease in 59.7% and 59.2% (p=0.95), respectively. KPS was ≥90 in 55.8% and 56.7% of pts, respectively (p=0.90). Donors were MSD in 24.6% and 25.9%, UD in 61.2% and 56.8%, and Haplo in 14.2 and 17.3%, respectively (p=0.77). Graft was peripheral blood in 94.8% and 88.9% of transplants (p=0.11) and TBI was administered to 20.1% and 27.2%, (p=0.24), respectively. The most frequent RIC was Fludarabine/ Busulfan (Flu/Bu)-13.2%, Flu/TBI-10.1%, and Flu/Melphalan (Mel)-9.3%, while the most frequent MAC was Flu/Bu-9%, Flu/Thiotepa (Thio)/Treosulfan (Treo)-9%, and Flu/TBI-6.4%. In vivo T-cell depletion with antithymocyte globulin (ATG) was used in 51.3% and 55.6 % of transplants (p=0.56). Graft-versus-host disease (GVHD) prophylaxis was cyclosporine A (CSA)/mycophenolate mofetil ± ATG in 31.9 % and 34.7%, and CSA/methotrexate + ATG in 15.9% and 19.4% of the pts. At 2-years the rel incidence was 58.3% vs 51.1% in MAC and RIC, respectively (p=0.24). The 2-y LFS was 26.6% vs 26%, (p=0.55), and the GRFS was 16.4% vs 12.1% (p=0.88), while OS was 31.4% and 39.7%, (p=0.41), respectively. 68% and 61.7% of pts receiving MAC and RIC died.Main cause of death was original disease 58.4% and 40.8% followed by infections and GVHD 10.1% and 10.2%; and 6.7% and 4.1%, respectively. MVA showed a significantly lower rel and improved LFS with MAC vs RIC, HR=0.46 (95% CI, 0.26-0.8, p=0.006) vs HR=0.62 (95% CI, 0.39-0.98, p=0.042), respectively, while OS, HR=0.72 (95% CI, 0.44-1. 17, p=0.18) and GRFS, HR=0.89 (95% CI, 0.59-1.36, p=0.6), respectively, did not differ significantly. Other significant prognostic factors for HSCT2 outcome were disease status, time from HSCT1 to relapse, and KPS.

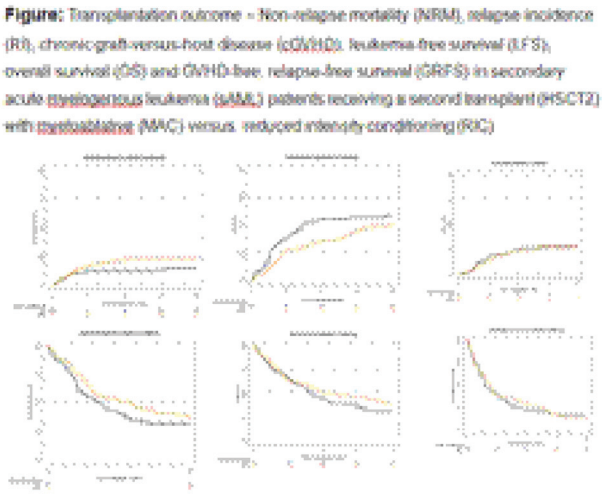


Figure: Transplantation outcome - Non-relapse mortality (NRM), relapse incidence (RI), chronic graft-versus-host disease (cGVHD), leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) in secondary acute myelogenous leukemia (sAML) patients receiving a second transplant (HSCT2) with myeloablative (MAC) versus reduced intensity conditioning (RIC)

Summary/Conclusion: In this EBMT registry study of HSCT2 for sAML, MAC was associated with a lower relapse risk and superior LFS. Disease status, time from HSCT1 to relapse, and KPS are additional prognostic factors for transplantation outcome. These results are consistent with our previously reported findings in pts with sAML undergoing HSCT1 (Blood Advances 2:2127-2135, 2018), in favor of MAC for pts with sAML who received an HSCT2 after relapse.

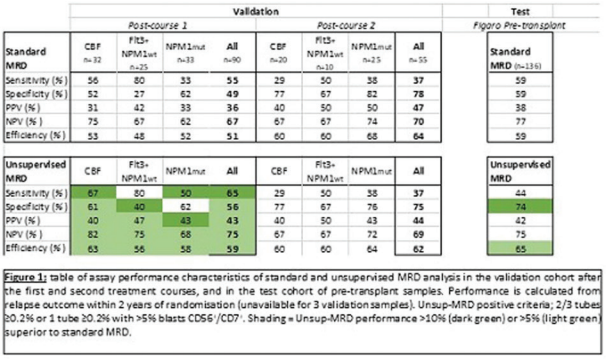
EP432 VALIDATION AND CLINICAL APPLICATION OF AN UNSUPERVISED ANALYSIS APPROACH TO MEASURABLE RESIDUAL DISEASE TESTING IN ACUTE MYELOID LEUKEMIA

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Background: Multiparameter flow cytometric assessment of measurable residual disease (MFC-MRD) in acute myeloid leukaemia (AML) has important prognostic value in predicting future relapse in patients who achieve a complete response to front-line chemotherapy. Efforts to harmonise MFC-MRD are ongoing but considerable expertise is still required for its analysis stage, with potential for variable interpretation and therefore prognostic value.
Aims: Prognostic evaluation of an unsupervised (Unsup) analysis method, developed to generate MFC-MRD results that are reproducible without reliance on significant expertise or diagnostic samples.
Methods: Comparison of the prognostic performance of our Unsup pipeline to conventional MFC-MRD analysis was performed, first for validation on post induction MFC-MRD samples and then on pre-transplantation samples from the FIGARO trial (*Craddock et al, JCO 2020*). Bone marrow samples (BM) were assessed in these trials for MFC-MRD as previously described (*Freeman et al, JCO 2018*). Phenograph clustering was performed on downsampled blast flow files in runs of up to 50 AML samples plus ~40 control BMs. Fluorescence intensity of markers on control blasts in each algorithm-defined cluster was used to statistically define the limits of normal marker expression per cluster. Blasts with aberrant expression defined by these cluster-specific reference range limits were quantified to produce Unsup-MRD results as a % of leukocytes.

Results: Results for assay validation were generated from 148 BMs after 1st and 2nd induction from 111 patients (39 CBF, 44 *NPM-1*^{mut} and 28 *Flt3-ITD*$^{+}$*NPM1*^{wt} AMLs).
Unsup-MRD values were higher than standard MFC-MRD (which estimates %MRD from a single leukemic aberrant immunophenotype) but correlated positively. Polynomial regression showed 0.32% Unsup-MRD to have equivalence to the ELN recommended cut-off of 0.1% for standard MFC-MRD positivity. Duplicate testing demonstrated result repeatability (r2=0.876; p<0.001). Minimum analytical sensitivity determined from clustering runs of control BMs tested against reference control BMs was 0.13% for the limit of blank / 0.20% for the limit of detection. From *in silico* spiking of AML blasts into control blasts, mean recovery was 84-108% with Unsup-MRD detected at >5% of blasts at the lowest dilution.
To optimise test specificity, Unsup-MRD positivity criteria were set at ≥0.2% in ≥2 tubes unless CD56+/ CD7+ at ≥0.2%. Importantly, assay statistics for relapse within 2yrs were highly similar between Unsup-MRD and standard MRD in the test cohort (Figure 1). Of note, the negative predictive value of Unsup-MRD post-C1 was 82% and 75% for CBF and *Flt3-ITD*$^{+}$*NPM1*^{wt} patients respectively.
We then applied the validated Unsup-MRD criteria to the pre-transplant BMs from 136 FIGARO patients. Assay performance was again comparable to standard MRD (Figure 1). 2yr cumulative incidence of relapse (CIR) was 22.2% for MRD^{neg} vs 42.1% for MRD^{pos} by Unsup criteria (p=0.03).
We next tested the higher cut-off (≥0.3%) equivalent to 0.1% standard MFC-MRD. This had little impact on test efficiency for the post-induction validation cohort but increased pre-transplant Unsup-MRD specificity (82% from 71%) with a 2yr CIR of 21.2% MRD^{neg} vs 51.9% MRD^{pos} (p<0.001). These results support previous observations that relapse risk after reduced intensity allogeneic transplant. may not be significantly increased when MFC-MRD is detected at low levels pre-transplant.



	Validation								Test
	Post-course 1				Post-course 2				Figaro Pre-transplant
Standard MRD	CBF n=32	Flt3+ NPM1wt n=25	NPM1mut n=33	All n=90	CBF n=20	Flt3+ NPM1wt n=10	NPM1mut n=25	All n=55	Standard MRD (n=136)
Sensitivity (%)	56	80	33	55	29	50	38	37	59
Specificity (%)	52	27	62	49	77	67	82	78	59
PPV (%)	31	42	33	36	40	50	50	47	38
NPV (%)	75	67	62	67	67	67	74	70	77
Efficiency (%)	53	48	52	51	60	60	68	64	59
Unsupervised MRD	CBF	Flt3+ NPM1wt	NPM1mut	All	CBF	Flt3- NPM1wt	NPM1mut	All	**Unsupervised MRD**
Sensitivity (%)	67	80	50	65	29	50	38	37	44
Specificity (%)	61	40	62	56	77	67	76	75	74
PPV (%)	40	47	43	43	40	50	43	44	42
NPV (%)	82	75	68	75	67	67	72	69	75
Efficiency (%)	63	56	58	59	60	60	64	62	65

Figure 1: table of assay performance characteristics of standard and unsupervised MRD analysis in the validation cohort after the first and second treatment courses, and in the test cohort of pre-transplant samples. Performance is calculated from relapse outcome within 2 years of randomisation (unavailable for 3 validation samples). Unsup-MRD positive criteria; 2/3 tubes ≥0.2% or 1 tube ≥0.2% with >5% blasts CD56^{+}/CD7^{+}. Shading = Unsup-MRD performance >10% (dark green) or >5% (light green) superior to standard MRD.

Summary/Conclusion: The prognostic performance of a novel unsupervised approach for assessing AML MFC-MRD is at least equivalent to standard MFC-MRD analysis.

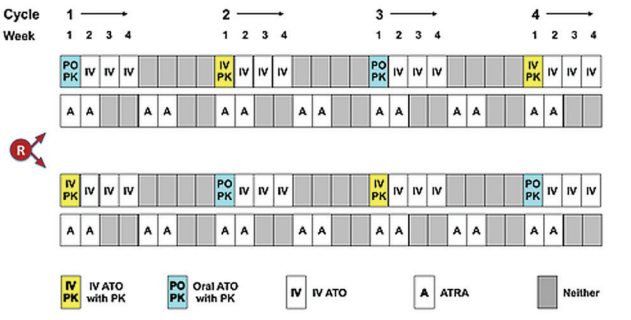
EP433 COMPARATIVE BIOAVAILABILITY OF A NOVEL ORAL FORMULATION OF ARSENIC TRIOXIDE IN PATIENTS UNDERGOING CONSOLIDATION THERAPY FOR ACUTE PROMYELOCYTIC LEUKEMIA: FINAL ANALYSIS OF THE ALLG APML5 TRIAL

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Background: All-*trans* retinoic acid (ATRA) and intravenous arsenic trioxide (IV ATO) cure most patients with acute promyelocytic leukemia (APL), but the requirement for 2-hourly ATO infusions over several months is problematic. Orally administered ATO has the potential to significantly reduce resource utilization and improve the therapeutic experience without compromising efficacy.
Aims: To characterize the bioavailability of encapsulated oral ATO (Phebra, Australia) in patients with APL by comparing the total arsenic $AUC_{0\text{-}24}$ and C_{max} in whole blood (WB) and plasma (PL) after oral and IV ATO administration.
Methods: The APML5 trial (ACTRN12616001022459) was a phase I, 2-part, 2-sequence, 4-period, bioavailability study in 31 consenting patients with previously untreated APL, embedded within a standard-of-care consolidation regimen (ATRA + IV ATO; Lo-Coco *et al*, NEJM 369:111,2013). Eligibility required documented hematological complete remission after induction with ATRA + IV ATO (+ idarubicin for high-risk APL). Initial pharmacokinetic (PK) data from the APML5 part 1 pilot (n=9) indicated oral and IV ATO provide comparable arsenic exposure over repeated cycles of consolidation (Iland *et al*, EHA 2019, HemaSphere doi:10.1097/01.HS9.0000562408.61553.8e).
To conclusively establish bioequivalence, 22 patients at 12 sites were randomised in APML5 part 2 (Jan 2019-June 2020) to IV or oral ATO 0.15mg/kg/d with PK sampling in week 1 of cycles 1 & 3, and the alternate route in week 1 of cycles 2 & 4 (Figure). Total arsenic was quantitated by inductively coupled plasma mass spectrometry. Point estimates of mean oral/IV arsenic ratios ± 90% confidence intervals (CI) for $AUC_{0\text{-}24}$ (μmol/l.h) and C_{max} (μmol/l) in WB and PL were calculated by linear mixed model analysis incorporating fixed and random effects.
Results: The target accrual of 20 evaluable patients was reached after 2 replacements (insufficient PK data as per protocol). Median age was 45.9 years (range 23.4-75.2), 10 male, 10 female, 14 Sanz standard-risk, and 6 high-risk. Both ATO formulations were associated with significant increases in $AUC_{0\text{-}24}$ and C_{max} in WB and PL from day 1 to day 4 of each cycle (p<0.001), indicative of short-term arsenic accumulation, but no accumulation occurred between sequential cycles. Estimates of the geometric mean of the oral/IV ratio for each PK parameter closely approximate unity (Table), and the 90% CI fall within the conventional bioequivalence limits (0.80, 1.25). Distinguishing adverse events (AEs) specifically related to oral ATO from those related to IV ATO is problematic, since IV ATO was also administered for 3 weeks in cycles that commenced with 1 week of oral ATO (Figure). Nevertheless, no excess of grade 3-4 AEs (including gastrointestinal toxicity) was noted in cycles that contained oral ATO, and no instances of oral or IV ATO-associated QTc prolongation were observed during part 2 of APML5, despite monitoring with twice weekly electrocardiograms in each cycle. One patient with high-risk disease relapsed after consolidation.

PK parameter	Estimated geometric mean of oral/IV ratio	Lower limit (90% CI)	Upper limit (90% CI)
WB $AUC_{0\text{-}24}$	0.9931	0.9542	1.034
PL $AUC_{0\text{-}24}$	1.030	0.9773	1.087
WB C_{max}	0.9174	0.8709	0.9663
PL C_{max}	0.9692	0.8923	1.053



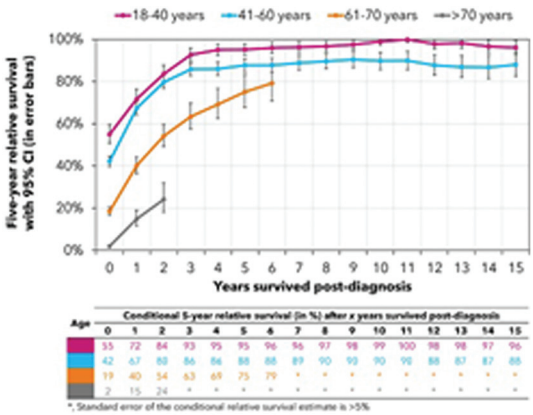
Summary/Conclusion: This randomized crossover bioavailability study confirmed bioequivalence of the oral and IV formulations of ATO when administered in the context of standard-of-care consolidation, and unexpected toxicity signals were not evident. Overall, the results of the APML5 trial provide a sound rationale for incorporating oral ATO in the management of patients with APL.

EP434 AGE-SPECIFIC CONDITIONAL RELATIVE SURVIVAL AMONG LONG-TERM ACUTE MYELOID LEUKEMIA (AML) SURVIVORS IN THE NETHERLANDS

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Background: The connotation surrounding AML is often grim because of the heightened risk of mortality within the first few years post-diagnosis. Therefore, survival estimates measured from diagnosis, which is usually presented in population-based cancer research, might be somewhat pessimistic for long-term AML survivors and their caregivers who desire to obtain information on the prognosis after having survived some years post-diagnosis.
Aims: Against this background, this population-based study aimed to estimate the conditional 5-year relative survival among AML patients up to 15 years post-diagnosis.
Methods: All adult (≥18 years) AML patients diagnosed between 1989-2018—with follow-up for survival through December 31, 2019—were selected from the Netherlands Cancer Registry. We excluded patients with acute promyelocytic leukemia. Relative survival (RS) was calculated to estimate disease-specific survival as the ratio of the observed to the expected survival, based on national life tables stratified by age, sex, and calendar year. We computed 5-year RS at diagnosis and for each additional year survived up to 15 years post-diagnosis. RS was estimated using a hybrid approach to predict up-to-date survival probabilities. This approach was applied for patients diagnosed between 1989-2018 who were alive during the follow-up interval 2008-2019. The produced estimates can be interpreted as the predicted survival probability of patients diagnosed during 2008-2019. Survival estimates were computed—with associated 95% confidence intervals (CIs)—according to age at diagnosis (18-40, 41-60, 61-70, and >70 years). Only survival estimates with a standard error of ≤5% were presented. This choice relates to the precision of the survival estimates. Excess mortality is minimal when RS is ≥95%.
Results: A total of 16,177 adult AML patients (median age, 68 years) were diagnosed in the Netherlands between 1989-2018, of whom 8,182 (51%) were alive at some point during the follow-up interval and contributed to the survival estimates. There was a prognostic effect of age on 5-year RS at diagnosis, with corresponding estimates (95% CI) of 55% (51% - 60%), 42% (40% - 45%), 19% (17% - 21%), and 2% (2% - 3%) across the four age groups (Figure). This effect essentially persisted up to 15 years post-diagnosis (Figure). Notwithstanding, excess mortality decreased with each additional year survived across all age groups (Figure). Encouragingly enough, patients aged 18-40 years at diagnosis hardly experienced excess mortality after four years post-diagnosis (Figure). In contrast, excess mortality remained substantial for patients aged >40 years, especially among those aged >60 years (Figure).



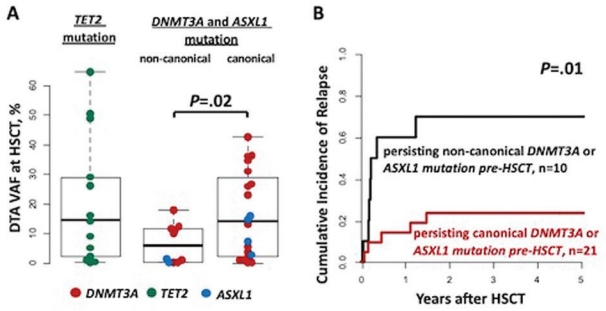
Summary/Conclusion: The prognosis of adult AML patients improved with each additional year survived. Reassuring is that patients aged 18-40 years at diagnosis can look forward to a near-normal life expectancy after four year post-diagnosis. This finding, unfortunately, does not hold for patients aged >40 years at diagnosis. Late treatment-related sequelae and late relapses might cause the ongoing excess mortality among patients aged 41-70 years, a group mostly considered for intensive, potentially curative treatment. The poor outcome among patients aged >70 years is inherently tied to the virtually incurable nature of AML in this age group. Statistics on CRS in AML may offer patients and physicians a better apprehension of the changing survival expectations with each additional year survived post-diagnosis. This information can also be used to tailor age-specific surveillance and follow-up activities.

EP435 CLINICAL IMPACT OF SENSITIVE DNMT3A, TET2, OR ASXL1 MUTATION DETECTION IN ACUTE MYELOID LEUKEMIA PATIENTS PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: In acute myeloid leukemia (AML), mutations in the genes *DNMT3A*, *TET2*, and *ASXL1* (DTA) are frequent and appear early in leukemogenesis. In older, otherwise healthy individuals DTA mutations may be present as clonal hematopoiesis of indeterminate potential (CHIP). While *TET2* mutations do not have a common hotspot, mutations in *DNMT3A* and *ASXL1* frequently occur at specific positions (*DNMT3A* in R882 and *ASXL1* as G646fs*12, referred to as "canonical"). The persistence of gene mutations prior to allogeneic hematopoietic stem cell transplantation (HSCT) as consolidation therapy may identify AML patients (pts) at high-risk of relapse. Until today, no study genuinely evaluated the applicability of DTA mutations - including canonical *vs.* non-canonical mutations - as residual disease markers in AML pts receiving HSCT consolidation.
Aims: To evaluate DTA mutations as residual AML disease markers in pts prior to allogeneic HSCT.
Methods: We analyzed 68 AML pts harboring at least one DTA mutation (*DNMT3A*, n=41; *TET2*, n=18; *ASXL1*, n=15) at diagnosis, who received HSCT (median age 64, range 35-75 years) in complete remission (CR; n=50) or CR with incomplete recovery (CRi, n=18). Conditioning regimens were non-myeloablative (n=57), reduced intensity (n=7) or myeloablative (n=4). At diagnosis, the mutational status of 54 genes was evaluated using next generation sequencing at diagnosis. Applying highly sensitive mutation-specific digital droplet PCR (ddPCR) assays at the timepoint of HSCT, we tested for the persistence of DTA mutations. Median follow up was 5.0 years.
Results: At diagnosis, 41 pts had a *DNMT3A* mutation (62%; canonical: 61%; non-canonical: 39%) 18 had a *TET2* mutation (33%) and 15 had an *ASXL1* mutation (22%; canonical: 80%; non-canonical: 20%). Most frequently co-mutated genes were *NPM1* (43%), *RUNX1* (19%), *IDH2* (16%), and *BCOR*, *IDH1*, and *FLT3*-ITD (each with 15%). At HSCT, DTA mutations persisted in the majority of pts (overall 84%; *DNMT3A* 86%, *TET2* 93%, and *ASXL1* 60%). The rate of sustained detection did not differ significantly between canonical and non-canonical mutations (*DNMT3A*: 89% *vs* 80%, *P*=1 and *ASXL1*: 57% *vs* 67%, *P*=1). Of the analyzed non-canonical mutations in *DNMT3A* 10% were frameshift, 60% were missense, and 30% were nonsense, while in *ASXL1* all non-canonical mutations were nonsense. In pts with persisting *DNMT3A* and *ASXL1* aberrations, non-canonical mutations persisted at significantly lower variant allele frequencies (VAFs) compared to canonical mutations (*P*=.02, Figure 1A). Overall, the retained detection of DTA mutations did not associate with a higher cumulative incidence of relapse (CIR, *P*=.37) or overall survival (OS, *P*=.34) after HSCT. However, in *DNMT3A* or *ASXL1* mutated pts, the persistence of a non-canonical mutation associated with significantly higher CIR (*P*=.01, Figure 1B) and shorter OS (*P*=.04) compared to the persistence of canonical mutations.



Summary/Conclusion: In general, the continuing detection of DTA mutations prior to HSCT did not associate with outcomes in AML pts transplanted in CR/CRi. In pts with *DNMT3A* or *ASXL1* mutations, non-canonical mutations persisted at lower VAF levels than canonical mutations. The persistence of non-canonical *ASXL1* or *DNMT3A* mutations associated with worse outcomes compared to the persistence of canonical mutations, challenging the paradigm that all DTA mutations are unsuitable as residual disease markers in AML.

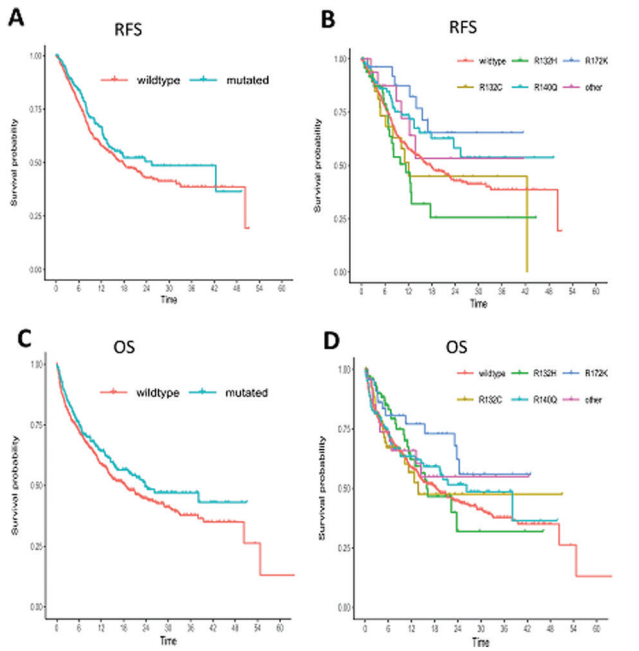
EP436 PREVALENCE AND PROGNOSTIC IMPACT OF IDH MUTATIONS IN THE REAL-WORLD SETTING: RESULTS FROM THE PROSPECTIVE IDH SCREENING COHORT OF THE SAL AML REGISTRY

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Background: Mutations in the *IDH1* and *IDH2* genes belong to the most frequent recurrent genetic alterations in AML. Whereas IDH mutations in total do not have a favorable nor adverse prognostic impact, certain subtypes may be associated with a more favorable or adverse clinical course. The majority of available data on prevalence and prognostic impact was obtained in selected patient groups, who were most commonly treated intensively as part of clinical trial protocols.
Aims: We set up a study to prospectively screen for *IDH* mutations and collect prognostic information on *IDH* in a large real-world cohort of patients (pts) enrolled in the AML registry of the SAL study group.
Methods: Between April 2016 and March 2020, all pts from centers participating in the SAL registry were screened for *IDH* mutations by a sensitive amplicon-based NGS approach. Both newly diagnosed and relapsed/refractory (r/r) pts receiving either intensive or non-intensive treatments were screened. Pts did not receive IDH inhibitors. The study was approved by the responsible Ethics Committee as part of the SAL AML registry (NCT03188874).
Results: 2690 pts were screened, of which 2457 were obtained at initial diagnosis and 233 in r/r AML. The prevalence of *IDH1* and *IDH2* mutations was 9.7% and 13.3%, respectively, which was identical at initial diagnosis and in r/r disease. Mutations R132C and R132H were the most common mutations in *IDH1*, whereas in *IDH2*, R140Q and R172K were most frequently found.
In newly diagnosed AML, the CR rate in *IDH*-mut versus (vs) *IDH*-wt was 68% vs 67% (p=0.919). The median relapse-free survival (RFS) in mut vs wt pts was 25.4 vs 17.8 months (m) (p=0.106). Subgroup analyses revealed a superior survival of *IDH2*-R172K mut pts with a 1-year RFS of 88% vs 58% in *IDH*-wt pts (p=0.037). A trend for superior overall survival (OS) was observed in *IDH*-mut pts with a median OS of 24 vs 18 m (p=0.066). *IDH2*-R172K pts had a significantly better prognosis than *IDH*-wt pts with a 1-year OS of 77% vs 59% (p=0.037). The described patterns were similar if pts eligible for intensive treatment were analysed separately.
In 137 pts with *de novo* AML ineligible for intensive treatment, median RFS in pts achieving a CR was longer in *IDH*-mut vs *IDH*-wt (8.5 vs 6.3 m; p=0.041); however, median OS in all unfit pts did not differ significantly between *IDH*-mut and *IDH*-wt (4.9 vs 4.3 m; p=0.326).
In 105 evaluable r/r AML, the CR rate in *IDH*-mut vs *IDH*-wt was 42% vs 59% (p=0.132), 1-year RFS 67% vs 40% (p=0.309) and 1-year OS identical with 67%.

Figure: RFS and OS depending on *IDH* mutational status in newly diagnosed AML (*IDH1*-R132C, *IDH1*-R132H, *IDH2*-R149Q, *IDH2*-R172K). A, RFS in *IDH*-mut vs *IDH*-wt; B, RFS in *IDH*-mut subgroups vs *IDH*-wt; C, OS in *IDH*-mut vs *IDH*-wt; D, OS in *IDH*-mut subgroups vs *IDH*-wt.



Summary/Conclusion: In this prospectively analyzed cohort of AML pts from a real-world setting, we detected *IDH* mutations in 23% of cases, irrespective of the disease status. Whereas *IDH* mutations were not associated with differences in RFS and OS in the total cohort, significantly prolonged survival outcomes could be identified for the subgroup of newly diagnosed pts with *IDH2*-R172K. Our results confirm the favorable prognosis of the *IDH2*-R172K subgroup. Furthermore, the results from this real-world cohort including r/r AMLs and pts ineligible for intensive treatment match the results of previously published newly diagnosed and fit patient groups from clinical trials.[1]

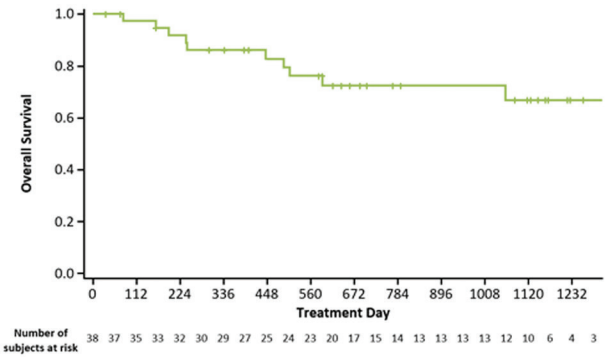
[1] Middeke JM, Metzeler KH, Röllig C et al. Clinical characteristics and outcome in IDH1/2 mutant AML pts. Oncol Res Treat 2019;42(suppl 4): abstract V1022

EP437 A PHASE 1 STUDY OF GILTERITINIB IN COMBINATION WITH INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED AML: FINAL RESULTS UPDATE

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Background: Gilteritinib, an oral *FMS*-like tyrosine kinase 3 (FLT3) inhibitor, demonstrated antileukemic responses in patients (pts) with *FLT3*-mutated (*FLT3*^{mut}) relapsed/refractory acute myeloid leukemia (AML).
Aims: We report updated final data from a phase 1 study of once-daily oral gilteritinib + intravenous chemotherapy in pts with newly diagnosed (ND) AML.
Methods: As detailed previously in Pratz et al. *Blood* 2020;136(supp1):16-17, this 4-part, open-label, phase 1 study (NCT02236013) assessed the safety/tolerability and antileukemic effects of gilteritinib plus 7 + 3 induction and ≤3 cycles of high-dose cytarabine consolidation, and as single-agent maintenance treatment (tx) in adults with ND AML. During induction, cohorts varied in their gilteritinib dose (40–200 mg during dose escalation and 120 mg in cohort expansion), gilteritinib administration schedule (days 4–17 or 8–21), and anthracycline choice (idarubicin or daunorubicin). Eligible patients could receive a second 7 + 3+gilteritinib induction cycle. During consolidation, gilteritinib was administered at induction dose on days 1–14 or 1–56 of each cycle (cohort dependent). During maintenance, gilteritinib was given daily (28-day cycles) for up to 26 cycles. Pts with a composite complete remission (CRc) or partial remission could undergo hematopoietic stem cell transplant (HSCT) and resume maintenance gilteritinib tx post HSCT. Safety and tolerability were the primary endpoints.
Results: As of 23 June 2020, 80 pts were allocated to tx (safety analysis set, n=79); median age was 59.0 y (range, 23–77) and 44 were *FLT3*^{mut}. Median follow-up was 35.8 mo. HSCT was performed in 30.4% (24/79) of pts. Dose-limiting toxicities (DLTs) occurred in 15/79 (19.0%) pts. DLTs in the 200 mg/d cohort were prolonged neutropenia (n=1) and neutropenic enterocolitis (n=1). The maximum tolerated dose was 120 mg/d. Serious tx-related adverse events (AEs) and AEs leading to discontinuation of gilteritinib occurred in 29.1% (n=23) and 22.8% (n=18) of pts, respectively. Grade ≥3 nonhematologic AEs (≥10% of pts) were increased alanine aminotransferase (13.9%), pneumonia (13.9%), sepsis (11.4%), and bacteremia (11.4%). A 120 mg/d dose of gilteritinib was received by 38 (86.4%) *FLT3*^{mut} pts. In Pratz et al. *Blood* 2020, we reported clinical responses at end-of-induction but now report response at end-of-treatment, consistent with previous disclosures. Among *FLT3*^{mut} pts who received gilteritinib 120 mg/d, the CRc rate was 89.5% (complete remission [CR], 71.1%; CR with incomplete hematological recovery, 18.4%) and median overall survival has not been reached (**Figure**). Anthracycline choice had no significant impact on CRc rate or toxicity. Estimated 1- and 2-year survival probabilities were 85.9% and 72.3% respectively. The 60-day mortality rate was 0%. Median (95% CI) disease-free survival was 13.3 (4.9–18.7) mo. In pts who received gilteritinib 120 mg/d and achieved CRc, mutational clearance of *FLT3* internal tandem duplication (ITD) (summed *FLT3* ITD:WT signal ratio of ≤10^{-4}) after induction or consolidation was 84.6% (11/13).



Summary/Conclusion: Gilteritinib + induction and consolidation chemotherapy is well-tolerated in pts with ND *FLT3*^{mut} AML and often leads to CR, clearance of *FLT3* ITD, and long-term survival. Based on these data, randomized trials of gilteritinib vs midostaurin as part of intensive frontline therapy of *FLT3*^{mut} AML have been initiated.

EP438 FOLLOW-UP OF PATIENTS WITH FLT3-MUTATED RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA IN THE PHASE 3 ADMIRAL TRIAL

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Background: The phase 3 ADMIRAL trial demonstrated the superiority of gilteritinib to salvage chemotherapy (SC) in patients with *FLT3*-mutated (*FLT3*$^{mut+}$) relapsed or refractory (R/R) acute myeloid leukemia (AML).
Aims: A follow-up of ADMIRAL assessed long-term survivors, hematopoietic stem cell transplantation (HSCT) outcomes, and gilteritinib safety beyond 1 year.
Methods: A data cut was performed on September 20, 2020—2 years after the primary analysis. Patients who were alive without relapse, patients who underwent HSCT, and adverse events (AEs) of interest in Years 1 (≤12 months) and 2 (>12 months) of gilteritinib therapy were evaluated.
Results: As of September 20, 2020, 17% (n=63/371) of patients in the intention-to-treat (ITT) population were alive (gilteritinib, n=49; SC, n=14); 16 patients assigned to gilteritinib remained on treatment. After a median follow-up of 37.1 months, 26 of the 49 patients in the gilteritinib arm who were alive were also without relapse; 18 of these 26 patients underwent HSCT, with 16 receiving post-HSCT gilteritinib maintenance therapy. Nineteen of the 26 patients in the gilteritinib arm without relapse continued gilteritinib beyond 1 year and remained in complete remission (CR).
Of the 371 patients in the ITT population, 83 (22%) underwent HSCT during the study (gilteritinib, n=64; SC, n=19). Pre-HSCT composite CR (CRc) rates were similar across arms (gilteritinib: n=40/64; 63%; SC: n=11/19; 58%); 10 of 11 patients preselected for low-intensity SC achieved pre-HSCT CRc (i.e., the sum of patients who achieved CR with or without complete hematologic or platelet recovery) (gilteritinib, n=9; SC, n=1). Forty of 64 (63%) transplanted patients in the gilteritinib arm received post-HSCT gilteritinib maintenance after achieving pre-HSCT CRc; the 24-month relapse rate in patients who resumed gilteritinib after pre-HSCT CRc was 19%. Post-HSCT treatment with chemotherapy or other tyrosine kinase inhibitors was administered in 26 patients who received gilteritinib before transplantation.
Cumulative 24-month relapse rates in gilteritinib-treated patients who achieved pre-HSCT CR and CRc were 20% and 45%, respectively. Median post-HSCT overall survival (landmarked to the date of HSCT) was similar across arms (gilteritinib, 16.1 months; SC, 15.3 months; HR=1.076; 95% CI: 0.536, 2.160).
Overall, 10.2% of patients (n=25/246) had ≥24 months of gilteritinib exposure. The most common AEs of interest during Years 1 and 2 of gilteritinib therapy were elevated alanine or aspartate aminotransferase levels. Incidences of all AEs of interest declined in Year 2. Cardiac AEs of interest in Year 2 were nonfatal cardiorespiratory arrest (n=1) and ventricular tachycardia (n=1). One case of differentiation syndrome and cutaneous squamous cell carcinoma occurred in Years 1 and 2, respectively.
Summary/Conclusion: A high proportion of gilteritinib-treated R/R *FLT3*$^{mut+}$ AML patients who were alive without relapse had received HSCT followed by gilteritinib maintenance. Among all transplanted patients in ADMIRAL, pre-HSCT remission rates and post-HSCT survival were similar across arms. Post-HSCT gilteritinib maintenance may relate to the low post-HSCT relapse rate in the gilteritinib arm. The safety profile of gilteritinib is stable at 2 years with no new or significant safety signals.

EP439 CYTOPENIA MANAGEMENT IN THE PHASE 3 VIALE-C STUDY OF VENETOCLAX PLUS LOW-DOSE CYTARABINE FOR PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA INELIGIBLE FOR INTENSIVE CHEMOTHERAPY

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Background: Patients (pts) with acute myeloid leukemia (AML) who are older or ineligible for intensive chemotherapy have low remission rates and poor survival. In the phase 3, randomized, placebo (Pbo)-controlled VIALE-C study (NCT03069352), median overall survival was 8.4 mo with venetoclax (Ven) + low-dose cytarabine (LDAC) vs 4.1 mo with Pbo+LDAC in older or unfit pts with newly diagnosed AML (*Blood*. 2020;135:2137-45).
Aims: To analyze the frequency and management of cytopenia in pts who achieved a best response of complete remission (CR) or CR with incomplete count recovery (CRi) in VIALE-C.
Methods: Enrolled pts had newly diagnosed AML and were ineligible for intensive chemotherapy due to age (≥75 y) or comorbidities. Pts were randomized 2:1 to once-daily 600 mg oral Ven or Pbo in 28-day cycles plus 20 mg/m^2 subcutaneous LDAC on Days 1–10. After pts achieved blast clearance (bone marrow blasts <5%), dose modifications were used to manage cytopenia (**Table 1**). Cytopenia was defined as Grade 4 neutropenia (absolute neutrophil count <500/μL) or Grade 4 thrombocytopenia (platelet count <25×10^3/μL) lasting ≥7 days and was assessed using laboratory data.
Results: Of randomized pts who received Ven+LDAC (n=142) and Pbo+LDAC (n=68), 69 (49%) and 9 (13%), respectively, achieved a best response of CR/CRi. Of 69 pts in CR/CRi in the Ven+LDAC arm, cumulatively, 74%, 84%, 88%, 97%, and 99% achieved blast clearance by the end of Cycles 1, 2, 3, 4, and ≥7, respectively (1 pt achieved clearance after treatment discontinuation). Of 9 pts in CR/CRi in the Pbo+LDAC arm, cumulatively, 33%, 56%, 56%, 89%, and 100% achieved blast clearance by the end of Cycles 1, 2, 3, 4, and ≥7, respectively. After achieving blast clearance, delayed start of the next cycle to allow for count recovery occurred in 71% and 44% of pts in the Ven+LDAC and Pbo+LDAC arms, respectively, with a median delay (min-max) to the next cycle of 8 (2–31) and 3 (2–7) days, respectively. More pts in CR/CRi who received Ven+LDAC vs Pbo+LDAC had postremission cytopenia (75% vs 33%). The proportion of pts in CR/CRi with in-cycle dose interruptions (ie, days without Ven/Pbo exposure between a cycle's first and last Ven/Pbo dose) was similar between arms (Ven+LDAC, 22%; Pbo+LDAC, 22%), with a median duration (min-max) of 3 days (1–12) for Ven+LDAC and 5 days (1–10) for Pbo+LDAC. A greater proportion of pts in CR/CRi who received Ven+LDAC vs Pbo+LDAC experienced postremission cycle delays due to cytopenia (62% vs 33%). More pts in CR/CRi had postremission reductions in Ven/Pbo dosing days and/or within cycle dose interruptions totaling ≥7 days due to cytopenia in the Ven+LDAC arm (61%) vs the Pbo+LDAC arm (22%). Of these pts, the median percentage of days (min-max) without Ven or Pbo administration while in remission (out of the total no. of remission days) was 14% (1–73) in the Ven+LDAC arm and 7% (4–9) in the Pbo+LDAC arm. Ultimately, 29 pts in CR/CRi (42%) in the Ven+LDAC arm and 1 (11%) pt in the Pbo+LDAC arm received ≤21-day Ven/Pbo dosing postremission, with a median (min-max) time from remission to first ≤21-day cycle of 71 days (1–339) for Ven+LDAC and 1 day (1–1) for Pbo+LDAC.

Table 1. Dose Modifications to Manage Cytopenia

Timing	Efficacy Assessment	Event	Action
After Cycle 1	CRi or MLFS at end of Cycle 1	Incomplete count recovery	**Delay upcoming cycle** • Ven/Pbo and LDAC interruption from Day 29 until ANC ≥500/μL and platelet count ≥25×10^3/μL up to 21 days[a] • Ven/Pbo and LDAC resumed on the same day after the interruption
After Cycle 2 and subsequent cycles	CR/CRi/MLFS at end of Cycle 1 or subsequent cycle	New Grade 4 neutropenia or thrombocytopenia lasting >1 week[b]	**Delay upcoming cycle** • Ven/Pbo and LDAC interruption once cycle completed and until ANC ≥500/μL and platelet count ≥25×10^3/μL (unless medically necessary to interrupt drug within cycle) • Ven/Pbo and LDAC resumed on the same day after the interruption
	CR/CRi/MLFS at end of Cycle 2 or subsequent cycle	Persistent cytopenia[c]	**Reduce Ven/Pbo duration or dose** • Ven/Pbo and LDAC interruption once cycle completed • The next treatment cycle is delayed until ANC ≥500/μL and platelet count ≥25×10^3/μL up to 21 days[a] • Dose reduction guidelines were followed in the next treatment cycle: ○ 1st reduction: Ven/Pbo 600 mg administered for 21/28 days for subsequent cycles ○ 2nd reduction: Ven/Pbo 600 mg administered for 14/28 days for subsequent cycles ○ 3rd reduction: Ven/Pbo 400 mg administered for 14/28 days for subsequent cycles • Ven/Pbo and LDAC resumed on the same day after the interruption

[a]If no recovery by Day 21, a discussion between the investigator and the AbbVie medical director was required.
[b]Unless due to underlying disease (eg, relapse).
[c]Cytopenias that occur after Day 28 of a cycle (ie, during Cycle 2 and beyond).
ANC, absolute neutrophil count; CR, complete remission; CRi, complete remission with incomplete count recovery; LDAC, low-dose cytarabine; MLFS, morphologic leukemia-free state; Pbo, placebo; Ven, venetoclax.

Summary/Conclusion: In this study, bone marrow blast clearance for responding pts at the end of Cycle 1 was higher among pts who received Ven+LDAC (74%) vs Pbo+LDAC (33%). Although postremission cytopenia and dose modifications were more frequent with Ven+LDAC, cytopenia was successfully managed with dose modifications, representing an important practice consideration in helping pts to prolong disease control.

EP440 PROGNOSTIC IMPACT OF CONVENTIONAL CYTOGENETICS IN ACUTE MYELOID LEUKEMIA (AML) TREATED WITH DECITABINE AND VENETOCLAX (DEC10-VEN)

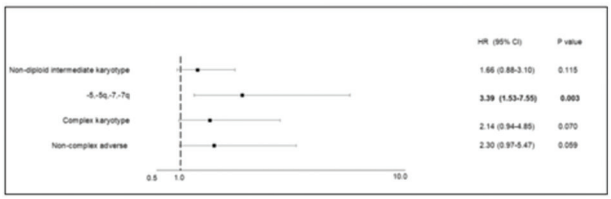
S. Venugopal [1,*], A. maiti [1], C. DiNardo [1], W. Qiao [2], J. Ning [2], S. Loghavi [3], N. Daver [1], T. Kadia [1], C. Rausch [4], Y. Alvarado [1], M. Ohanian [1], K. Sasaki [1], N. J. Short [1], K. Takahashi [1], M. Yilmaz [1], F. Ravandi [1], H. Kantarjian [1], M. Konopleva [1]

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Background: Cytogenetic risk (CGR) is an important prognostic factor in AML, but its role is less established for VEN based lower intensity therapy.
Aims: To determine the prognostic impact of CGR in pts treated with DEC10-VEN (NCT03404193)
Methods: Older pts with newly diagnosed (ND) (>60 years) and adult pts >18 years with secondary AML (sAML) with or without prior therapy, and relapsed/refractory (R/R) AML, with ECOG performance status <3 without prior BCL-2 inhibitor exposure were enrolled. Patients received 10-day decitabine at 20 mg/m2/day for induction followed by 5-days for consolidation. VEN dose was 400 mg PO daily or equivalent. Cytogenetic subgroups, response and outcomes were per ELN2017 criteria. Written informed consent was obtained from all pts.
Results: We included 179 pts including ND (N=74), untreated sAML (N=16), treated sAML (N=27), and R/R AML (N=62). The median age was 71 yrs (range 59-74 yrs). Overall response rate was 74% in the entire cohort, and negative MRD by flow cytometry was attained in 69 (64%) of 108 responding pts. In the treatment naïve cohort: the CR/CRi was 88% in diploid, 92% in non-diploid intermediate, 67% with abnormalities of chr 5,7,17, 66% in complex, and 66% in non-complex karyotype abnormalities and 63%,73%,11%,22%,26% CR in the pretreated cohort. On multivariable analysis: compared to diploid CG, pts with complex (OR 0.17; 95% CI 0.06,0.48; P <.001) and non-complex adverse (OR 0.07; 95% CI 0.01, 0.76; P=.028) groups are significantly less likely to achieve CR, and patients harboring Chr 5,7,17 abnormalities were significantly less likely to achieve CR/CRi (OR 0.17; 95% CI 0.05,0.65; P=.009), and at increased chance of death (HR 3.39; 95% CI 1.53, 7.55; P=.003). In the treatment naïve cohort, the median OS was 29.6 months (95% CI 0.6 to 3.7 mo) in diploid, 19.4 mo (95% CI 0.3 to 1.6 mo) in non-diploid intermediate;9.3 mo in in Chr 5,7,17 subgroup,6.9 mo in complex and 17.1 mo in the non-complex adverse subgroup. In the previously treated cohort, the median OS was 13.7 mo (95% CI 0.6 to 2.7 mo) with diploid,11.1 mo (95% CI 0.4 to 1.8 mo) in

non-diploid intermediate (95% CI 0.4 to 1.8 mo),7.1 mo in Chr 5,7,17 subgroup, 4.9 mo in complex, and 6.8 mo in non-complex adverse group. Achievement of complete cytogenetic response (CCyR) was an independent predictor of improved OS compared to those who did not achieve CCyR (mOS 16.2 vs. 8.0 mo, HR 0.4, 95% CI 0.2, 0.9, p=.01).

Patient characteristics	Treatment-naïve patients		Previously treated patients	
	Newly Diagnosed AML (N=74)	Untreated Secondary AML (N=16)	Treated Secondary AML (N=27)	Relapsed or Refractory AML (N=62)
Age, years	74 (63-86)	72 (64-89)	70 (49-84)	59 (18-85)
ELN 2017 cytogenetic risk				
Diploid	24 (32)	3 (19)	8 (30)	14 (23)
Others	18 (24)	5 (31)	6 (22)	23 (37)
(-5, -5q, -7, -17)	7 (10)	2 (13)	5 (19)	7 (15)
Complex	21 (28)	6 (38)	5 (19)	13 (21)
Other adverse	3 (4)	0	1 (4)	4 (6)
ORR	65 (88)	13 (81)	18 (67)	36 (79)
CR/CRi	45 (61)/15(20)	7 (44)/ 4 (25)	7 (26)/ 5 (19)	14 (23)/ 11 (18)
MRD neg by FCM	37/60 (62)	5/11 (45)	9/12 (75)	18/25 (72)
CCyR (in other than diploid)	25/36 (51)	5/10 (50)	4/8 (50)	13/23 (57)



Summary/Conclusion: CGR remain highly prognostic for response and survival, with CCyR conferring significant survival benefit in pts with AML receiving DEC10-VEN.

EP441 OUTCOMES IN GILTERITINIB-TREATED FLT3-MUTATED R/R AML PATIENTS WHO UNDERWENT TRANSPLANTATION

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Background: Gilteritinib is an oral FLT3 inhibitor approved for patients with *FLT3*-mutated (*FLT3*$^{mut+}$) relapsed or refractory (R/R) acute myeloid leukemia (AML) based on findings from the phase 3 ADMIRAL trial, which demonstrated the superiority of gilteritinib to salvage chemotherapy in this patient population.
Aims: To evaluate response and safety outcomes in patients with *FLT3*$^{mut+}$ R/R AML treated with gilteritinib who underwent hematopoietic stem cell transplantation (HSCT) during the ADMIRAL trial.
Methods: Outcomes were evaluated for patients with *FLT3*$^{mut+}$ R/R AML treated with gilteritinib who underwent HSCT during the phase 3 ADMIRAL trial and were without relapse for 60 days after HSCT.
Results: Of the 63 *FLT3*$^{mut+}$ R/R AML patients treated with gilteritinib who underwent HSCT during the trial, 51 were without relapse for 60 days after transplantation. Of these 51 patients, 35 (69%) resumed gilteritinib therapy post-HSCT after a median of 1.9 months. Median gilteritinib exposures in patients who resumed gilteritinib were 3.0 months pre-HSCT and 6.4 months post-HSCT, respectively. With a median follow-up of 12.4 months, patients who resumed gilteritinib had longer median overall survival than patients who did not (16.2 vs 8.4 months; hazard ratio for death: 0.387; 95% CI: 0.164, 0.915). In patients who resumed gilteritinib, pre-HSCT rates of complete remission (CR), composite CR, and CR with full or partial hematologic recovery were 11%, 71%, and 31%, respectively. Common adverse events during the post-HSCT period in patients who resumed gilteritinib were increased alanine aminotransferase (46%) and pyrexia (37%); common grade ≥3 adverse events were thrombocytopenia and lung infection (both 14%). Fatal adverse events included cardiac arrest, acute graft-versus-host disease in the intestine, pneumothorax, and pulmonary embolism (all n=1).
Summary/Conclusion: Overall, patients with *FLT3*$^{mut+}$ R/R AML who resumed gilteritinib post-HSCT had high response rates prior to HSCT and longer overall survival than patients who did not resume gilteritinib therapy. No new safety signals during the post-HSCT period were identified in patients who resumed gilteritinib therapy.

EP442 PRELIMINARY RESULTS OF V-FAST, A PHASE 1B MASTER TRIAL TO INVESTIGATE CPX-351 COMBINED WITH TARGETED AGENTS IN NEWLY DIAGNOSED AML

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Background: CPX-351 (EU: Vyxeos® Liposomal; US: Vyxeos®), a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar drug ratio, is approved by the EMA and US FDA for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes. Preclinical data suggest CPX-351 may exert synergistic activity when combined with agents such as the BCL-2 inhibitor venetoclax or FLT3 inhibitor midostaurin.
Aims: The objective of the V-FAST study is to evaluate the safety and establish the recommended phase 2 dose (RP2D) of CPX-351 combined with other agents for the treatment of adults with previously untreated AML.
Methods: V-FAST (*V*yxeos – *F*irst Phase *A*ssessment With *T*argeted Agents) is an open-label, multicenter, phase 1b master trial (NCT04075747) to evaluate CPX-351 in combination with targeted agents in patients aged 18 to 75 years with untreated AML who are fit for intensive chemotherapy. The study includes a dose-exploration phase (3 + 3 design) and subsequent expansion phase. Patients received CPX-351 (dose level 1 for first induction [DL1]: 100 units/m^2 on Days 1, 3, and 5) plus venetoclax (Arm A; DL1: 400 mg on Days 1 to 14), midostaurin (Arm B; DL1: 50 mg BID on Days 8 to 21), or the IDH2 inhibitor enasidenib (Arm C; DL1: 100 mg on Days 8 to 28) based on mutation testing.
Results: Among 21 patients with available data enrolled by 06 November 2020 (24 pts enrolled total; data cut-off: 19 January 2021), the median age was 54 years (range: 35, 69). In Arm A (n=17), 11 (65%) patients had *de novo* AML, 5 (29%) had an antecedent hematologic disorder (2 [12%] had myelofibrosis), and 2 (12%) had t-AML; 12 (71%) had adverse-risk AML; and 6 (35%) had mutated *TP53*. In Arms B (n=3) and C (n=1), all patients had intermediate-risk *de novo* AML. DL1 was the RP2D in Arms A and B; the RP2D in Arm C is still under investigation. In Arm A, 1 of 6 patients in the dose-exploration phase had 2 dose-limiting toxicities (DLTs) of grade 4 neutropenia and thrombocytopenia that extended beyond 49 days; no DLTs have occurred for Arms B and C. The combinations exhibited manageable safety profiles (**Table**). Of patients with available response data, complete remission (CR) or CR with incomplete platelet or neutrophil recovery was achieved by 6 of 14 (43%) patients in Arm A, including 4 (29%) with CR. All patientts in Arms B and C achieved CR.

n (%)	Arm A CPX-351 + venetoclax (n=17)	Arm B CPX-351 + midostaurin (n=3)	Arm C CPX-351 + enasidenib (n=1)
Any TEAE	17 (100)	3 (100)	1 (100)
Thrombocytopenia	11 (65)	2 (67)	0
Febrile neutropenia	10 (59)	2 (67)	1 (100)
Nausea	9 (53)	2 (67)	1 (100)
Neutropenia	9 (53)	2 (67)	0
Constipation	9 (53)	1 (33)	0
Headache	7 (41)	3 (100)	0
Any grade ≥3 TEAE	15 (88)	3 (100)	1 (100)
Thrombocytopenia	11 (65)	2 (67)	0
Febrile neutropenia	10 (59)	2 (67)	1 (100)
Neutropenia	9 (53)	2 (67)	0
Early mortality			
Day 30	0	0	0
Day 60	2 (12)	0	0

TEAE, treatment-emergent adverse event.
TEAEs reported in ≥40% of patients overall.

Summary/Conclusion: These preliminary results suggest CPX-351 can be combined with venetoclax or midostaurin with manageable toxicities in newly diagnosed AML patients, with DL1 determined to be the RP2D. The study is ongoing and actively enrolling patients; updated results will be presented at the meeting.

EP443 PHASE 1 FIRST-IN-HUMAN STUDY OF IRREVERSIBLE FLT3 INHIBITOR FF-10101-01 IN RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

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Background: FF-10101-01 is a selective and irreversible FMS-like tyrosine kinase 3 (FLT3) inhibitor with potent *in vitro* activity against *FLT3*-mutated AML. FF-10101-01 is highly active against *FLT3* internal tandem duplication (ITD) mutations associated with high relapse and low survival/remission rates, as well as resistance-conferring D835 and F691 tyrosine kinase domain (TKD) and non-canonical FLT3 activating mutations.
Aims: Here we report on a Phase 1 dose escalation trial examining the safety, efficacy, pharmacokinetics, and pharmacodynamics of FF-10101-01 in patients (pts) with relapsed/refractory primary or secondary AML.
Methods: To determine the recommended Phase 2 dose, pts with or without a FLT3 mutation received FF-10101-01 orally once (QD) or twice (BID) daily until unacceptable toxicity was observed or pts had no further clinical benefit (1 cycle = 28 days). Composite complete remission (CRc) and partial remission (PR) rates were assessed. Inhibition of FLT3 phosphorylation was evaluated using a plasma inhibitory activity assay and was correlated with associated FF-10101-01 exposure.
Results: Fifty-two pts [median age 61 (range, 21-84); 52% female; FLT3: ITD [22 (42%)], TKD [5 (10%)], ITD+TKD [1 (2%)], Wt [24 (46%)] received continuous dosing of FF-10101-01 at 10 - 225 mg QD or 50 - 100 mg BID. Median number of prior therapies was 3 (range, 0-6) and the majority [23/28 (82%)] of pts with known FLT3 mutations had received prior FLT3 inhibitors. The median duration on study was 5.7 (range, 0.1-36) weeks. FF-10101-01 was generally well-tolerated up to total daily doses of 150 mg. The most common treatment related adverse events included nausea [n=18 (35%)], diarrhea [14 (27%), 2 Grade (Gr) 3/4], elevations in creatine kinase [CK; 14 (27%), 4 Gr 3/4], vomiting [10 (19%)] and increased AST [10 (19%), 2 Gr 3]. Grade 3/4 differentiation syndrome (n=4, 8%) was observed at 75 - 150 mg/day. Dose-limiting cardiac toxicity (heart failure with reduced ejection fraction; Gr 3 increased troponin/CK) was observed at total daily doses ≥200 mg. The CRc rate was 13% (4/30 pts evaluable for response): 1 CR at 75 mg BID (FLT3-ITD); 1 CRp at 100 mg BID (Wt-FLT3); and 2 CRi's at 50 mg BID, one that previously progressed on gilteritinib. The median time to overall response was ~13.3 weeks. Four pts achieved a PR (≥50% decrease in BM blasts to 5 - 25% abnormal cells) at total daily doses of 50 - 150 mg; 2 had ITD mutations, and all had received prior FLT3 kinase inhibitors. At ≥75 mg BID, trough plasma concentrations were >90 ng/ml and associated with >90% p-FLT3 inhibition maintained over the dosing interval.
Summary/Conclusion: The FF-10101-01 FLT3 inhibitor has shown activity in pts with refractory/relapsed AML, including those with activating FLT3-ITD mutations resistant to gilteritinib and other FLT3 kinase inhibitors. Doses of 50-75 mg BID were well tolerated and resulted in sustained FLT3 inhibition.

EP444 RELATIONSHIP BETWEEN VENETOCLAX EXPOSURE AND POST-REMISSION CYTOPENIAS IN SUBJECTS WITH TREATMENT-NAÏVE ACUTE MYELOID LEUKEMIA TREATED WITH VENETOCLAX PLUS AZACITIDINE IN THE VIALE-A STUDY

D. Brackman [1,*], R. Menon [1], D. Miles [2], A. H. Salem [1], Y. Duan [1], J. Potluri [1], B. Jonas [3], K. Pratz [4], M. Montez [2], M. Werner [1], J. Zha [1]

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Background: Venetoclax (VEN) is an orally bioavailable selective BCL-2 inhibitor that promotes apoptosis in cancer cells. VIALE-A, a placebo-controlled randomized Phase 3 trial comparing VEN in combination with azacitidine (VEN+AZA) to placebo in combination with azacitidine (PBO+AZA), showed superior efficacy with VEN combination on key endpoints such as overall survival and overall response rates in subjects with treatment-naïve acute myeloid leukemia (AML) who were ineligible for intensive chemotherapy. Hematologic adverse events including anemia, neutropenia, febrile neutropenia, and thrombocytopenia are common in AML patients due to their underlying disease. In VIALE-A, subjects taking VEN+AZA had higher rates of neutropenia and febrile neutropenia than subjects taking PBO+AZA (DiNardo et al. *N Engl J Med*. 2020).
Aims: Here, we aimed to describe the relationship between VEN exposure, overall survival, and post-remission cytopenias, as defined by Grade 4 neutropenia or thrombocytopenia lasting ≥7 days, in subjects who achieved complete remission (CR) or complete remission with partial hematological recovery (CRh) in the VIALE-A study.
Methods: Data from 185 subjects treated with VEN+AZA and 33 subjects treated with PBO + AZA who achieved CR or CRh (blast clearance with neutrophil count > 0.5×10^3/μL and platelet count > 0.5×10^5/μL) in the VIALE-A study were included in the analysis. The VIALE-A protocol recommended dose interruptions and reduced VEN dosing duration per cycle for management of cytopenias following blast clearance. Therefore, VEN exposure was calculated as the average plasma concentration (C_{avg}) from blast clearance to the event of interest to account for these dosing modifications. Logistic regression and Cox proportional-hazards models were used to characterize the relationships between venetoclax exposure (C_{avg}) and frequency or timing of cytopenias. Cox proportional-hazards models were also used to characterize the relationships between venetoclax exposure (C_{avg}) and overall survival in subgroups based on dosing duration.
Results: Subjects taking VEN+AZA had a range of 0 to 15 post-remission cytopenias lasting ≥7 days in VIALE-A. Within subjects experiencing post-remission cytopenias on VEN+AZA, there was no apparent relationship between VEN exposure and frequency of post-remission cytopenias. However, subjects with no post-remission cytopenias on VEN+AZA had significantly ($p < 0.01$) lower VEN exposure than those with one or more post-remission cytopenias. Consistently, higher VEN exposure was associated ($p < 0.01$) with a shorter time to first episode of post-remission cytopenia. There were no apparent relationships between VEN exposure and overall survival in VEN+AZA subjects who achieved CR/CRh and experienced post-remission cytopenias, including in a subset of subjects who switched to 21-day dosing in 28-day cycles following the first episode of post-remission cytopenia. These results indicate that lower exposures associated with VEN dose reductions to manage cytopenias in patients who achieved a CR/CRh did not affect OS.
Summary/Conclusion: For treatment-naïve AML patients who achieve CR/CRh on VEN+AZA, VEN exposure may be a contributing factor to post-remission cytopenias.

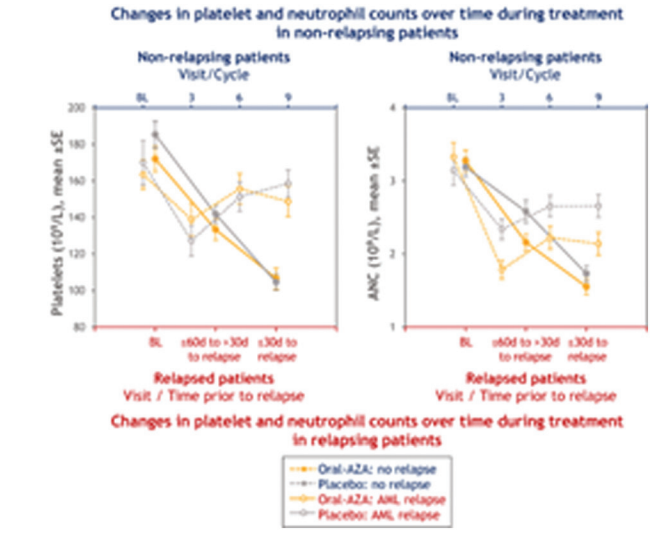
EP445 HEMATOLOGIC ADVERSE EVENTS AND MANAGEMENT STRATEGIES FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) IN FIRST REMISSION RECEIVING ORAL AZACITIDINE (ORAL-AZA) IN THE PHASE 3 QUAZAR AML-001 TRIAL

F. Ravandi [1,*], G. Roboz [2,3], A. Wei [4,5], H. Döhner [6], C. Pocock [7], D. Selleslag [8], P. Montesinos [9], H. Sayar [10], M. Musso [11], A. Figuera-Alvarez [12], H. Safah [13], W. Tse [14], S. K. Sohn [15], D. Hiwase [16], T. Chevassut [17], F. Pierdomenico [18], I. La Torre [19], B. Skikne [20,21], R. Bailey [21], J. Zhong [21], C. Beach [21], XX. Dombret [22,23]

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Background: Most older patients (pts) who attain AML remission with intensive chemotherapy (IC) eventually relapse. Oral-AZA is a hypomethylating agent (HMA) that allows for extended dosing schedules to sustain drug activity. In the phase 3 QUAZAR AML-001 trial, Oral-AZA significantly prolonged overall and relapse-free survival (OS/RFS) *vs* placebo (PBO) in older pts with AML in first remission after IC. Neutropenia (N), thrombocytopenia (T), and anemia (A) were the most common hematologic adverse events (AEs) in both treatment (Tx) arms, occurring more often with Oral-AZA *vs* PBO. Cytopenias are a known side effect of HMAs, especially during early Tx, but may also portend AML relapse. Thus, it can be challenging to discern whether cytopenias during Oral-AZA Tx are related to Tx or to disease progression.
Aims: Assess the rate of cytopenias over time, via AE reporting and laboratory parameters, for pts receiving Oral-AZA in the QUAZAR AML-001 study, and determine whether cytopenias presaged impending AML relapse.
Methods: Pts were aged ≥55 yrs, had intermediate- or poor-risk cytogenetics and ECOG PS score ≤3, and were not candidates for transplant. Within 4 months (mo) of achieving first complete remission (CR) or CR with incomplete blood count recovery (CRi) after induction ± consolidation, pts were randomized 1:1 to Oral-AZA 300 mg or PBO QD for 14d/28d Tx cycles. Pts who received ≥1 study drug dose were monitored for AEs from first dose until 28d after last dose.
In these *post hoc* analyses, we report hematology parameters (ANC, platelets, hemoglobin [Hgb]) for pts who relapsed on-study at baseline (BL), at 1–2 mo (≤60 to >30d) before relapse, and during the 1 mo (≤30d) before relapse, inclusive of relapse date. For context, we also assessed these parameters at BL and at cycles 3, 6, and 9 for pts who did not relapse on-study.
Results: 469 pts (Oral-AZA 236, PBO 233) were followed for safety. Median age was 68 yrs (range 55–86). Pts received a median of 12 (range 1-80) Oral-AZA Tx cycles and 6 (1-73) PBO cycles.
Rates of any grade N, T, and A in the Oral-AZA arm were 44%, 33%, and 20%, respectively. At cycles 1–2, 3–4, and 5–6, rates of N in the Oral-AZA arm were 22%, 20%, and 18%, respectively; of T were 16%, 9%, and 6%; and of A were 6%, 4%, and 4%. Oral-AZA Tx was interrupted or dose reduced, respectively, in 45% and 12% of 105 pts who experienced N; in 25% and 5% of 79 pts with T; and in 6% and 2% of 48 pts with A. Only 1 pt (1%) discontinued Oral-AZA due to N, T, or A (T). 23% of pts in the Oral-AZA arm (PBO 22%) received RBC transfusions on-study and 19% (PBO 22%) received platelet transfusions. G-CSF use was infrequent: 8 pts (3.4%) in the Oral-AZA arm and 7 pts (3%) in the PBO arm. 154 Oral-AZA pts (65%) and 179 PBO pts (77%) relapsed on-study; median RFS was 10.2 *vs* 4.8 mo, respectively ($P<0.001$). Pts who relapsed showed steep decreases in ANC and platelets (**Figure**) but not Hgb, in the 2 mo before AML relapse. Pts who did not relapse showed initial decreases in platelet counts and ANC, but signs of recovery were evident after cycle 3 (**Figure**).



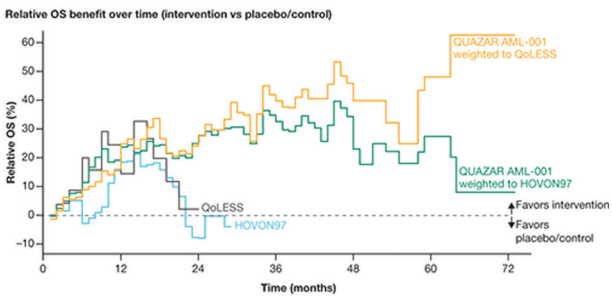
Summary/Conclusion: Hematologic AEs with Oral-AZA, particularly N, occurred most often during early Tx. N, T, and A were mainly managed with temporary Tx interruptions. Infrequent G-CSF use and rare Tx discontinuation indicate cytopenias were manageable with dosing modifications. Non-relapsing pts showed early decreases in platelets and ANC, with recovery after cycle 3. Relapsing pts showed steep declines in platelets and ANC with clear differences from non-relapsing pts within 30d of relapse.

EP446 COMPARATIVE EFFICACY OF ORAL VERSUS INJECTABLE AZACITIDINE IN PATIENTS WITH AML IN FIRST REMISSION AFTER INTENSIVE CHEMOTHERAPY: AN INDIRECT TREATMENT COMPARISON (SUB-ANALYSIS UPDATE)

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Background: Maintenance therapy with oral azacitidine (AZA) significantly improved overall survival (OS) versus placebo in patients (pts) with acute myeloid leukemia (AML) who achieved remission after intensive induction chemotherapy in the phase 3 QUAZAR AML-001 study. Although there are no head-to-head trials comparing oral and injectable AZA, results from a recent indirect treatment comparison (ITC) favored oral AZA (Chen C, et al. ASH 2020); however, ITCs do not fully account for potentially effect-modifying variables between trials.
Aims: To compare the relative efficacy of maintenance therapy with oral versus injectable AZA in pts with AML in first remission after chemotherapy.
Methods: Anchored matching-adjusted indirect comparisons (MAICs) for OS were performed by matching individual pt data (IPD) from QUAZAR AML-001 (oral AZA vs placebo) to summary-level data from the comparator trials, HOVON97 (SC AZA vs control) and QoLESS (SC/IV AZA vs control). The QUAZAR AML-001 population was adjusted to comparators based on age, sex, AML disease stage, and cytogenetic risk; additionally, adjustment to HOVON97 included platelet count, response status at baseline, and ECOG performance status, and adjustment to QoLESS included minimal residual disease. After matching and adjustment, relative OS benefit was calculated within each trial as the difference in the Kaplan–Meier (KM) estimates of OS between the intervention and placebo/control arms, divided by the KM estimate of OS for placebo/control. The difference in restricted mean survival time (RMST) between intervention and placebo/control was estimated with a parametric survival model at 1, 2, 3, 4, and 5 years.
Results: Of 472 pts in QUAZAR-AML-001, 402 and 328 were included in the analysis populations after matching to HOVON97 (N=116) and QoLESS (N=54), respectively; after adjustment, the effective sample size for the primary analysis population was reduced to 310 and 222 pts, respectively. Matching and adjustment led to small changes in estimates of oral AZA versus placebo/control compared with unweighted analyses. The weighted oral AZA population showed a sustained and numerically higher relative OS benefit through 60 months versus SC AZA and SC/IV AZA (Figure). The relative benefit of injectable AZA versus control observed in the initial 12 months appeared to fade, reaching close to zero around month 20. Difference in the area under the curve (ΔAUC) between the weighted oral AZA populations and placebo/control showed improvement over time in point estimates of mean survival time. RMST from QUAZAR-AML-001 IPD weighted to HOVON97 showed a statistically meaningful improvement compared with placebo/control in mean survival time at 1, 2, 3, 4, and 5 years (ΔAUC: 0.94, 2.43, 3.68, 4.68, and 5.48); a similar effect was observed with QUAZAR-AML-001 IPD weighted to QoLESS (ΔAUC: 0.75, 2.41, 4.18, 5.83, and 7.32), whereas injectable AZA was not associated with significant benefits at any time-point in HOVON97 (ΔAUC: 0.46, 0.95, 1.17, 1.18, and 1.08) or QoLESS (ΔAUC: 1.12, 2.01, 2.11, 1.70, and 0.96). All scenario analyses conducted supported the results of the primary analyses.



Summary/Conclusion: Adjustment via MAIC resulted in consistent conclusions to the previously reported unadjusted analyses of oral versus injectable AZA. Weighted analysis of oral versus injectable AZA continued to show early and sustained relative OS benefits with oral AZA. Additionally, weighted estimates of oral AZA showed statistically meaningful improvement in mean survival time versus placebo/control, and numerical superiority to injectable AZA.

EP447 MIDOSTAURIN PLUS INTENSIVE CHEMOTHERAPY VERSUS INTENSIVE CHEMOTHERAPY IN FLT3 MUTATED ACUTE MYELOID LEUKEMIA. A RWE STUDY

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Background: Introduction. Midostaurin has been approved by EMA and FDA in combination with IC for FLT3-mutated AML based on improved overall survival noted in the RATIFY phase 3 trial (Stone et al, N Engl J Med 2017) The experience with midostaurin in day to day practice is limited.
Aims: Aim: The aim of this study is to analyze effectiveness and tolerability of midostaurin plus intensive chemotherapy (midos+IC) vs intensive chemotherapy alone (IC) as first lines in AML FLT3 positive patients and to identify risk factors.
Methods: Methods: We carried out the analysis on previously untreated AML FLT3 mutated patients included in PETHEMA AML epidemiological registry (NCT02607059). Selection criteria for the study were as follows: Age >18, diagnosis of AML FLT3 positive (ITD and TKD) under WHO criteria, treated with midos+IC or IC (IC defined as 7+3 induction and HiDAC or intermediate dose AraC consolidations) during the period 01/01/2010 to 01/03/2020, patients who died before day 7 of treatment were excluded. Response were assessed using the ELN-2010 criteria, toxicity by the CTCAE v4.0 scale, OS by Kaplan-Meier and early mortality as mortality within the first 8 weeks (M8wks).
Results: Results: A total of 385 of previously untreated AML FLT3 positive patients were analyzed (54 treated with Midos+IC and 331 with IC), median age 52yrs (20-70) and 53yrs (18-70), ECOG ≥2: 18.5% and 12.7% respectively. Baseline characteristics are summarized in table 1. Antifungal triazole prophylaxis was the standard in both cohorts. Early mortality M8wks was 3.7% and 6.6% and complete response rate (CR after 1 or 2 Inductions) 86% vs 66% (p 0.005) for midos+IC and IC respectively.
Overall survival is significantly longer in the mido+IC group than in the IC group (not reached vs 19 months, p=0.022), 24mOS 79.2% vs 54.2% (p0.026).
We observed a trend of benefit in all the following subgroups, a: FLT3 ITD low with NPM1 mut, b: FLT3 ITD low with NPM1 wt plus FLT3 ITD high with NPM1 mut; and c: FLT3 high with NPM1 wt. In our study we observe in midos+IC cohort a higher rate of patients consolidated in CR1 with alloSCT and a significantly longer OS for these patients (42.5% vs 28.7%) and (not reached vs 44.7 months).

Total 385 p	Midos+IC (54)	IC (331)
Age median	52 (20-70)	53 (18-70)
M/F	24/30	139/192
ECOG ?2	18.5%	12.7%
FLT3 ratio available	28p	251p
FLT3 ITD low with NPM1 mut	9 (32%)	68 (27%)
FLT3 ITD low with NPM1 wt	11 (39.2%)	134 (53.3%)
FLT3 ITD high with NPM1 mut		
FLT3 high with NPM1 wt	7 (25%)	40 (16%)
alloSCT consolidation in CR1	42.5%	28.7%

Summary/Conclusion: Conclusions: The results of this study confirm in a real-world setting that midostaurin associated with IC improve the outcome of AML FLT3 positive patient compared versus IC alone.

EP448 CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA TREATED WITH GILTERITINIB WHO RECEIVED PRIOR MIDOSTAURIN OR SORAFENIB

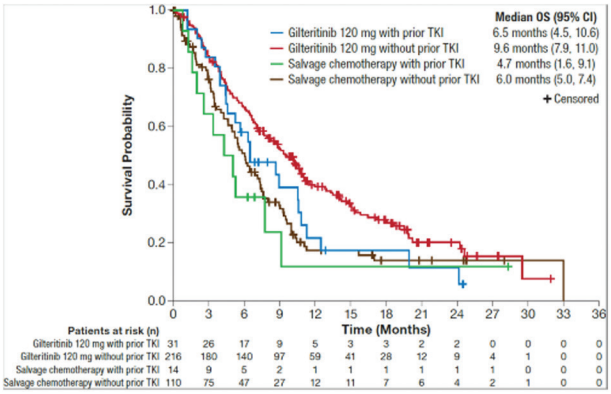
A. E. Perl [1,*], J. K. Altman [2], N. Hosono [3], P. Montesinos [4], N. Podoltsev [5], G. Martinelli [6], C. C. Smith [7], M. J. Levis [8], C. Röllig [9], M. Groß-Langenhoff [10], N. Hasabou [11], Q. Lu [11], R. V. Tiu [11]

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Background: Gilteritinib is a FLT3 inhibitor with demonstrated efficacy and safety in patients with *FLT3*-mutated relapsed or refractory (R/R) AML. The phase 1/2 CHRYSALIS trial demonstrated the safety and antileukemic activity of gilteritinib in a *FLT3*-mutation–enriched R/R AML population (Perl AE, et al. *Lancet Oncol.* 2017). The phase 3 ADMIRAL trial demonstrated the superiority of gilteritinib to salvage chemotherapy (SC) in *FLT3*-mutated patients based on longer median overall survival (OS) with gilteritinib (9.3 vs 5.6 months; hazard ratio [HR]=0.64 [95% CI: 0.49, 0.83]; *P*<0.001) (Perl AE, et al. *N Engl J Med*. 2019).
Aims: To determine whether prior TKI therapy affected response and survival in these two trials.
Methods: We retrospectively analyzed clinical outcomes in patients with R/R AML previously treated with TKIs midostaurin or sorafenib, before receiving 120- or 200-mg gilteritinib in the CHRYSALIS trial, or before receiving 120-mg gilteritinib in the ADMIRAL trial. Patients randomized to SC in the ADMIRAL trial were also assessed. Patients in the CHRYSALIS trial had received at least one line of prior AML therapy; patients in the ADMIRAL trial received only one line of prior AML therapy.
Results: Of the 145 *FLT3*-mutation–enriched patients who received 120- or 200-mg gilteritinib in the CHRYSALIS trial, 33 (23%; 120 mg, n=15; 200 mg, n=18) had received a prior TKI (all received sorafenib). Baseline characteristics among patients who received (n=33) or did not receive prior TKIs (n=112) were similar. Rates of composite complete

remission (CRc) were similar in patients who received prior TKIs (42%; n=14/33) and in those who did not (43%; n=48/112). Among patients who received prior TKIs, rates of CRc were 53% (n=8/15) in the 120-mg dose group and 33% (n=6/18) in the 200-mg dose group; rates of CRc in patients who did not receive prior TKIs were similar across both the 120- and 200-mg dose groups (44% [n=18/41] and 42% [n=30/71], respectively). Among patients treated with prior TKIs across the 120- or 200-mg dose groups (n=33), most (73%; n=24) had received ≥3 lines of any prior AML therapy.

In the phase 3 ADMIRAL trial, 31 of 247 (13%) R/R *FLT3*-mutated AML patients in the gilteritinib arm and 14 of 124 (11%) patients in the SC arm had received prior TKIs. Demographic and baseline characteristics were well balanced between treatment arms and were also similar between prior TKI–treated (n=45) and non-treated patients (n=326). In the gilteritinib arm, CRc rates were comparable in patients who received (48%; n=15/31) and did not receive prior TKIs (55%; n=119/216); lower CRc rates were observed in the SC arm in both TKI–treated and non-treated groups (21% [n=3/14] and 22% [n=24/110], respectively). Median OS in patients treated with prior TKIs, albeit not statistically significant, remained high in patients treated with gilteritinib compared with those treated with SC (6.5 vs 4.7 months, respectively; HR=0.671 [95% CI: 0.328, 1.376]) (**Figure**). In patients who did not receive prior TKIs, median OS was 9.6 months in the gilteritinib arm and 6.0 months in the SC arm (HR=0.625 [95% CI: 0.474, 0.824]) (**Figure**).



Summary/Conclusion: Patients with R/R AML who received prior TKIs (midostaurin or sorafenib) were able to achieve remission with gilteritinib. High response rates with gilteritinib were observed in heavily pretreated *FLT3*-mutation–enriched patients in the CHRYSALIS trial who received prior TKIs. Higher response rates with gilteritinib than with SC were observed in prior TKI–treated patients with *FLT3* mutations in the ADMIRAL trial.

EP449 CLONAL HEMATOPOIESIS IN PERIPHERAL STEM CELLS AT LEUKAPHERESIS AS PREDICTIVE FACTOR FOR THERAPY-RELATED MYELOID NEOPLASMS AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: The detection of mutations in genes known to be associated with hematologic malignancies has been termed clonal hematopoiesis (CH). CH detected in cryopreserved cells of patients (pts) undergoing autologous stem-cell transplantation (ASCT) for hematologic neoplasia has been associated with an increased risk of therapy-related myeloid neoplasm (t-MN), but its role in the development of t-MN and the variations of the mutational profile occurring in the single pt between ASCT and t-MN are still partially known.

Aims: The primary objective of this study was the comparison of the mutational profile and of variant allele frequency (VAF) of mutated genes at leukapheresis and at t-MN in ASCT pts who actually developed t-MN. The mutational profile at leukapheresis was also compared with that of matched control ASCT pts, who did not develop t-MN.

Methods: Among the entire cohort of lymphoma and myeloma pts treated with high-dose chemotherapy and ASCT at the Hematology Dpt of Spedali Civili in Brescia between 2001 and 2019, we selected pts who developed t-MN after ASCT and had available backup cryopreserved CD34+ stem cells. Pts who did not experience t-MN, matched for demographic and clinical characteristics, acted as controls. Pre- and post-ASCT samples were sequenced on the Genestudio S5 Prime, using an On-Demand NGS panel designed with Ion Ampliseq Designer software, that included 45 genes known to be associated with either CHIP, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

Results: Out of 1075 lymphoma or myeloma pts undergoing ASCT, 35 developed t-MN (3.3%). Frequency was significantly higher in lymphoma (27/592, 4.6%) than in myeloma (8/483, 1.7%) (p=0.0088). In 19 of them (lymphoma: n. 16; myeloma: n. 3), the mutational profile was assessed both at ASCT and at t-MN (AML: n.8; MDS: n.11). Their median follow up was 6 years (range 2-14). A higher number of mutations of 20 genes was detected at t-MN diagnosis (n. 46 in 16/19 patients; 84%), as compared to ASCT (n. 16 in 11/19 patients; 58%;). Control pts had a significantly lower number of mutations at ASCT (n. 7 in 6/26; 23%) compared to pts developing t-MN (n. 16, in 11/19; 58%; p=0.029); median follow-up of controls was 7 years (range 3-13). Epigenetic regulation, including DNMT3A, and DNA repair gene mutations, specifically PPM1D, were most frequently mutated at ASCT. At t-MN mutations in these genes showed a modest increase and their VAF did not change except in one patient. Conversely, TP53 mutations were the most represented at t-MN (28% of total); they appeared de novo in 8 pts and VAF increased from 14% to 49% in the single pt with mutated TP53 also at ASCT. In addition, mutations in genes of intracellular signaling or encoding transcription factors (e.g. RAS, RUNX1) were also commonly detected at t-MN. They were absent in controls, whose mutations at ASCT also occurred mainly in epigenetic genes.

Summary/Conclusion: These data confirm that CH at ASCT is associated with a higher risk of developing t-MN. They also show that the mutational profile varies markedly between ASCT and t-MN. Epigenetic and DNA repair gene mutations are characteristic at ASCT and do not increase significantly at t-MN; they may represent a marker of genetic instability favoring the development of t-MN. Conversely, mutations of TP53 and transcription factor encoding or intracellular signaling genes appear more strictly associated with the pathogenesis of t-MN and their emergence may be promoted by the high-dose cytotoxic treatments delivered as conditioning regimens before ASCT.

EP450 ALICE MAINTAINS HIGH CLINICAL RESPONSE RATES SUPPORTING THE EFFICACY OF IADADEMSTAT COMBINATION WITH AZACITIDINE IN AML MANAGEMENT

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Background: Acute Myeloid Leukemia (AML) in elderly unfit patients remains a challenge. Recently approved combinations have improved the treatment of unfit patients. Yet, a significant percentage of patients is refractory or relapse during the first year. Iadademstat (iada) is a first, and best in class LSD1 inhibitor that produces differentiation in leukemic stem cells. In different clinical trials, iada has been administered so far to ~100 oncology patients showing a good safety profile. Based on iada's ADME profile and low dosing regimen, a low DDI risk is anticipated. This makes iada suitable for drug combinations with hypomethylating agents or targeted therapies and may offer additional therapeutic options for this patient population.

Aims: This is an update of the ongoing ALICE study (EudraCT 2018-000482-36).

Methods: ALICE is a Phase IIa study to assess the safety, tolerability and dose finding of iada in combination with azacitidine for the treatment of elderly AML patients. Secondary endpoints investigate anti-leukemic activity including overall response rate (ORR), time to response (TTR) and duration of responses (DOR). Additional assessments include hematological improvement, overall survival and PK/PD measures. ALICE includes adult patients diagnosed with AML (as per WHO classification),

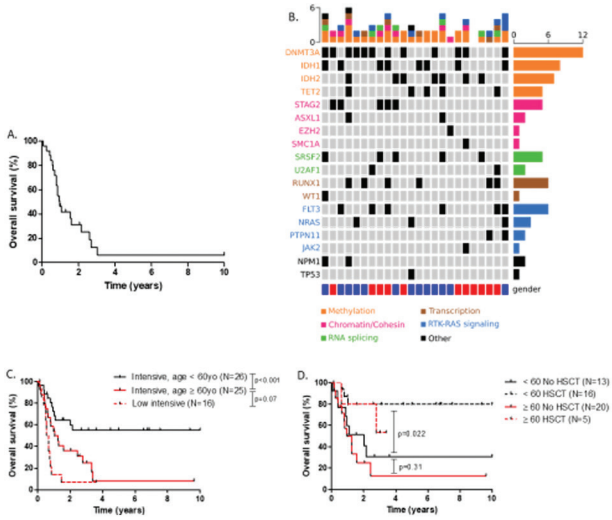
who have not received prior treatment for AML other than hydroxyurea and are ineligible for intensive chemotherapy (or refuse this treatment option).
Results: At EHA 2020, ALICE data from 18 patients (median age 78 y) were reported. Main safety events included 96 grade 3-4 AEs related to the study drugs in 12 patients, most of them neutropenia and thrombocytopenia. Only 3 non-hematological AEs were observed, asthenia and dysgeusia in one patient and weight reduction in another patient. Among the 38 SAEs reported, only one was considered related to iadademstat, a differentiation syndrome (Grade 3) and another, a fatal intracranial hemorrhage on C1D15 was considered as possibly related to the combination therapy. Besides the hematological impact, the combination was safe and well tolerated by older AML patients. From the 18 patients recruited in 2020, 13 had at least 1 bone marrow evaluation (evaluable as per protocol). Ten (77%) achieved an objective response (4 CR, 2 CRi and 4 PRs) with a mean TTR of 37 days. The longest response in CR at that time was 488 days. Those patients with longer treated periods had also improved or overcome their dependency on blood transfusions.
By the time this abstract is written, 24 patients have been included (median age 77) and 18 are evaluable; ORR has increased to 87%, TTR is now 35 days and median DOR is 335 days, with 5 patients having a response longer than one year and one longer than 2 years. 4 out of the current 8 durable responses (longer than 6 months) also show transfusion independence. The safety findings continue to support an acceptable tolerability profile of the combination, with most of the adverse effects being transient or amenable. At EHA 2021, an update on the trial results will be provided, with all patients recruited by the cut-off of May 2021.
Summary/Conclusion: ALICE data sets confirm that the combination of iadademstat with azacitidine in unfit AML patients has a manageable safety and tolerability profile. ALICE maintains encouraging response ratios as the trial progresses. Current efficacy data support iadademstat as a suitable candidate for combination therapies in AML.

EP451 ALLOGENIC STEM CELL TRANSPLANTATION ABROGATES NEGATIVE IMPACT ON OUTCOME OF AML PATIENTS WITH KMT2A PARTIAL TANDEM DUPLICATION

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Background: KMT2A partial tandem duplication (PTD) has been reported in 3–10% of adult AML cases and is mutually exclusive of 11q23 rearrangements. Clinical implications of KMT2A-PTD on outcome remain unclear with conflicting results in the literature. As a consequence, if KMT2A-rearranged AML are considered of unfavorable prognosis within ELN 2017 classification, KMT2A-PTD is not included in current AML prognostic classifications, and so, not considered as an independent factor for hematopoietic stem cell transplantation (HSCT) allocation.
Aims: In this study, we aimed to evaluate KMT2A-PTD impact on outcome in newly diagnosed AML patients according to treatment intensity and HSCT.
Methods: Seventy-nine patients treated in Lyon and Bordeaux, France, with newly diagnosed KMT2A-PTD mutated AML were included in this retrospective study, between November 2005 and August 2019.
Results: Median age of the entire cohort was 66 years old (range 19-87). Overall, most of the patients had a normal karyotype (65.3%). Regarding 2013 ELN classification, 11.4, 77.2 and 11.2% were favorable, intermediate I/II and unfavorable respectively. The median overall survival (OS) was 12.1 months with an OS rate of 50.1 % at 1 year and 30.9% at 3 years (Figure A). NGS was available for 24 intensively treated patients. The most frequently observed mutations were those affecting DNA methylation (DNMT3A, TET2, IDH1/2), found in 91% (21/23) of cases. Receptor tyrosine kinase (RTK) and RAS pathways were mutated in about 44% of patients. Other pathways commonly found altered was the chromatin/cohesin complex (ASXL1, STAG2, SMC1A, EZH2), spliceosome (U2AF1, SRFS2) and transcription factors (RUNX1, WT1) in 39%, 30% and 30% of cases respectively (figure B). Regarding the impact of co-mutations on survival, the presence of FLT3-ITD was associated with an inferior outcome (median OS: 9.36 vs 33.4 months, p=0.033). Median OS was not reached, 33.4 and 29.4 months for NPM1, IDH1/2 and DNMT3A mutated patients respectively. In contrast, median OS was shorter for patients harboring RTK (FLT3-ITD, NRAS, PTPN11) and TP53/ASXL1/RUNX1 mutations (9.6 and 11.9 months respectively).
In patients younger than 60 years old treated with intensive chemotherapy, median overall survival was not reached compared to 12.6 months in older ones (p<0.001). In contrast, there was no statistical difference in OS in elderly patients treated with intensive or low intensive regimens (Figure, C). Twenty-one patients underwent HSCT in first CR (CR1). For patients receiving HSCT at any time in CR, median OS was not reached, whatever was the age group. For those who did not underwent HSCT, median OS was 24.2 and 13.2 months in patients younger and older than 60 years old respectively, with no statistical significance between age group in these settings (Figure D). In the multivariate analysis only HSCT at any time in CR (HR=2.35; p0.034) and FLT3-ITD status (HR=0.29; p=0.014) were independent variables associated with OS.



Summary/Conclusion: This study is one of the largest KMT2A-PTD cohort emphasizing mutation impact according to treatment intensity and HSCT. In real life settings, patients harboring such mutation are characterized by a poor outcome especially in elderly. We showed that the negative impact of this mutation might be overcome by HSCT in younger patients. In elderly unfit patient, targeted therapies such as IDH inhibitors and venetoclax-based regimens might be of interest.

EP452 A PHASE 1A/B DOSE ESCALATION STUDY OF THE MYC REPRESSOR APTO-253 IN PATIENTS WITH RELAPSED OR REFRACTORY AML OR HIGH-RISK MDS

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Background: APTO-253 represses expression of the MYC oncogene by targeting a conserved G-quadruplex structure in its promoter, down-regulates MYC mRNA and protein levels and induces apoptosis in AML cell lines and marrow samples from patients with AML, MDS, and MPN. After injection, a large fraction of APTO-253 binds iron and transforms to the $Fe(253)_3$ adduct which retains full activity. APTO-253 has been granted orphan drug designation for AML by the US FDA and is being studied in a Phase 1a/b clinical trial in patients with relapsed or refractory AML (R/R AML) or high-risk myelodysplasias (high-risk MDS) (NCT02267863).

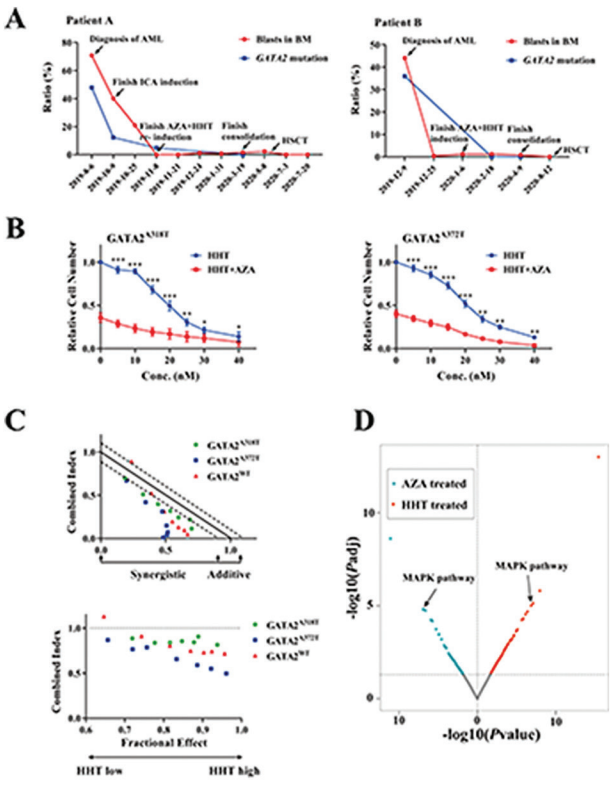
Aims: Primary objectives are to determine the safety and tolerability of APTO-253, MTD, dose limiting toxicities (DLT), and the RP2D. Key secondary objectives are to assess the pharmacokinetic (PK) profile, pharmacodynamic (PD) activity, and preliminary evidence of antitumor activity.
Methods: Eligible patients have R/R AML or high-risk MDS for which either standard treatment has failed, is no longer effective, or can no longer be administered safely. Treatment- emergent adverse events (TEAEs) and tumor responses are evaluated using International Working Group criteria. APTO-253 is administered by IV infusion once weekly on days 1, 8, 15, and 22 of each 28-day cycle; ascending dose cohorts were enrolled at a starting dose of 20 mg/m^2 with planned escalation to 403 mg/m^2.
Results: As of January 4, 2021, a total of 14 patients (age 64.4 ± 15.5, 12 AML and 2 high-risk MDS) with a median of 2.5 prior treatments (range of 1 – 9) have been treated with APTO-253 at doses of 20 (n=1), 40 (n=1), 66, 100 and 150 mg/m^2 (n=4 each). All but 1 AML patient were RBC and/or platelet transfusion-dependent. No DLTs or drug-related serious adverse events have been reported. Possible drug-related grade 2 TEAEs included fatigue, increased alkaline phosphatase, decreased appetite, hematoma, hypokalemia, thrombophlebitis, upper respiratory tract infection in 1 (7.1%) patient each. Only 1 drug-related TEAE of grade 3 or greater (fatigue, possibly related) has occurred to date. Preliminary PK analysis showed that serum levels of APTO-253 were dose proportional. C_{max} and $AUC_{0\text{-}24h}$ on C1D1 were 0.06, 0.02, 0.11 ± 0.04 and 0.44 ± 0.41 µM and 0.11, 0.15, 1.14 ± 0.57, 2.38 ± 0.90 µM*h for dose levels of 20, 40, 66, and 100 mg/m^2, respectively. Plasma levels for $Fe(253)_3$ were significantly higher than those for the APTO-253 monomer. For example, C_{max} and $AUC_{0\text{-}24h}$ of $Fe(253)_3$ on C1D1 of patients in Cohort 100 mg/m^2 were 2- and 8-fold higher than the native ATPO-253 at 0.91 ± 0.33 µM and 16.14 ± 6.26 µM*h, respectively. Following dosing at 100 mg/m^2, serum concentrations of $Fe(253)_3$ were above 0.1 µM for >72 h (0.66 ± 0.12, 0.39 ± 0.11 and 0.24 ± 0.08 µM at 24, 48 and 72 hours post dosing, respectively) which approaches the therapeutic range based on *in vitro* studies. The levels of MYC mRNA in the whole blood, a PD biomarker of APTO-253 and $Fe(253)_3$ measured by RT-qPCR, were reduced 20-48% at 24 h post-dose as compared to pre-dose in the first 3 cohorts, suggesting target engagement by the drug.
Summary/Conclusion: APTO-253 has been well-tolerated at doses of 20, 40, 66, 100 and 150 mg/m^2 over multiple cycles. PK analysis revealed that APTO-253 is rapidly transformed to and co-exists with the $Fe(253)_3$ in serum and their exposures resulted in suppression of MYC expression in whole blood samples from R/R AML and high-risk MDS patients. Enrollment of patients at the 150 mg/m^2 dose level is ongoing and updated clinical data will be presented at the meeting.

EP453 SYNERGISTIC EFFECT OF AZACITIDINE AND HOMOHARRINGTONINE IN ACUTE MYELOID LEUKEMIA WITH GATA2 MUTATION

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Background: Homoharringtonine (HHT) is a natural alkaloid derivate from Cephalotaxus which has potent anti-leukemia effect in acute myeloid leukemia (AML). Azacitidine (AZA), a DNA hypomethylation agent, has been approved to treat AML. GATA2 is an essential transcription factor in hematopoietic differentiation. Mutations in *GATA2* have been detected in AML and are widely recognized as to be associated with inferior clinical outcome. However, no specific treatment regimen has been tested or recommended for AML with GATA2 mutations.
Aims: This study is to investigate the synergistic anti-leukemia effect of combination of AZA and HHT in *GATA2*-mutated AML in a registered clinical study (ClinicalTrials.gov ID: NCT04248595) and explore the potential underlying mechanisms of AZA+HHT in *GATA2*-mutated AML.
Methods: U937 AML cell line was used to construct *GATA2* mutated cells ($GATA2^{A318T}$ and $GATA2^{A372T}$) and *GATA2* wild type cells ($GATA2^{WT}$) by lentiviral transfection. CCK-8 cell proliferation assay and CalcuSyn software were used to analyze the synergistic effect of AZA+HHT in *GATA2* mutated and wild type cells in vitro. RNA sequencing (RNA-seq) was performed before and after U937 cells treated with AZA, HHT and vehicle control for 48 hours.
Results: Two *GATA2* mutations were identified in two AML patients. Patient A is a transformed AML (M2) with a history of granulocytic sarcomas. Flow cytometry revealed 86.38% blasts in the bone marrow at the diagnosis of AML. Whole exome sequencing (WES) showed that there was a 47.8% missense mutation in *GATA2* (c.1114G>A, p.A372T). No remission was achieved after one cycle of induction therapy with ICA regimen. Then, the patient was recruited to the Clinical study and AZA+HHT based regimen was given as the re-induction therapy. A complete remission (CR) was achieved after 14 days and the *GATA2* mutation ratio significantly declined to 4.82%. Allogeneic hematopoietic stem cell transplantation (allo-SCT) was performed after two cycles of high-dose cytarabine consolidation (Figure 1A). Patient B is a de novo AML (M2) with 44% blasts and 35.95% *GATA2* missense mutation (c.952G>A, p.A318T) at diagnosis. The patient was recruited to the Clinical study and achieved CR with negative *GATA2* mutation after AZA+HHT based regimen as the induction therapy. Two cycles of high-dose cytarabine consolidation were received followed by allo-SCT (Figure 1A). In vitro assay revealed a synergistic effect of AZA+HHT on cell proliferation arrest in $GATA2^{A318T}$ and $GATA2^{A372T}$ cells compared with single drug (P<0.05 in all concentration groups) (Figure 1B). The synergistic effect was stronger (lower combined index) in both $GATA2^{A318T}$ and $GATA2^{A372T}$ cells than $GATA2^{WT}$ cells in low HHT concentration groups (Figure 1B). AZA+HHT presented more potent synergistic effect in $GATA2^{A372T}$ cells compared with $GATA2^{WT}$ and $GATA2^{A318T}$ cells in all HHT concentration groups, suggesting that $GATA2^{A372T}$ was more sensitive to AZA+HHT (Figure 1C). Furthermore, RNA-seq revealed that MAPK pathway was significantly altered in both AZA and HHT treated groups (Padj<0.001), indicating that AZA+HHT exhibited strong synergistic anti-leukemia effect in *GATA2*-mutated AML and may rely on their common effect of targeting MAPK pathway (Figure 1D).



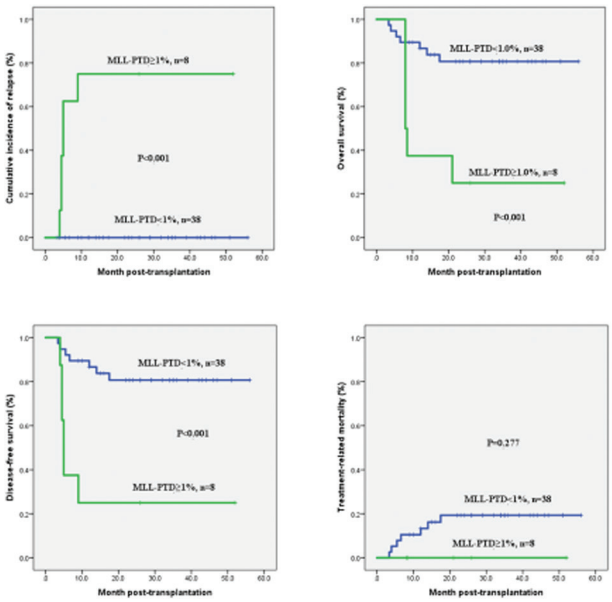
Summary/Conclusion: Our data for the first time showed that the synergistic efficacy of novel combination-based regimen AZA+HHT in *GATA2*-mutated AML. Targeting MAPK pathway may be one of the potential downstream mechanisms of AZA+HHT in treating *GATA2*-mutated AML.

EP454 MONITORING OF POST-TRANSPLANT MLL-PTD AS MINIMAL RESIDUAL DISEASE CAN PREDICT RELAPSE AFTER ALLOGENEIC HSCT IN PATIENTS WITH ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

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Background: MLL-PTD is a special MLL rearrangement gene that occurs in about 5-10% of acute myeloid leukemia (AML) with a normal karyotype and in 5-6% of myelodysplastic syndrome (MDS) patients. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently one of the curative therapies available for AML and MDS with excess blasts (MDS-EB). However, how the prognosis of patients with high levels of MLL-PTD after allo-HSCT, including AML and MDS, and whether MLL-PTD could be used as a reliable indicator for minimal residual disease (MRD) monitoring in transplant patients remains unknown.
Aims: Our study purposed to analyze the dynamic changes of MLL-PTD peri-transplantation and the best threshold for predicting relapse after transplantation.
Methods: We retrospectively collected the clinical data of 48 patients with MLL-PTD AML or MDS-EB who underwent allo-HSCT in Peking University People's Hospital. The MLL-PTD was examined by real-time quantitative polymerase chain reaction (RQ-PCR) at the diagnosis, before transplantation and the fixed time points after transplantation. Detectable MLL-PTD/ABL>0.08% was defined as MLL-PTD positive in this study.
Results: The 48 patients included 33 AML patients and 15 MDS-EB patients. The median follow-up time was 26(0.7-56) months after HSCT. In AML patients, 7 patients (21.2%) died of TRM, 6 patients (18.2%) underwent hematological relapse and died ultimately. Of the 15 patients with MDS-EB, 2 patients (13.3%) died of infection. The 3-year cumulative incidence of relapse (CIR), overall survival (OS), disease-free survival (DFS) and treatment-related mortality (TRM) were 13.7%±5.2%, 67.8%±6.9%, 68.1%±6.8% and 20.3%±6.1%, respectively. ROC curve showed that post-transplant MLL-PTD≥1.0% was the optimal cut-off value for predicting hematological relapse after allo-HSCT. There was statistical difference between post-transplant MLL-PTD≥1.0% and MLL-PTD<1.0% groups (3-year CIR: 75%±15.3% vs. 0%, P<0.001; 3-year OS: 25.0±15.3% vs. 80.7%±6.6%, P<0.001; 3-year DFS: 25.0±15.3% vs. 80.7%±6.6%, P<0.001; 3-year TRM: 0 vs. 19.3±6.6%, P=0.277). However, whether MLL-PTD≥1% or MLL-PTD<1% before transplantation has no significant difference on the prognosis.



Summary/Conclusion: Our study indicated that MLL-PTD had a certain stability and could effectively reflect the change of tumor burden. The expression level of MLL-PTD after transplantation can serve as an effective indicator for predicting relapse.

EP455 RESULTS FROM DIAMOND-01 (CLI24-001) TRIAL: FIRST IN HUMAN STUDY OF SEL24/MEN1703, A DUAL PIM/FLT3 KINASE INHIBITOR, IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: SEL24/MEN1703, a dual PIM/FLT3 kinase inhibitor shows activity in both primary Acute Myeloid Leukemia (AML) cells and AML cell lines, regardless of FLT3 status. In the dose escalation (DE) part of the First in Human, Phase I/II DIAMOND-01 trial (CLI24-001, NCT03008187, EudraCT No. 2019-000941-10), SEL24/MEN1703 demonstrated an acceptable safety profile up to the recommended dose (RD) of 125 mg along with initial evidence of single agent activity and meaningful target engagement in heavily pre-treated AML patients (pts) (Solomon et al, EHA 2020; Tomirotti et al, ASH 2020). Here we present updated data including pts enrolled in the Phase II, cohort expansion (CE) of the study.
Aims: The key objectives of the CE part of the study were the confirmation of the safety profile determined in the DE part along with further investigation of the single agent activity.
Methods: DIAMOND-01 trial enrolled pts unsuitable for chemotherapy having relapsed or refractory (R/R) (DE and CE) or previously untreated (DE) AML. Previous target therapies were allowed with the only exception of previous PIM inhibitors treatments. SEL24/MEN1703 was given orally, QD, 14 days ON / 7 days OFF until disease progression/unacceptable toxicity. In the DE of the study MEN1703 escalating doses ranging from 25 to 150 mg were tested, whereas in the CE the RD (125 mg) was administered. Adverse events (AEs) were graded according to NCI-CTCAE v.4.03; responses assessed as per ELN 2017 criteria.
Results: As of January 21, 2021 (cut-off date), n=48 pts were treated across DE (n=25) and CE (n=23). All pts signed the informed consent form prior to undergoing any study procedure. Median age was 69 (25-84) years. Overall, 20 (43%) and 15 (32%) pts had non de novo AML and primary refractory AML, respectively. Adverse karyotype was reported in 7 (15%) pts. Most frequently reported mutations were FLT3/ITD (23%, n=11), DNMT3A (15% n=7), NPM1 (15%, n=7), IDH1 (13%, n=6) and IDH2 (4%, n=2), CEBPA (4%, n=2), FLT3/TKD (2%, n=1). Median number of cycles was 2 (1-8). At the RD (n=30), most frequent serious treatment-emergent AEs (serious TEAEs) were pneumonia (23%), sepsis and febrile neutropenia (13%) and pulmonary mycosis (10%), whereas most frequent G≥3 TEAEs were febrile neutropenia and pneumonia (23%), leukocytosis (20%) and neutrophil count decrease, platelet count decrease, lymphocyte count decrease and sepsis (13%). Responses occurred in 2 pts in the CE, both with IDH1 mutant disease (naïve to IDH inhibitors) who achieved complete remission with incomplete hematologic recovery (CRi). Both responses occurred by Cycle 3, with a duration of 79 (ongoing at cut-off date) and 43 days, respectively. Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations. A total of 3 out of 6 pts with IDH mutations treated at doses ≥75 mg achieved CR/CRi, including a CR in a patient with IDH2 mutant AML relapsed on Enasidenib.
Summary/Conclusion: SEL24/MEN1703 confirmed a manageable safety profile at RD and showed preliminary single agent efficacy in R/R AML, particularly clustering in pts with IDH mutant disease either naïve or previously exposed to IDH inhibitors. These results warrant further

investigation of SEL24/MEN1703 in AML, with potential focus in the IDH mutated subset.

EP456 AZACITIDINE IN COMPARISON TO INTENSIVE CHEMOTHERAPY AND BEST SUPPORTIVE CARE IN RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA, A DATAML REGISTRY STUDY

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Background: Azacitidine is a hypomethylating agent was until recently offered as monotherapy for older and frail patients as first line treatment. In relapsed or refractory (R/R) acute myeloid leukemia (AML), no randomized trial was conducted to position azacitidine (AZA) respective to other standards of care.
Aims: To compare the outcome of R/R AML treated with AZA, intensive chemotherapy (IC) or best supportive care (BSC).
Methods: Our work studied 526 AML refractory (Ref, N=171, 32.5%) to one course of intensive chemotherapy or relapsed after first complete remission (Rel, N=355, 67.5%) in Toulouse or Bordeaux university hospitals (DATAML registry) between 2007 and 2016. At R/R, they received either intensive chemotherapy (IC, N=270; Ref=112, Rel=158), azacitidine (AZA, N=97; Ref=13, Rel=84) or best supportive care (BSC, N=159; Ref=46; Rel=113).
Results: Median age was 64.3 years (IC: 60.1; AZA: 66.3; BSC: 69.4); ECOG performance status (PS) was 0-1 in 77.7% (IC: 82.7%; AZA: 86.6%; BSC: 64.4%). CCI comorbidities score was ≥1 in 34.7%, without difference between groups. Median WBC was $3.0.10^9$/L (IQR, 1.54-7.2). Bone marrow blasts (BMB) at R/R were ≥20% in 63.9% (IC: 72%; AZA: 51.6%; BSC: 61.5%). Karyotypes were intermediate or adverse in 71.7% and 28.3% respectively. Myelodysplasia-related changes (MRC) were observed in 34.8%. At relapse, *FLT3*-ITD mutations were identified in 19/87 (22.4%; IC: 36.2%, AZA: 4.2%; BSC: 7.1%) and *NPM1* mutations in 27/67 (40.3%; IC: 53.3%, AZA: 6.2%; BSC: 33.3%). IC regimens were mainly high-dose cytarabine associated to an anthracycline (N=105, 48.2%). In total, 148 patients received an anthracycline (54.8%) and median total cytarabine dose was 10 grams/m² (IQR, 5-24). 39.3% underwent alloSCT. Median number of AZA cycles was 4 (IQR: 2-8, range: 1-27). 10.3% underwent alloSCT. Complete response (CR or CRi) was 32.2% (IC: 37.0%, AZA: 18.6%; P=0.0008), and early death at day 30 rate was 11.6% (IC: 4.8%, AZA: 3.1%; BSC: 28.3%; P<0.0001). With AZA, CR (7.2%) or CRi (11.3%) occurred in median after 4.6 months (IQR, 2.8-7.3). Partial response (PR) was obtained in 2.1%, stable disease (SD) in 20.6%, hematological improvement (HI) in 15.5%. AZA was independently associated to a significantly lower rate of CR/CRi (OR, 0.23; P<0.0001).With a median follow-up of 56.1 months, the overall survival (OS) was 6.2 months (IC: 8.2 months [5-year: 15.6%]; AZA: 9.6 months [5-year: 6.0%]; BSC: 2.2 months [5-year: 1.7%]). With AZA, OS varied depending on response (CR/CRi: 27.2 months; PR/HI/SD: 12.5 months; failure: 5.3 months (P<0.0001). Independent predictive factors for OS were: for IC, age (HR, 1.53; P=0.002), ECOG PS (HR, 1.53; P=0.02), WBC (HR, 1.78; P=0.02), MRC-AML (HR, 1.57; P=0.002); for AZA, AML status (post-MDS/CMML: HR, 2.70; P=0.023; t-AML: HR, 0.26; P=0.001), BMB ≥20% (HR, 1.85; P=0.011), adverse cytogenetics (HR, 2.22; P=0.006), alloSCT at R/R (HR, 0.30; P=0.012). We then analyzed the effect of treatment using a Royston and Parmar model: after adjustment on confounding factors, death risk is significantly inferior in the AZA group during the first month, is not statistically different between 1 and 7 months, and becomes significantly superior from 8 months.
Summary/Conclusion: At R/R, AZA gives response and overall survival rate similar to those obtained at first line and could represent a fair therapeutical option for the most frail and older patients, but with few late survivors. Nevertheless, these results will need to be updated in a few years, when the treatment of 2nd line will involve associations between azacitidine and targeted therapies or immunotherapies.

EP457 A PHASE 3 STUDY OF ENASIDENIB (ENA) VERSUS CONVENTIONAL CARE REGIMENS (CCR) IN OLDER PATIENTS WITH LATE-STAGE MUTANT-IDH2 (MIDH2) RELAPSED/ REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML)

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Background: Prognosis is bleak for older patients (pts) with R/R AML, especially if multiple lines of treatment (Tx) have failed. Attaining response is more difficult after each Tx failure. *IDH2* mutations occur in ~8-19% of pts with AML. ENA is an oral mIDH2 inhibitor shown to induce responses in pts with R/R AML.
Aims: Report clinical outcomes with ENA *vs* CCR from a phase 3 trial in older pts with late-stage m*IDH2* R/R AML.
Methods: This open-label trial enrolled pts aged ≥60 yrs with ECOG PS ≤2 and who received 2-3 prior AML Tx. Pts were first preselected to 1 of 4 CCR—azacitidine (AZA; 75 mg/m² ×7d), intermediate-dose Ara-C (IDAC; 0.5–1.5 g/m² ×3–6d), low-dose Ara-C (LDAC; 20 mg BID ×10d), or best supportive care (BSC) only—and then randomized 1:1 to ENA (100 mg QD) or preselected CCR in 28d cycles. Endpoints in the ITT cohort included overall survival (OS; primary), event-free survival (EFS), time to Tx failure (TTF), overall response rate (ORR), hematologic improvement (HI), and transfusion independence (TI). OS was also estimated in pts with m*IDH2*-R172 AML; in pts preselected for lower intensity Tx (AZA, LDAC, BSC) before randomization; and in efficacy-evaluable (E-E) pts (received ≥1 study drug dose and had ≥1 response evaluation on-Tx).
Results: 319 pts were randomized to ENA (n=158) or to CCR (n=161; AZA 69, IDAC 33, LDAC 37, BSC 22). Baseline (BL) characteristics were similar between Tx arms. Median age was 71 yrs, 21% of pts received ≥3 prior AML Tx, 40% had primary refractory AML, and 63% had ELN adverse-risk AML. In the ENA and CCR arms, respectively, median numbers of Tx cycles were 6 (range 1–44) and 2 (1–37), and Tx durations were 142d (3–1270) and 36d (1–1166). 20 CCR pts (12%) and 1 ENA pt did not receive any study Tx. 47 ENA pts (30%) and 69 CCR pts (43%) received subsequent AML Tx, including 19 CCR pts (12%) who received subsequent ENA.
Median OS (ITT) was not significantly different between ENA and CCR: 6.5 mo *vs* 6.2 mo (HR 0.86; *P*=0.23); 1-yr survival rates were 37.5% *vs* 26.1%. ENA also prolonged EFS and TTF *vs* CCR: median EFS

was 4.9 *vs* 2.6 mo (*P*=0.008) and TTF was 4.9 *vs* 1.9 mo (*P*<0.0001). ORR was higher with ENA (40.5% *vs* 9.9%; *P*<0.0001), as were rates of CR (23.4% *vs* 3.7%; *P*<0.0001), HI (42% *vs* 11%; *P*<0.0001), and TI (**Table**). For pts preselected to lower-intensity Tx (ENA n=139; CCR n=128), median OS was 6.8 *vs* 6.2 mo with ENA *vs* CCR (HR 0.74; *P*=0.029). At BL, 88 pts had m*IDH2*-R172 AML; pts with the R172 variant had fewer BL co-mutations than m*IDH2*-R140 pts. In m*IDH2*-R172 pts, median OS was ~2-fold longer with ENA (n=43) *vs* CCR (n=45): 14.6 *vs* 7.8 mo (HR 0.59; *P*=0.039). In E-E pts (ENA 147; CCR 129), median OS was 6.8 *vs* 5.7 mo with ENA *vs* CCR (HR 0.77; *P*=0.047).

ENA safety was consistent with prior studies. IDH differentiation syndrome occurred in 14% of ENA pts, with median time to onset of 22d, and 17d to resolution. Tx-related G ≥3 hyperbilirubinemia occurred in 9% of pts.

	ENA N=158	CCR N=165
Overall survival (ITT), months, median [95%CI]	**6.5 [5.5, 9.5]**	**6.2 [4.6, 7.7]**
HR [95%CI], log-rank *P*	0.86 [0.67, 1.10], *P* = 0.23	
Overall survival (Efficacy Evaluable)	n=147	n=129
months, median [95%CI]	6.8 [5.7, 9.8]	5.7 [4.6, 7.6]
HR [95%CI], log-rank *P*	0.77 [0.59, 1.00], *P* = 0.047	
Event-free survival,* months, median [95%CI]	4.9 [3.7, 5.9]	2.6 [1.9, 4.4]
Time to treatment failure,† months, median [95%CI]	4.9 [4.0, 6.0]	1.9 [1.4, 2.5]
Overall response rate (ORR),‡ n (%)	64 (40.5)	16 (9.9)
CR rate, n (%)	37 (23.4)	6 (3.7)
Stable disease, n (%)	64 (40.5)	54 (33.5)
Disease progression, n (%)	13 (8.2)	29 (18.0)
Not evaluable,§ n (%)	17 (10.8)	62 (38.5)
Time to first response (ORR), days, median (range)	92 (24–337)	59 (29–177)
Duration of response (ORR),¶ months, median [95%CI]	7.3 [5.6, 11.1]	NE [2.5, NE]
RBC-Transfusion independence (TI),‖ n/N (%)		
RBC-TD at BL, achieved TI on-study	33/104 (31.7)	9/97 (9.3)
RBC-TI at BL, retained TI on-study	32/53 (60.4)	7/44 (15.9)
Platelet TI,‖ n/N (%)		
Platelet-TD at BL, achieved TI on-study	26/88 (29.5)	8/74 (10.8)
Platelet-TI at BL, retained TI on-study	48/69 (69.6)	22/67 (32.8)
Any Hematologic Improvement (HI),# n (%)	67 (42.4)	18 (11.2)
HI-Erythroid	21 (13.3)	9 (5.6)
HI-Platelet	31 (19.6)	7 (4.3)
HI-Neutrophil	57 (36.1)	13 (8.1)

*Time from randomization to relapse, PD, or death.
†Treatment discontinuation for any reason.
‡ORR includes CR, CRi/CRp, PR, and MLFS, per International Working Group (IWG) 2003 response criteria for AML.
§No postbaseline marrow collected (considered nonresponders; included in denominator for response assessments)
¶Date of first morphologic response to relapse, PD, or death.
#Per IWG 2006 response criteria for MDS.
BL, baseline; CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count/platelet recovery; ENA, enasidenib; HR, hazard ratio; MLFS, morphologic leukemia-free state; PR, partial remission; PD, progressive disease; RBC, red blood cell; TD, transfusion-dependent.

Summary/Conclusion: Median OS was not significantly different between Tx arms in ITT analysis but results may be confounded by number of pts randomized but not treated, early Tx discontinuation, and subsequent Tx (including ENA)—which were all higher in the CCR arm. When the influence of no Tx or early Tx discontinuation was reduced (E-E analysis), OS was superior with ENA. ENA provided meaningful improvements in 1-yr survival, EFS, and morphologic response *vs* CCR, and ENA prolonged OS for pts preselected to lower-intensity Tx and pts with m*IDH2*-R172 AML. HI and TI benefits also support ENA as appropriate oral outpatient Tx for pts with m*IDH2* R/R AML.

EP458 INDUCED SYSTEMIC T-CELL SPECIFIC RESPONSES TO MULTIPLE TUMOR-ASSOCIATED ANTIGENS AFTER ALLOGENIC LEUKEMIA-DERIVED DENDRITIC CELL VACCINE DCP-001 IN AML PATIENTS WITH PERSISTENT MRD

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Background: Patients with acute myeloid leukemia (AML) and persistent measurable residual disease (MRD) have a poor prognosis and new treatment modalities for prevention of relapse i.e. by conversion of MRD status are being investigated. In a phase I study it was shown that the allogeneic leukemia-derived dendritic cell vaccine, DCP-001, induces both humoral and cellular immune responses (van de Loosdrecht et al., Cancer Immunol. Immunother. 2018).

Aims: A phase II trial is currently conducted to investigate the ability of DCP-001 to generate an anti-leukemia response in patients with AML in CR but MRD positive and to convert patients to from MRD positive to a MRD negative status (Clinicaltrials.gov: NCT03697707). Immunological analyses are planned to elucidate the height and breadth of the vaccination on the local and systemic immune responses before, during and after the vaccination regimen.

Methods: An intended total of 20 patients (10 at 25e6 and 10 at 50e6 dose) ineligible for HSCT will receive a primary regimen consisting of 4 doses given biweekly (week 0, 2, 4 and 6) followed by the booster regimen with 2 doses (10e6) at week 14 and 18. MRD status (flow cytometry and/or qPCR based according to ELN guidelines) is assessed at baseline, before booster vaccination (week 14) as well as 2 weeks and 3 months after the booster to monitor clinical efficacy of the vaccinations. At present (March 1, 2021), the 25e6 dose cohort has been fully enrolled and most patients have completed the 32 week end of treatment visit, while the 50e6 cohort has been nearly completed with 7 patients having received at least one vaccination.

Results: First analyses of skin biopsies taken 2 days after the 1st, 4th and 6th dose of patients whom have completed the full vaccination schedule showed acute inflammation in the skin reflected by induration and redness of the skin. Infiltrating immune cells consisted mainly of CD4 and CD8 T-cells as well as CD68+ cells.

Flow cytometric analysis on PBMC showed an increase in antigen experienced CD8+ CD137+ T-cells already 2 days after vaccination. After the primary schedule, immune responses to known AML tumor-associated antigens such as PRAME and WT-1 were induced post- DCP-001 vaccination as measured by IFNγ ELISPOT. Patients showed multiple detectable responses, either boosted from preexisting or as an induced primary response upon DCP-001 vaccination. Up to a 4-fold median increase to baseline levels after initial vaccinations was detected, in patients with positive ELISPOT responses. After primary vaccinations, retraction of the cellular responses was observed, but could be boosted, with a 1.5 fold median increase compared to pre-boosting levels.

Consecutive samples of 3 patients were analyzed by TCRbeta sequencing and showed increased breadth and height of T-cell clones after DCP-001 vaccination. As DCP-001 is known to induce responses to tumor associated antigens, not only expressed by DCP-001, such a NY-ESO-1, a broad range of different TCRs to several published TAA was detected.

At time of reporting, 2 of 5 patients with immune response data available, MRD negativity was achieved. In both patients multiple antigenic responses after DCP-001 vaccination and high levels of immune cells infiltrates at the injection site were observed.

Table 1. Overview of immune responses after DCP-001 vaccination in 5 patients with full data set available. Skin biopsy: ++ or +++ (level 4 or 5 on scale of 5 of pathologist evaluated immunohistochemistry of the skin biopsy). Flow and ELISPOT +: increase.

	skin biopsy		Flow	IFNγ ELISPOT		
	T-cells	CD68	CD8+CD137+ increase	WT1	PRAME	RHAMM
M, 41y	+++	+++	+	+	-	+
M, 63y	+++	+++	-	+	+	-
F, 73y	++	++	+	-	+	+
M, 64y	++	++	+	-	-	-
M, 67y	+++	+++	-	-	+	-

Summary/Conclusion: DCP-001 used as a relapse vaccine in AML patients, showed recruitment of immune cells to the skin, increased cellular responses to a broad range of tumor associated antigens, and resulted in reversion of the MRD status in some patients.

EP459 PROGNOSTIC IMPACT OF MINIMAL REDISUAL DISEASE ASSESSMENT IN ELDERLY PATIENTS WITH SECONDARY ACUTE MYELOID LEUKEMIA. A COMPARISON BETWEEN CPX-351 AND INTENSIFIED FLUDARABINE-BASED REGIMENS

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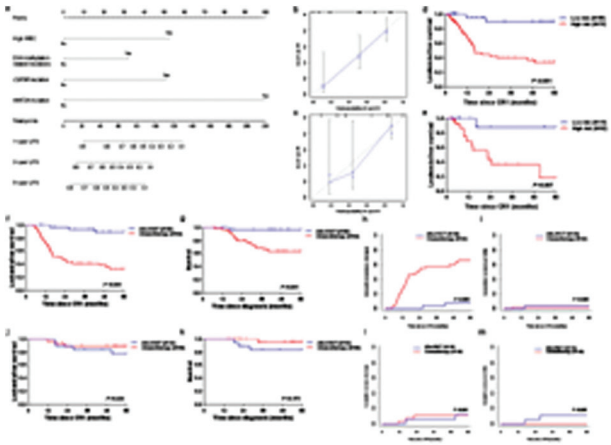
Background: Minimal residual disease (MRD) assessment retains high prognostic value in Acute Myeloid Leukemia patients (AML) undergoing intensive induction therapy. Widely available MRD techniques include multicolour flow cytometry (MFC), RT-PCR for recurrent genetic lesion and, for patients lacking specific markers, RT-PCR for the pan-leukemic marker WT1. However, most of the data on the prognostic value of MRD come from trials including younger patients treated with conventional 3+7 regimen. AML arising from a previous myelodisplastic syndrome (s-AML) and therapy-related AML (t-AML) are usually under-represented in trial involving younger patients and are unlikely to respond to conventional induction. Few data are therefore available on the kinetics and the prognostic value of MRD in elderly s-AML and t-AML patients, particularly in the context of alternative induction regimens.
Aims: We evaluated MRD in a cohort of elderly s-AML or t-AML patients receiving induction therapy either with a fludarabine-containing regimen or CPX-351, in order to compare the probability of achieving MRD negativity, to disclose the prognostic value of MRD in this setting and to define the best time-points for MRD assessments.
Methods: A total of 136 elderly (>60 year, median age 67, range 60-75) patients were analyzed in this study. Patients were treated between January 2005 and January 2020 in our Center, either with CPX-351 (n=35) or fludarabine- high dose cytarabine-idarubicin (FLAI), with (n=72) or without (n =29) gemtuzumab-ozogamicin (GO). MRD was retrospectively analyzed in all patients achieving hematological complete remission (CR) with both MFC and WT1 expression levels.All patients were affected by s-AML or t-AML, defined according to the WHO 2016 criteria.
Results: After induction, CR was achieved in 83 patients (61%). CR rate was 28/35 in patients treated with CPX-351 (80%), significantly higher when compared to patients receiving FLAI (55/101, 54.5%, p<0.05). The addition of GO to FLAI did not increase CR rate. Among CR patients, a total of 41 (49.4%) and 44 patients (53%) achieved MRD negativity, with MFC or WT1-based methods, respectively. MFC MRD negativity probability was higher among patients receiving CPX-351 as induction therapy (MFC MRD negativity rate of 16/28, 57% and 25/55, 45% in CR patients who received CPX-351 or FLAI, respectively, p<0.05). Adding GO to FLAI did not improve MRD negativity probability. Moreover, MRD showed significant prognostic value in terms of Overall Survival in all treatment group (2-year OS of 74 and 36% in patients with or without residual MFC MRD after induction, respectively, p<0.05). WT1-based MRD lead to similar results.
Summary/Conclusion: In conclusion MRD assessment retains a strong prognostic value and may help to identify patients with suboptimal response to treatment. The higher rate of MRD negativity observed with CPX-351 may be related with a more efficient anti-leukemic activity of the drug in this particular setting. The evaluation of MRD with both MFC and WT1-based assessment lead to superimposable conclusions and allowed us to obtain MRD data from virtually all AML patients treated in the selected time period.

EP460 ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION WAS SUPERIOR TO CONSOLIDATION CHEMOTHERAPY IN HIGH-RISK CN-AML WITH BIALLELIC CEBPA MUTATIONS BASED ON A MUTI-GENE PANEL AND NOMOGRAM MODEL

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Background: Cytogenetically normal acute myeloid leukemia (CN-AML) patients with biallelic *CEBPA* (bi*CEBPA*) mutations have a favorable prognosis compared with patients with wild-type or monoallelically mutated *CEBPA*. However, this subgroup is still not homogeneous with relapse rate reaching approximately 40% and the best post-remission therapy remains unclear.
Aims: Elucidate the cooperating events in CN-AML with bi*CEBPA* mutations, identify the risk factors and explore the optimal post-remission therapy in different risk subgroups.
Methods: A total of 158 CN-AML patients with bi*CEBPA* mutations were enrolled for targeted region sequencing by a panel with 236 genes. Patients were assigned to a training cohort (*N* =111) and a validation cohort (*N* =47) at a ratio of 7:3 randomly to construct a nomogram model. Risk factors identified in nomogram were incorporated to stratify the cohort. Post-remission therapies were compared in different risk subgroups. Receiving an allo-HSCT was recorded as a censored event to identify the prognostic factors before an allo-HSCT. Landmark analysis was performed to revise bias from early relapse or death when comparing the outcomes of post-remission therapies.
Results: We identified 1,306 mutations in 203 genes other than *CEBPA*. The median mutation number was 8 (1–20). Patients with low mutational context (mutation number <8) showed significantly higher 5-year leukemia-free survival (LFS) (61.6% *vs.* 39.0%, *P* =0.033) and 5-year survival (85.6% *vs.* 62.9%, *P* =0.030), lower 5-year cumulative incidence of relapse (CIR) (38.4% *vs.* 59.5%, *P* =0.0496) and comparable 5-year non-relapse mortality (NRM) (0 *vs.* 1.5%, *P* =0.407). Four variables were in the nomogram model: WBC (high *vs.* low, represents >18.30×10^9/L *vs.* ≤18.30×10^9/L), *CSF3R* mutation (+ *vs.* -), *KMT2A* mutation (+ *vs.* -) and DNA methylation related mutation (mutations in *TET2*, *DNMT3A*, *IDH2*, *BAZ2A* and *IDH1*) (Figure 1a). The C-index was 0.750 (95% CI, 0.670–0.830) in training cohort and 0.771 (95% CI, 0.661–0.881) in the validation with good calibration in the two cohorts (Figure 1b-c). According to the nomogram model, patients with none of the risk factors were classified as the low-risk subgroup (*N* =50) and the remain were high-risk (*N* =108). Low-risk patients had significantly lower positive MRD after induction (25.5% *vs.* 57.7%, *P* <0.001) and better prognosis both in training and validation cohorts (5-year LFS, 89.3% *vs.* 33.8%, *P* <0.001; 87.5% *vs.* 18.2%, *P* =0.009) (Figure 1d-e). Post-remission therapies analyses indicated that allo-HSCT had better 5-year LFS (89.6% *vs.* 32.6%, *P* <0.001), 5-year survival (96.9% *vs.* 63.6%, *P* =0.001) and lower 5-year CIR (7.2% *vs.* 65.8%, *P* <0.001) compared with consolidation chemotherapy in high-risk subgroup (Figure 1f-h). However, in low-risk subgroup, these two post-remission therapies did not show significant difference (allo-HSCT *vs.* consolidation chemotherapy, 5-year LFS, 77.4% *vs.* 88.9%, *P* =0.424; 5-year survival, 83.9% *vs.* 95.5%, *P* =0.173; 5-year CIR, 11.7% *vs.* 11.1%, *P* =0.901) (Figure 1j-l). The 5-year NRM was comparable in high- (3.1% *vs.* 1.6%, *P* =0.685) (Figure 1i) and low-risk (10.9% *vs.* 0, *P* =0.099) (Figure 1m) subgroups.



Summary/Conclusion: CN-AML patients with bi*CEBPA* mutations were prognostically heterogeneous with different mutational context. Only approximately one third of these patients represented the low-risk subgroup, and consolidation chemotherapy should be given as the first line post-remission therapy. While in the high-risk subgroup, allo-HSCT is recommended.

EP461 N-TERMINAL FRAGMENT OF BRAIN NATRIURETIC PEPTIDE (PBNP) IS A NOVEL INDEPENDENT PROGNOSTIC MARKER FOR SURVIVAL AND RESPONSE TO INTENSIVE CHEMOTHERAPY IN AML

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Background: Acute myeloid leukemia (AML) is a heterogeneous hematologic neoplasm resulting from abnormal proliferation and differentiation of clonal myeloid precursor cells. Karyotype, genomic abnormalities and patient-related factors are known to play an important role in the prognostication of AML. However, little is known about the effects of serologic markers like N-terminal fragment of brain natriuretic peptide (pBNP) on the outcome of AML patients.
Aims: The aim of the present study was to evaluate the role of pBNP as prognostic marker in patients with AML.
Methods: We analyzed 312 AML patients (median age: 61 years; range 17-89 years; f:m-ratio: 1:1.15) treated between February 1998 and September 2020 with 3+7-based induction chemotherapy and consolidation with up to 4 cycles of intermediate-dose or high-dose ARA-C.
Results: In 199 patients (63.8%), elevated pBNP levels were detected, and in 113 patients (36.2%), pBNP levels were within normal range (0-125 pg/ml). In 20 patients (6.4%), pBNP exceeded 2000 pg/mL. We found a weak correlation between age and pBNP (R=0.18) and a significant difference in pBNP levels when comparing high-risk (226.5 pg/mL), intermediate-risk (156.0 pg/mL) and low-risk patients (139.3 pg/mL) by Charlson comorbidity index (CCI) (p=0.002). No significant difference in pBNP levels was observed between male (median pBNP 193.5 pg/mL; range: 1-19833) and female (median pBNP 192 pg/mL; range: 1-15930) patients (p=0.33) or when comparing the body mass index (BMI) with pBNP levels (p=0.94). Following induction therapy, 219 patients (70.2%) achieved a complete remission (CR), 63 (20.2%) had no remission (NR), and 30 (9.6%) died from early death (ED). Median pBNP levels differed significantly among CR, NR and ED patients, with 153.3, 225.9, and 735.5 pg/mL, respectively (p=0.001). In multivariate analyses including age, sex, the ELN-2009 classification, BMI, CCI and pBPN, only pBNP and the ELN-2009 classification were independent predictors for response to induction therapy (p=0.007 and p<0.0001, respectively). Overall survival (OS) differed significantly between patients with normal, moderately elevated (125-2000 pg/mL) and highly elevated pBNP (>2000 pg/mL) (p<0.001). This difference was also observed when analyzing OS in patients <60 years (p=0.012), but was not seen in patients aged ≥60 years. Inmultivariate analysis (including age, the ELN-2009 classification, white blood counts, sex, CCI and pBNP) age, the ELN-2009 classification and pBNP remained independent predictive variables for OS (p=0.002, p<0.0001, and p=0.035, respectively). There was no significant difference in pBNP levels at diagnosis between patients who died from progressive disease, bleedings, infections, multi organ failure, pulmonary deterioration, cardiac problems or other reasons during the observation period (p=0.26). With regard to continuous complete remission pBNP was of prognostic significance in the cohort aged <60 years (p=0.011) but not in patients aged ≥60 years.
Summary/Conclusion: Together, pBNP is an independent prognostic factor and new biomarker indicating the risk of induction failure, early death and reduced OS in AML. Our data also show that the predictive power of pBNP as independent risk factor is most evident and most useful in patients <60 years.

EP462 EFFICACY AND SAFETY OF ASPACYTARABINE (BST-236) AS A FIRST-LINE MONOTHERAPY FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA UNFIT FOR STANDARD CHEMOTHERAPY

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Background: Cytarabine, the backbone of acute myeloid leukemia (AML) standard of care chemotherapy, is associated with a toxicity which precludes its administration to older patients and those with comorbidities. Aspacytarabine (BST-236) is a prodrug of cytarabine. Its pharmacokinetics and metabolism lead to gradual release of cytarabine with shorter duration at peak toxic levels compared to direct cytarabine administration, resulting in relative sparing of normal tissues and enabling delivery of high cytarabine doses to patients otherwise unfit to receive it.
Aims: To evaluate the efficacy and safety of aspacytarabine as a first-line, single-agent therapy in newly-diagnosed AML patients unfit for standard induction therapy.
Methods: Aspacytarabine is administrated at a dose of 4.5 g/m^2/d (equimolar of 3 g/m^2/d cytarabine). Therapy is time-limited, with only 1-2 induction courses and 1-3 consolidation courses, each consists of 6 daily 1-hour intravenous infusions. Newly-diagnosed AML patients unfit for standard chemotherapy, including those with secondary AML, previously treated with HMA, and patients with therapy-related AML, are eligible.
Results: To date, 71 AML patients were treated with aspacytarabine; 47 newly-diagnosed AML patients unfit for standard chemotherapy (median age 75 years) completed 1-4 courses of 4.5 g/m^2/d aspacytarabine in an ongoing phase 2b study, including 30 patients (64%) with *de novo* AML and 17 (36%) with secondary AML. Six patients (13%) were previously treated with HMA (median 12 courses), and 21 (45%) patients had ECOG Performance Status 2. The median baseline bone marrow blast percentage was 45 (range 13-94), and 54% and 29% of patients had adverse or intermediate ELN score, respectively.
Aspacytarabine is safe and well-tolerated in repeated-course administration. Grade >2 drug-related adverse events include mainly hematological events and infections. The 30-day mortality rate is 11%.
Of the 43 phase 2b patients evaluable for efficacy analysis to date, 15 patients (35%) reached a complete remission (CR) following 1 (13 patients) or 2 (2 patients) aspacytarabine induction courses. All responders reached a complete hematological recovery (median 27.5 days, range 22-39 days). The CR rate excluding patients with prior HMA therapy is 41%, and 46% in *de novo* AML patients. The CR rate in patients at the age of ≥75 years and patients with adverse ELN score is 33%.
Of note, of the 11 patients evaluable to date for minimal residual disease (MRD) analysis, 8 (73%) are MRD negative.
While aspacytarabine treatment consists of a limited number of courses, median duration of response (DOR) and median overall survival (OS) for responders are not reached (NR) at end of follow up, 12 (95% CI 5-NR) and 24 (95% CI 6-NR) months, respectively. The median OS for all patients is 6.8 (95% CI 6-NR) months (Figure 1A). Median OS for *de novo* AML patients is NR (95% CI 6-NR) and 6.8 (95% CI 2.7-NR) for secondary AML patients (Figure 1B).
Follow-up is ongoing with additional patients enrolling on study; updated analysis will be presented at the meeting.

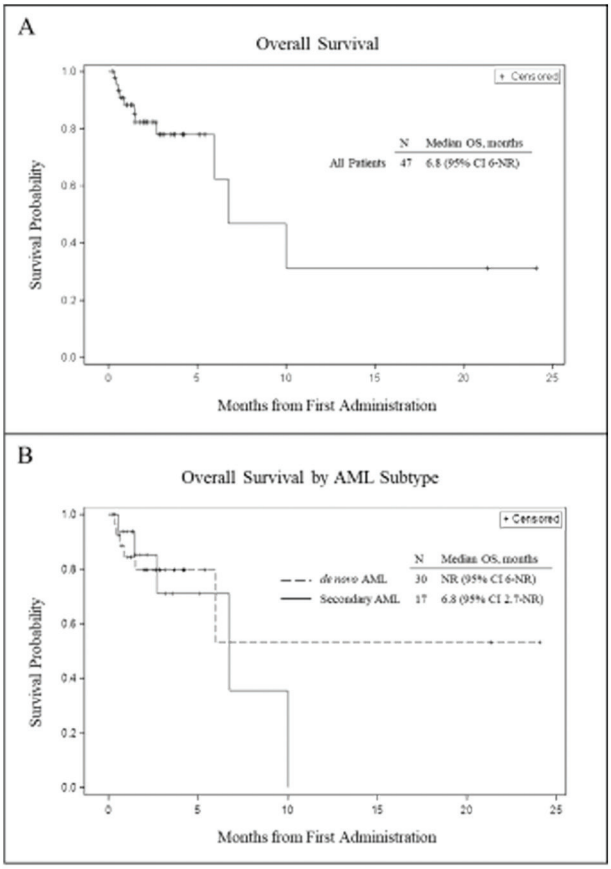


Figure 1. Overall Survival

Summary/Conclusion: The cumulative clinical data suggest that aspacytarabine monotherapy is safe and efficacious as a first-line therapy for patients who are unfit for intensive chemotherapy, including patients with adverse cytogenetics and patients ≥75 year of age. The data may establish aspacytarabine, already granted Fast Track designation from the FDA, as a new intensive therapy backbone of AML and may, for the first time, allow older adults benefit from standard intensive therapy.

EP463 THE COMBINATION OF AXL INHIBITOR BEMCENTINIB AND LOW-DOSE CYTARABINE IS WELL TOLERATED AND EFFICACIOUS IN ELDERLY RELAPSED AML PATIENTS: UPDATE FROM THE ONGOING BGBC003 PHASE II TRIAL (NCT02488408)

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Background: Low-dose cytarabine (LDAC) in elderly relapsed (REL) & refractory (REF) (r/r) AML patients (pts) unfit for intensive therapy shows limited response (CR rate up to 17%) and survival benefit (mOS 4-6mos). This population has significant unmet need for new treatments. Bemcentinib (BEM) is an oral selective small molecule inhibitor of AXL, a RTK mediating poor prognosis, resistance to chemotherapeutics and decreased antitumor immune response. AXL is overexpressed on leukemic cells, especially in the stem cell compartment, and represents an important novel target in pts with AML.

Aims: The ongoing BGBC003 PhII trial cohorts receiving BEM+LDAC (B+L) include newly diagnosed (ND) and r/r AML pts unfit for intensive therapy. Based on observed activity, r/r AML pts were selected in an expansion cohort, to explore safety and efficacy and to undertake translational biomarker analysis. Here, we report on preliminary efficacy in r/r pts, with a safety overview for all pts treated with the combination.

Methods: Pts received BEM at the RP2D (200mg PO/d)+LDAC SoC schedule. Efficacy endpoints included objective response (OR) and clinical benefit (OR+SD [unchanged disease for at least 3 BEM cycles]). Secondary objectives include overall survival (OS) and exploratory biomarker analyses. Single cell RNA sequencing and T-cell repertoire analysis are being conducted to unravel the immunotherapeutic MOA of B+L.

Results: As of 06 Jan 21, the B+L cohorts (n=31) comprised 7 ND and 24 r/r (17 REL, 7 REF) AML pts; here, we focus on r/r pts. Median prior lines of therapy: 1 [1-8] in REL, 3 [1-4] in REF. Median age: 75yrs [66-86] for REL, 75 [71-81] for REF. Adverse cytogenetic risk profile: 5/17 (29%) in REL, 2/7 (29%) in REF. Median bone marrow (BM) myeloblast count at screening: 32% [6-94] for REL, 40% [3-54] for REF.

12 REL pts were evaluable for efficacy (BM assessment at C2D1). 5/12 (42%) achieved remission (4 CR/CRi, 1PR). Notably, first CR/CRi's were reported between wk13(C5)–wk19(C7). These later onset responses may reflect the importance of AXL-related immunological mechanisms for relatively chemo-resistant relapsed pts and contribute to a longer time-on-treatment (ToT).

An additional 3 had SD; with clinical benefit rate 67%.

Median ToT was 28.0wks for CR/CRi pts. mDOR was 13.1wks [2.1-43.1+] in all responders and 14.0wks [10.0-43.1+] in CR/CRi pts. 7 pts remain on treatment. Survival outcomes continue to mature.

In contrast, no REF pts showed response (0/7), with 2/7 (28%) reporting clinical benefit; median ToT was 8.0wks. No pts remain on treatment.

Previously-reported results of preliminary scRNAseq analysis of these pts indicated differences in the T- and NK cell compartment associated with treatment response, pointing to BEM-mediated immune MOA in context of synergy of B+L. Further analyses of scRNAseq and CITE-seq data are ongoing.

Overall, the safety of B+L (compared with previously published BEM monotherapy) was in keeping with the known safety profile of LDAC. TRAEs of ≥G3 observed in ≥10% of pts were anemia (29% B+L; 0% BEM), platelet count decr. (29% B+L; 0% BEM), thrombocytopenia (19% B+L; 8% BEM), neutrophil count decr. (13% B+L; 0% BEM), white blood cell count decr. (13%B+L; 0% BEM) and ECG QT prolonged (10% B+L; 6% BEM). No G5 TRAEs reported.

Summary/Conclusion: These data show that B+L is efficacious and well tolerated in the elderly/unfit REL AML population. An in-depth translational research program aiming to identify predictive molecular and biological factors associated with response is ongoing. B+L should be considered for evaluation in a randomized pivotal trial in this population.

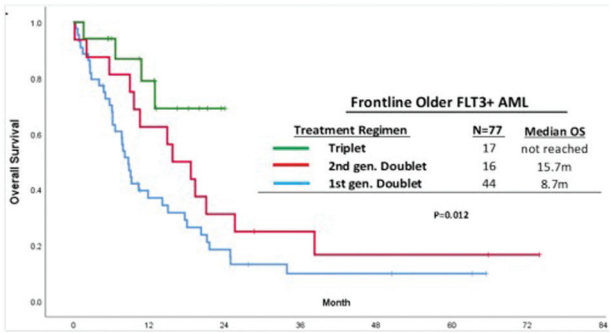
EP464 TRIPLE COMBINATION OF HMA, VENETOCLAX, AND FLT3 INHIBITOR PRODUCES HIGHER FLT3 PCR CLEARANCE, FLOW MRD NEGATIVITY, AND IMPROVED MEDIAN OS COMPARED WITH DOUBLETS OF HMA WITH FLT3 INHIBITOR

M. Yilmaz [1,*], F. Ravandi [1], S. Loghavi [1], S. Wang [1], G. Borthakur [1], C. Dinardo [1], T. Kadia [1], R. Kanagal-Shammanna [1], N. Pemmaraju [1], B. Oran [1], U. Popat [1], S. Pierce [1], E. Jabbour [1], N. Short [1], G. Issa [1], M. Ohanian [1], G. Garcia-Manero [1], M. Andreeff [1], K. Patel [1], M. Konopleva [1], H. Kantarjian [1], N. Daver [1]

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Background: First-generation FLT3i's (sorafenib, midostaurin) combined with low-intensity chemotherapy (LIC) failed to improve outcomes (median overall survival (OS) ~8 months in frontline) in intensive chemotherapy (IC) non-eligible older patients (pts) with acute myeloid leukemia (AML) [Ohanian AJH 2018, Gallogly Blood 2017]. The expected median OS in *FLT3-ITD* mutated (m) pts with a frontline hypomethylating agent (HMA) with venetoclax (VEN) was 11.5 months [Konopleva Blood 2020]. Clinical trials exploring triplet combinations (HMA+VEN+ FLT3i) are ongoing.

Aims: We retrospectively analyzed IC non-eligible older pts with newly diagnosed *FLT3*m AML treated with HMA + VEN + FLT3i (triplet regimen) at MDACC between 2012-2020 and compared CR/CRi rates, measurable residual disease (MRD) dynamics, and OS with pts who received LIC + FLT3i (doublet regimen).
Methods: We identified 77 adult pts with newly diagnosed *FLT3*m (ITD and/or TKD) AML who were treated with LIC including first-generation (sorafenib, midostaurin) LIC doublet (n=44), second-generation (quizartinib) LIC doublet (n=16), and HMA-VEN-FLT3i (sorafenib, gilteritinib, midostaurin) triplet (n=17). Measurable residual disease (MRD) assessments were done at initial CR/CRi and longitudinally on therapy by multiplex PCR for ITD and D835, sensitivity 10^{-3} (Luthra, 2014, Haematologica), and by multicolor flow-cytometry (MFC), sensitivity 10^{-4} (Jaso, 2014, BMT).
Results: The median age was 71 [51-83], 71 [64-83], and 69 [40-80] year-old among first-generation LIC doublet, second-generation LIC doublet, and HMA-VEN-FLT3i triplet groups.
Among 77 pts treated with LIC (60 doublets, 17 triplets), 74% (57/77) achieved CR/CRi with the best PCR and MFC MRD-negativity rates of 67% (36/54) and 56% (31/55). Comparing pts treated with second-generation (n=16) versus first-generation (n=44) FLT3i based LIC doublets we noted increased CR/CRi (88% vs 64%, P=0.07) but no statistically significant difference in best FLT3 PCR (62% vs 50%, p=0.5) and best MFC MRD (50% vs 42%, p=0.6) clearance. Pts who received triplet regimens (n=17) achieved a 88% CR/CRi (similar to second-generation doublet), but with a significantly higher best FLT3 PCR (100% vs 54%, p=0.001) and higher best MFC MRD (87% vs 45%, p=0.006) clearance, compared with all patients treated with LIC doublets (n=60).
With a median follow-up of 28 months, pts treated with triplets achieved the best median OS compared with pts treated with first- or second-generation FLT3i based LIC doublets (not reached vs 15.7 vs 8.7 months (m), respectively, p=0.01) [Figure].
Across the 55 evaluable LIC patients, the achievement of MRD negativity by MFC at any time on therapy was associated with improved med OS (21m vs 12m, p=0.04. Achieving FLT3 PCR clearance at any time on therapy was associated with a non-statistically significant improved med OS (21m vs 9m, p=0.18). Pts who achieved both PCR and MFC vs MFC or PCR only clearance vs clearance of neither at any time on therapy had med OS of 21m, 20m, and 9m, resp (p=0.06).



Summary/Conclusion: The outcomes in older patients who received LIC+FLT3i (doublets) are poor, although combining LIC with second-generation inhibitors such as quizartinib appeared to improve OS. Triplet combination of HMA-VEN-FLT3i appeared to be most effective in improving OS, FLT3 PCR, and MFC clearance. Achievement of MRD negativity (especially MFC negativity) significantly improved OS, irrespective of LIC or IC backbones, and may be a surrogate endpoint to consider for future FLT3 frontline trials.

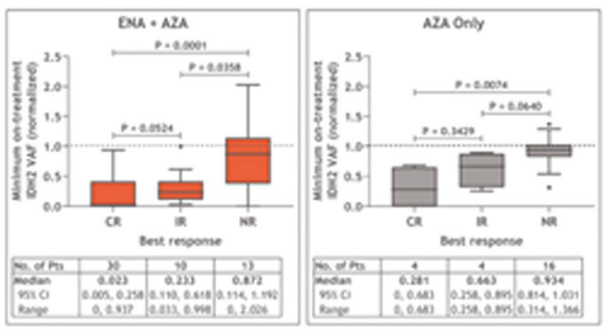
EP465 UPDATED PHARMACODYNAMIC AND SURVIVAL OUTCOMES FROM THE AG221-AML-005 TRIAL OF ENASIDENIB (ENA) PLUS AZACITIDINE (AZA) IN PATIENTS WITH MUTANT IDH2 NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (ND-AML)

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Background: Adding ENA to AZA *in vitro* enhances leukemic apoptosis *vs* AZA alone. ENA suppresses the oncometabolite, 2-hydroxyglutarate (2-HG), restoring function to α-ketoglutarate-dependent enzymes. In the AG221-AML-005 trial, combination ENA+AZA significantly improved overall response and complete remission (CR) rates *vs* AZA alone in patients (pts) with mutant-*IDH2* (m*IDH2*) ND-AML not eligible for intensive chemotherapy. At an August 2019 data cutoff, median overall survival (OS) was impressive at 22 mo in both arms; OS in the AZA only arm was far longer than previously reported for AZA in ND-AML (~10-14 mo).
Aims: Assess longitudinal changes in 2-HG and *IDH2* variant allele frequency (VAF) and their correlations with response, and update survival outcomes for pts in AG221-AML-005.
Methods: Pts were randomized 2:1 to ENA+AZA or AZA only. Pts received SC AZA 75mg/m^2/day (d) ×7d ± ENA 100mg PO QD (continuous) in repeated 28d cycles (C). Blood 2-HG was assessed by HPLC, and BMMC m*IDH2* VAF by digital PCR (LLQ 0.02–0.04%). Changes from baseline (BL) in 2-HG and *IDH2* VAF were assessed in pt subgroups defined by response: CR, incomplete response (IR; CRi/CRp, PR, MLFS), or no response (NR). Updated event-free survival (EFS) and OS were assessed in August 2020. EFS was the time from randomization to relapse, PD, or death, and OS was the time from randomization to death.
Results: 101 pts were randomized to ENA+AZA (n=68) or AZA only (n=33). Median age was 75 yrs (57-85). At BL, median 2-HG concentration was similar between treatment (Tx) arms (*P*=0.97). Median maximum 2-HG reduction from BL was –98% with ENA+AZA *vs* –54% with AZA (*P*<0.01). Median 2-HG reductions from BL with ENA+AZA were not significantly different among pts who achieved CR (–100%; n=37), IR (–98%; n=12), or NR (–93%; n=14), but in the AZA arm, median 2-HG reductions were significantly greater for pts who achieved CR (–79%; n=4) or IR (–85%; n=8) *vs* NR (–28%; n=17).
Median BL *IDH2* VAF was 28% in the ENA+AZA arm and 34% in the AZA arm (*P*=0.06). *IDH2* VAF was significantly reduced from BL in the ENA+AZA arm by C3 (–23%; *P*≤0.01) and continued to decrease through C11 (–98%; *P*≤0.001); maximal median change from BL was significantly greater with ENA+AZA *vs* AZA (–83.4% *vs* –17.7%; *P*<0.01). In the ENA+AZA arm, median *IDH2* VAF reductions were significantly greater for pts who achieved CR (–98%; n=30) or IR (–77%; n=10) *vs* NR (–13%; n=13), and in the AZA arm, for pts who achieved CR (–72%; n=4) *vs* NR (–7%; n=16) (**Figure**). 10 pts achieved *IDH2* molecular clearance, 9 of whom achieved CR (ENA+AZA n=8).
In August 2020, median ENA+AZA exposure was 12.1 mo and AZA exposure was 6.2 mo; 12 ENA+AZA pts remained on Tx. During follow-up, 24% of pts (16/68) in the ENA+AZA arm and 58% (19/33) in the AZA arm received subsequent AML Tx, including 11 pts in the AZA only arm (33%) who received commercially available ENA. Median EFS was nominally longer with ENA+AZA *vs* AZA (15.7 *vs* 11.9 mo; HR 0.59 [95%CI 0.31, 1.12]; *P*=0.10). Median OS was 22.0 mo with ENA+AZA *vs* 18.6 mo with AZA (HR 0.78 [0.46, 1.33]; *P*=0.36); 2-yr survival rates were 48.3% *vs* 39.9%.

Figure. Reductions from baseline in IDH2 variant allele frequency by clinical response category and randomized treatment arm



Clinical responses were classified per International Working Group (IWG) 2003 response criteria for AML. The IR category includes CR with incomplete blood count or platelet recovery (CRi/CRp), partial remission (PR), and morphologic leukemia-free state (MLFS). The NR category includes stable disease (SD) and disease progression (PD).
AZA, azacitidine; CI, confidence interval; CR, complete response; ENA, enasidenib; IDH2, isocitrate dehydrogenase 2; IR, incomplete response; No, number; NR, no response; Pts, patients; VAF, variant allele frequency.

Summary/Conclusion: Reductions in 2-HG and *IDH2* VAF were significantly greater with ENA+AZA *vs* AZA only. 2-HG changes with ENA+AZA were not correlated with response but changes in *IDH2* VAF were greater in responding pts. Survival was promising in both arms, and may be confounded by the high rate of subsequent AML Tx, including commercial use of ENA, in the AZA only arm during survival follow-up. Approximately one-half of pts treated with ENA+AZA were alive at 2 yrs.

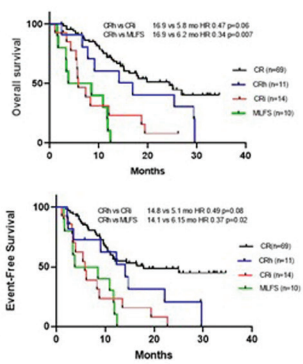
EP466 PROGNOSTIC VALUE OF CRH IN ACUTE MYELOID LEUKEMIA TREATED WITH VENETOCLAX AND DECITABINE

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Background: Recent FDA approvals of novel therapies and hypomethylating agents / venetoclax has transformed therapy of newly diagnosed older patients with AML. While achievement of complete remission (CR) has been the gold standard for AML response, novel therapies with different response dynamics warrant re-evaluation of response criteria. CR with partial hematological recovery (CRh, bone marrow blasts ≤ 5%, ANC > 0.5 x 10^9 /L *and* platelet count >50 x 10^9 /L) has been employed as a surrogate marker for efficacy and clinical benefit.
Aims: We evaluated the impact of CRh on long-term outcomes of older pts with newly diagnosed AML treated with 10-day decitabine and venetoclax (DEC10-VEN, NCT03404193).
Methods: Patients with newly diagnosed AML ages >60 years, or secondary AML were included. Patients received decitabine 20 mg/m^2 IV for 10 days with oral venetoclax 400 mg daily for induction and decitabine for 5 days with daily venetoclax for consolidation. Definitions of best response were as following: CR (Bone marrow blasts ≤ 5% blasts, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease and ANC > 1 x 10^9 /L with platelet count >100 x 10^9 /L), CR with incomplete hematologic recovery, CRi (All CR criteria but with residual cytopenia such as ANC < 1 x 10^9 /L or platelet count <100 x 10^9 /L) and morphological leukemia free state, MLFS (CR criteria without hematologic recovery). Outcomes of interest included overall survival (OS) and event-free survival (EFS). Full study protocol and interim results have been published previously (DiNardo et al. Lancet Haematol. 2020;7:e724-36.)
Results: From January 2018 - February 2021 125 patients with a median age of 71 yrs (range 48-89) were included. 79 (63%) pts were newly diagnosed AML and 46 (37 %) had secondary AML with antecedent hematological disorder (**Figure 1**). 69 patients achieved CR (55%), 11 (8%) pts achieved CRh, 14 (11%) pts achieved CRi, 10 (8%) pts achieved MLFS and 21 (17%) pts were refractory. Of the 11 pts who met the criteria for CRh, 8 (73%) patients were previously classified as CRi and 3 (27%) as MLFS. Among 69 pts achieving CR, the median OS was 24.5 months (mo) and median EFS was 18.0 mo. CRh was achieved with a median of 1 (range 1-3) cycles. Median OS of CRh as compared to CRi was 16.9 vs 5.8 mo (HR 0.47, 95% CI 0.19-1.13, p=.06) and CRh vs MLFS was 16.9 vs 6.2 mo (HR 0.34, 95% CI 0.13-0.93, p=.007). Median EFS of pts with CRh vs CRi was 14.1 vs 5.8 mo (HR 0.49, 95%CI 0.21-1.14, p=.08) and CRh vs MLFS was 14.1 vs 6.2 mo (HR 0.37, 95% CI 0.14-1.01, p=.016). Pts achieving CRh defined a group with durable remission with duration of response of 6.0 vs 2.5 mo with CRi and 1 mo with MLFS. Additional analyses are ongoing and will be presented.

	n (%) median (range)
Patients	125
Age, years	71 [48-89]
Male sex	70 (56)
White blood cell count, x10^9/L	2.9 [0.3-25.5]
ECOG PS	0 - 17 1- 72 >2 - 36
Bone marrow blasts %	37.5% [2-90%]
Diagnosis	De novo - 79 (63) Untreated sAML with AHD – 20 (16) Treated sAML with AHD – 26 (21)
Mutations	*NPM1* – 27 *FLT3 ITD or TKD* – 21 *TP53* – 38 *RUNX1* – 20 *IDH1* – 10 *IDH2* - 19 *K/NRAS* - 28
ELM 2017 cytogenetic risk	Intermediate - 51 Adverse - 36 Insufficient metaphases - 1



Summary/Conclusion: In pts with newly diagnosed AML and secondary AML treated with DEC10-VEN, pts achieving CRh had a trend towards improved OS and EFS compared to pts with CRi or MLFS. These findings support the use of CRh as an endpoint demonstrating clinical benefit for patients receiving venetoclax-based therapy. Larger analyses are warranted.

EP467 ACTIVITY OF DECITABINE COMBINED WITH ALL-TRANS RETINOIC ACID IN OLIGOBLASTIC AML: RESULTS FROM A RANDOMIZED 2X2 PHASE II TRIAL

C. Rummelt [1,*], O. Grishina [2], C. Schmoor [2], M. Crysandt [3], E. Jost [3], F. Thol [4], M. Heuser [4], K. S. Götze [5,6], R. F. Schlenk [7,8,9], K. Döhner [7], H. R. Salih [10], M. M. Schittenhelm [11], G. Heil [12], C. Schwaenen [13,14], C. Mueller-Tidow [8,15,16], W. Brugger [17], A. Kündgen [18,19], U. Germing [18,19], M. de Wit [20], S. Kremers [21], A. Giagounidis [22], S. Scholl [23], A. Neubauer [24], J. Krauter [25], G. Bug [26,27], R. Wäsch [1], H. Becker [1,28], A. M. May [29], J. Duyster [1,28], A. Ganser [4], H. Döhner [7], B. Hackanson [1,30], M. Lübbert [1,28]

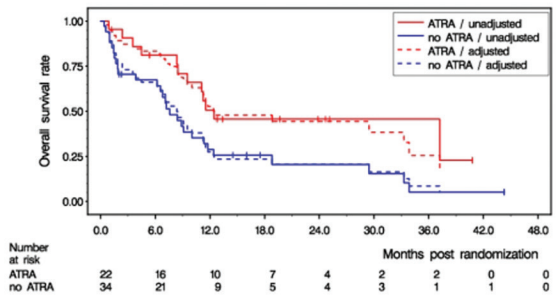
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Background: DNA-hypomethylating agents are the backbone for non-intensive combination treatments of AML/MDS patients (pts). In elderly AML pts, the decitabine (DAC) + all-trans retinoic acid (ATRA) combination resulted in an improved response rate and survival compared to DAC without ATRA (DECIDER, Lübbert et al., *J. Clin. Oncol.* 2020), also in pts with prior hematologic disorder (mostly MDS).
Aims: We hypothesized that the outcome of pts with oligoblastic AML may also be improved by the addition of ATRA to DAC. Therefore, pts from the DECIDER cohort with 20-30% bone marrow blasts were analyzed for clinical outcome in this exploratory subgroup analysis.
Methods: Key inclusion criteria: newly diagnosed pts >60 years (yr), unfit for induction with non-M3 AML, ECOG performance status (PS) 0-2. Treatment: DAC 20 mg/m^2 day 1-5 (treatment arms A/B/C/D), ATRA p.o. day 6-28 (arms C/D), VPA p.o. continuously from day 6 (arms B/D) of each 28-day course (repeated until relapse/progression, prohibitive toxicity, withdrawal or death). Key endpoints: objective response rate (ORR): CR/CRi/PR, overall (OS) and event-free survival (EFS). For a power of 80% (test in this phase II study at 1-sided alpha=0.1) for an

increase of ORR to 40% with ATRA or VPA, 176 pts were necessary, planned sample size 200. Between 12/2011 and 2/2015, 200 pts were randomized and treated. Efficacy analyses were performed in the intention-to-treat (ITT) population. ATRA was investigated by comparing arms C+D vs arms A+B, VPA by comparing arms B+D vs arms A+C, ORR was analyzed with logistic regression estimating odds ratios (OR), OS/EFS with Cox regression estimating hazard ratios (HR), each with 95% confidence intervals (CI), and presented with descriptive two-sided p values of the tests of no treatment effect.

Results: Bone marrow blasts were 20-30% (median, 25%) defining oligoblastic AML in 56/200 pts of the DECIDER cohort. The number of pts in the randomized arms were: 13 in arm A, 21 in arm B, 9 in arm C, 13 in arm D. Baseline pt characteristics: male 77%, median age: 75 yr (range 61-88), median WBC: 3400/µl (range 500-52,600), adverse genetics (ELN 2010) present in 25%, ECOG 2 in 13%, comorbidities (HCT-CI) ≥ 3 in 48%, AHD in 68%, tAML in 11%. A median of 5 DAC courses were administered (per arm: 2/5/11/4). Six pts attained a CR, 7 pts a CRi, and 1 pt a PR, resulting in an ORR of 25% (arm A: 7.7%, arm B: 28.6%, arm C: 33.3%, arm D: 30.8%, respectively). Effect on ORR of ATRA vs no ATRA (31.8 vs 20.6%): OR 1.85, CI [0.54,6.37], p=0.33; and of VPA vs no VPA (29.4 vs 18.2%): OR 1.93, CI [0.51,7.24], p=0.33. With 40 deaths out of 56 pts, median OS was 9.5 mths (arm A: 7.6 mths, arm B: 8.9 mths, arm C: 37.2 mths, arm D: 11.2 mths, respectively). Effect on OS of ATRA vs. no ATRA (12.5 vs 7.6 mths median OS, Fig. 1): HR 0.47, CI [0.24,0.94], p=0.032 (after adjustment for PS, HCT-CI, WBC, LDH, genetic risk: HR 0.42, CI [0.19,0.90], p=0.025); and of VPA vs. no VPA (10.0 vs 8.4 mths median OS): HR 0.99, CI [0.51,1.92], p=0.98. A comparable benefit on EFS of ATRA vs. no ATRA (but not VPA vs. no VPA) was observed.

Fig. 1: Overall survival of patients with oligoblastic AML is improved when decitabine is combined with ATRA (red curves) compared to decitabine without ATRA (blue curves, Kaplan-Meier method). Solid curves: unadjusted; broken curves: adjustment for performance status (ECOG), comorbidities (HCT-CI), WBC, LDH, genetic risk (ELN 2010)



Summary/Conclusion: In elderly pts with oligoblastic AML ineligible for induction chemotherapy, the addition of ATRA, but not VPA, to DAC resulted in a clinically meaningful survival benefit. It is tempting to speculate that the combination of an HMA with a retinoid may also be active in MDS pts with excess of blasts. In this regard, a novel and potent RARα receptor agonist (SY-1425) is under clinical development combined with an HMA in AML/MDS (De Botton S. et al., *ASH Abs. 112*, 2020).

EP468 FLT3 INHIBITOR BASED INDUCTION AND ALLOGENEIC STEM CELL TRANSPLANT IN CR1 IMPROVE OUTCOMES IN PATIENTS WITH NEWLY DIAGNOSED AML VERY LOW FLT3 ALLELIC BURDEN

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Background: The use of FLT3 inhibitors (FLT3i) has improved overall survival (OS) in patients with newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML). However, the role of FLT3i in patients with very low *FLT3*-ITD allelic burden is unclear.

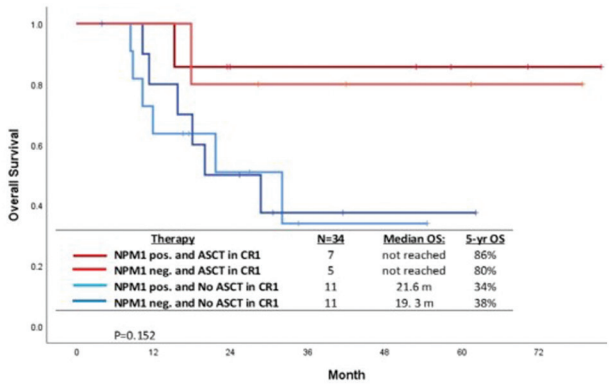
Aims: To analyze the role and impact of FLT3i's, NPM1 co-mutation, and allogeneic stem cell transplantation (ASCT) in patients with a very low FLT3 allelic burden.

Methods: A multiplex PCR-based DNA analysis followed by capillary electrophoresis was utilized to detect *FLT3*-ITD mutations at diagnosis and relapse. Allelic frequency (AF) is defined as the ratio of mutated *FLT3*-ITD divided by wild type plus mutated FLT3-ITD. We identified 50 patients with newly diagnosed AML (excluding core-binding factor AML and acute promyelocytic leukemia) from 2012 – 2020 at our institusion who had a *FLT3*-ITD AF ≤0.10 (i.e. ≤10%) at baseline.

Results: Of the 50 patients, 30 (60%) received frontline therapy not including a FLT3i (no FLT3i cohort), and 20 with a FLT3i (FLT3i cohort) containing regimen. Patients in the FLT3i cohort were younger than the no FLT3i cohort (median age 58 [28-83] vs. 67 [23-84] years old, p=0.03), and more often received intensive (cytarabine and antracycline based) induction (80% vs 43%, p=0.01). Otherwise, there were no other significant baseline clinical difference between the two cohorts. Baseline median ITD AFs were not significantly different between FLT3i (0.05) and no FLT3i (0.03) cohorts. Of the 20 patients in FLT3i group, 19 (95%) received sorafenib, and 1 (5%) received quizartinib based therapies.

Overall, 37 of 50 (74%) patients achieved a complete remission (CR). With a median follow-up of 42 months, 12 (32%) patients relapsed. The incidence of *FLT3*-ITD positivity at relapse was 42% (5 of 12). All *FLT3* positive relapses were identified in the no FLT3i cohort (5 of 8), with no FLT3 positive relapses observed in the FLT3i cohort (0 of 4): 63% vs. 0%, respectively (p=0.04). There was a trend for better OS in the FLT3i cohort compared with no FLT3i cohort, not reached vs. 17 months (p=0.31). The 5-year OS rate was improved in patients who received a FLT3i with induction and ASCT compared with patients who did not receive a FLT3i with induction and did not receive ASCT (100% vs 27%, p=0.08).

Overall, 14 patients underwent ASCT (6 FLT3i and 8 no FLT3i cohort) in first remission with a median time to ASCT from induction of 114 days (range 79-230 days). A landmark analysis (at 3-month post ASCT) showed that 5-year OS rate was superior in patients who underwent ASCT in CR1 (N=14) compared with those who did not (N=22), 85% vs. 34%, respectively (p=0.01). Interestingly in this low FLT3-ITD VAF (≤0.1) population the 5-year OS in patients with NPM1 co-mutation who received ASCT (N=7), NPM1 without ASCT (N=11), no NPM1 with ASCT (N=5), and no NPM1 without ASCT (N=11) were 86%, 34%, 80%, and 38%, respectively (p=0.15) [Figure].



Summary/Conclusion: The use of FLT3i reduced the incidence of FLT3 positive relapses. The use of FLT3i with induction and ASCT showed improved OS in AML patients with very low FLT3-ITD AFs. Even among patients with very low FLT3-ITD VAF and NPM1 comutations, ASCT appeared to improve 5-year OS (86% vs 34%). We recommend that all FLT3-ITDm patients receive a FLT3i with induction and be considered for ASCT in CR1 irrespective of baseline FLT3 AF and/or NPM1 co-mutation status. To better understand the impact of very low FLT3 burden, future clinical trials investigating FLT3i should include low VAF FLT3-mutated AML patients.

EP469 RE-STRATIFYING THE PROGNOSES OF ACUTE MYELOID LEUKEMIA PATIENTS WITH CEBPA DOUBLE MUTATIONS BY CSF3R MUTATIONS AND MINIMAL RESIDUAL DISEASE

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Background: Although AML with *CEBPA*^{dm} indicates a favorable outcome, both our study and data from other studies showed that approximate half of the patients finally relapsed consolidated with chemotherapy alone. Therefore, the heterogeneity of acute myeloid leukemia (AML) with *CEBPA*^{dm} attracts much attention in recent years.
Aims: The aim of this study was to evaluate the influence of *CSF3R* mutations and chemosensitivity indexes on prognoses of AML patients with *CEBPA*^{dm}.
Methods: Sixty-six AML patients with complete genetic mutations and sequential minimal residual disease (MRD) information were retrospectively analyzed in this study.
Results: In AML patients with *CSF3R* mutations, 56.25% (9/16) of the patients achieving negative MRD after two courses of chemotherapy, which was significantly lower than those without mutation (82.00%, 41/50, P = 0.049). Both *CSF3R* mutations and MRD status after the second course of chemotherapy associated with long-term outcomes of patients. *CSF3R* mutated patients showed inferior relapse-free survival (RFS) (5-year RFS: 15.19% *vs.* 38.7%, *P* = 0.006) and overall survival (OS) (5-year OS: 8.2% *vs.* 60.6%, *P* = 0.038) compared with those with wide-type *CSF3R*. Negative MRD after the second course of chemotherapy was also an unfavorable indictor for both RFS (5-year RFS: 0.00% *vs.* 45.5%, *P* = 0.004) and OS (5-year OS: 0.00% *vs.* 65.4%, *P* = 0.050). Finally, a new prognostic model was proposed for AML with *CEBPA*^{dm} in this study.
Summary/Conclusion: Both *CSF3R* mutations and positive MRD after the second course of chemotherapy were associated with poor outcomes for AML patients with *CEBPA*^{dm}. An integrity model based on *CSF3R* mutations and MRD status may be beneficial for evaluating the prognoses of these patients.

EP470 SUPERIOR OUTCOMES FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION IN FIRST REMISSION FOR NPM1/FLT3-ITD MUTATED AML

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Background: Multiple studies have revealed the prognostic utility of combining *FLT3*-ITD and *NPM1* mutation status to identify patients benefiting from allogeneic stem cell transplantation (alloSCT) in first remission (CR1). In recent years, analysis of peripheral blood measurable residual disease (MRD) has superseded genetic risk stratification for *NPM1* mutated (*NPM1*+) AML within the UK. This strategy aims to reduce SCT-related toxicity, but requires demonstration of chemo-sensitivity at relapse for higher-risk genotypes, in particular patients with *FLT3*-ITD mutations.
Aims: We aimed to assess clinical outcomes in *NPM1*+ AML, comparing the impact of *FLT3*-ITD mutations in patients receiving consolidation with chemotherapy versus alloSCT in CR1 and reviewing responses to second-line therapies at relapse.
Methods: Retrospective analysis identified 115 patients with *NPM1*+ AML eligible for intensive therapy between 2014-2020. The median age was 59y, 53% were male and median follow-up was 3.2y. *FLT3*-ITD mutations were detected in 38% of cases (*NPM1*+/*FLT3*-ITD+, n=44), for the purposes of this study, *FLT3* tyrosine kinase domain mutations (n=16) were classified as *FLT3*-ITD negative (*FLT3*-ITD-ve) AML.
Results: CR rates were comparable for both *FLT3*-ITD+ and *FLT3*-ITD-ve cases following induction therapy (91% vs 94%, p=0.48). Within *FLT3*-ITD+ cases, 32% (n=14) underwent alloSCT in CR1, compared with only 11% (n=8) of *FLT3*-ITD-ve cases. Notably, *FLT3*-ITD+ AML demonstrated lower survival (hazard ratio, 2.18, p=0.02) and a higher risk of relapse (HR 1.88, p=0.03) compared to *FLT3*-ITD-ve cases, regardless of therapy.
Further analysis revealed a significantly higher risk of relapse (HR 3.84, p=0.02), inferior median disease-free survival (0.80y vs not reached, p=0.002) and median overall survival (1.21y vs not reached, p=0.02) for *FLT3*-ITD+ cases receiving chemotherapy consolidation, compared with alloSCT in CR1. Interestingly, the small number of *FLT3*-ITD-ve cases undergoing alloSCT in CR1 (n=8) also demonstrated superior outcomes, with no deaths or relapses, compared with those receiving chemotherapy alone (median DFS not reached vs 2.0y, p=0.03 and median OS not reached vs 5.7y, p=0.34), Fig 1 a) and b).
Relapse was observed in 47% of patients receiving chemotherapy alone (n=44); of these cases 39% (n=17) were *FLT3*-ITD+ and exhibited a significantly shorter median time to relapse vs *FLT3*-ITD-ve cases (247 days vs 413 days, p=0.01). In contrast, only 18% (n=4) of all patients undergoing alloSCT in CR1 relapsed and each harboured *FLT3*-ITD mutations. Importantly, 52% (n=14) of *FLT3*-ITD-ve cases achieved a second remission (CR2) with chemotherapy, while only 24% (n=5) of *FLT3*-ITD+ cases were able to reach CR2 (p=0.049 [data precede availability of Gilteritinib at relapse]). These findings highlight the chemo-refractory nature of relapsed *FLT3*-ITD mutated AML, with a significantly reduced median survival post-relapse, compared with *FLT3*-ITD-ve cases (0.5y vs 1.1y, p=0.03).

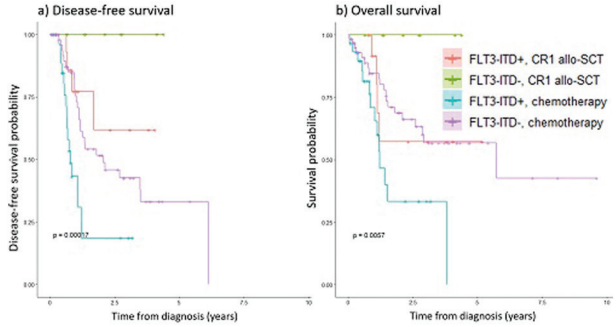


Figure 1. (a) Disease free survival (DFS) (b) Overall survival (OS) for NPM1+ AML cases comparing FLT3-ITD positivity and consolidation with chemotherapy vs alloSCT in CR1. Both median DFS and OS were significantly improved in FLT3-ITD+ patients undergoing alloSCT vs consolidation with chemotherapy alone.

Summary/Conclusion: This study demonstrates favourable survival for patients with *NPM1*+/*FLT3*-ITD+ AML undergoing alloSCT in CR1. Significantly higher relapse rates were observed in *FLT3*-ITD+ cases treated with chemotherapy alone, followed by poor responses to salvage chemotherapy and fewer patients achieving CR2. Collectively, our data suggest that alloSCT consolidation should be prioritised in *NPM1*+/*FLT3*-ITD+ AML to achieve improved long-term outcomes within this higher risk cohort.

EP471 EFFICACY AND SAFETY OF ENASIDENIB AND AZACITIDINE COMBINATION IN PATIENTS WITH IDH2 MUTATED ACUTE MYELOID LEUKEMIA AND NOT ELIGIBLE FOR INTENSIVE CHEMOTHERAPY

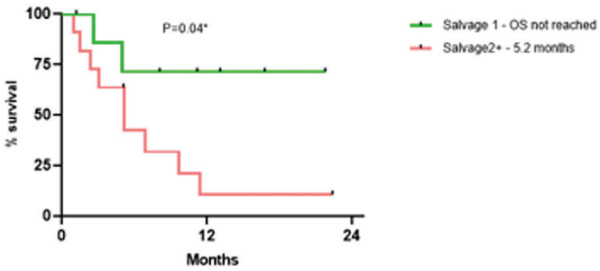
S. Venugopal [1,1,*], K. Takahashi [1], N. Daver [1], G. Borthakur [1], S. Loghavi [2], N. J. Short [1], M. Ohanian [1], L. Masarova [1], G. C. Issa [1], C. Bueso-Ramos [2], M. Yilmaz [1], T. Kadia [1], M. Andreef [1], F. Ravandi [1], M. Konopleva [1], H. Kantarjian [1], C. DiNardo [1]

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Background: ENA is approved in the US for adult pts with relapsed/refractory (R/R) m*IDH2* AML. Azacitidine (AZA) is a hypomethylating agent that prolongs survival *vs*. conventional care regimens in older unfit pts with newly diagnosed (ND) AML. *In vitro*, combination ENA + AZA enhances cell differentiation. Venetoclax (VEN), a small molecule BCL2 inhibitor (i) is also effective in m*IDH2* AML related to 2-hydroxyglutarate mediated inhibition of cytochrome C oxidase. In preclinical models, the combination of ENA+VEN demonstrates synergistic anti-leukemic activity.
Aims: Evaluate the efficacy and safety of combination ENA + AZA +/- VEN in ND and R/R m*IDH2* AML
Methods: Patients (pts) with documented m*IDH2* AML: ≥ 60 yrs with ND AML and ineligible for intensive chemotherapy; >18 yrs with secondary AML (sAML) and/or R/R AML were enrolled. All pts received AZA 75 mg/m2/d x 7 d/cycle and ENA 100 mg QD continuously on NCT03683433. Cytoreduction prior to start, and concomitant BCL2 i and FLT3 i were allowed as indicated. Primary objective was overall response rate (ORR) and secondary objectives included safety and overall survival (OS).
Results: This high-risk cohort included 26 patients with a median age of 68 years (46% of pts ≥70 yrs), 28% pts had ECOG PS ≥2, 42% had received ≥2 salvage therapy, and 41% pts had ELN2017 adverse-risk AML (Table 1). 30 and 60-day mortality were both 0 for ND pts,5% and 5%, respectively, in R/R pts. Treatment-emergent adverse events (TEAE) of grade 3-4 were reported in 22/26 pts (85%), with the most frequent TEAEs including febrile neutropenia (23%), indirect hyperbilirubinemia (35%), and vomiting and diarrhea (12% each). Most AEs were manageable without dose interruption. Differentiation syndrome was reported in 2 pts (8%), occurring on days 18 and 31 of treatment.

The CR/CRi rate in ND AML was 100% (n=7/7), and in R/R AML was 58% (n=11/19) (Table). CR/CRi rate was 75% in pts in first relapse (n=6/8); and 45% in ≥2 relapse (n=5/11). CR/CRi rate in pts with prior HMA was 67% (n=6/9), in pts with prior ENA was 75% (n=3/4), and in pts with prior stem cell transplantation (SCT) was 60% (n=3/5). 39% of all responders (n=7/18) achieved MRD negativity by flow cytometry (MRD ^{neg} FCM) and MRD ^{neg} status was associated with longer OS (NR vs 6.9 mo, HR 0.16, 95% CI 0.05-0.5, p=0.04). At median follow-up of 13.1 months (mo), the 1-year OS in ND AML was 85%, in first relapse was 75%, in ≥2 relapse was 10%. Median OS was not reached in ND AML; Pts treated in first relapse had a significantly superior OS than those in ≥2 relapse. (median OS not reached vs 5.2 mo; HR 0.24, 95% CI 0.07-0.79, p=0.04, Fig.)
In the m*IDH2* R/R AML cohort, 7 pts received the ENA+AZA+VEN triplet, among which 4 had received prior HMA and one had received prior HMA and ENA separately. None had received prior VEN. The CR/CRi rate was 86% (n=6/7) with 33% MRD^{neg} FCM (n=2/6) with one patient proceeding to SCT. At a median follow up of 11.2 mo, median OS was not reached, and 6-mo OS was 70% in those who received ENA+AZA+VEN. With a median follow-up of 13.1 mo, 38% (n=9) remain on treatment and 54% alive (n=14) at last follow up. Reasons for treatment discontinuation(n=17): relapse (n=1, 4%), SCT (n=4, 15%), death (n=8, 31%), refractory disease (n=3, 12%), and personal choice (n=1,4%).

	ND N= 7	R/R N=19
ORR, n (%)	7 (100)	11 (58)
Complete remission (CR)	5 (72)	5 (26)
MRD neg CR	5 (100)	2/5 (40)
Complete remission with incomplete hematological recovery	2 (28)	6 (32)
Not evaluable	0	1 (5)
No response	0	7 (37)
Median number of cycles given (range)	3 (1-8)	4 (1-17)
Median time to best response, months (range)	1.6 (1.0-4.2)	1.8 (0.8-5.4)



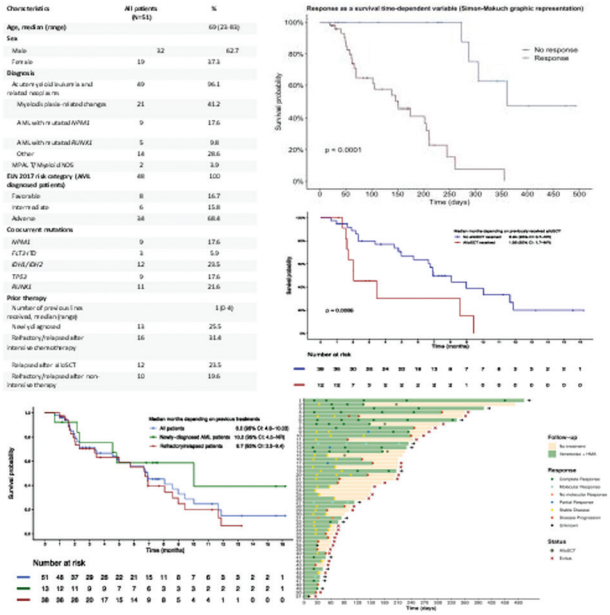
Summary/Conclusion: AZA+ENA is an effective therapy for IDH2-mutated AML.ENA+AZA+VEN may be an effective combination therapy for mIDH2 R/R AML, even in patients having received prior enasidenib.

EP472 REAL-LIFE PRELIMINARY EXPERIENCE OF TREATMENT OF NEWLY-DIAGNOSED AND REFRACTORY/RELAPSED (R/R) ACUTE MYELOID LEUKEMIA PATIENTS WITH COMBINATION OF VENETOCLAX WITH HYPOMETHYLATING AGENTS

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Background: Combination of venetoclax (Ven), a specific BCL-2 inhibitor, with hypomethylating agents (HMA) provides a clinical benefit to newly-diagnosed acute myeloid leukaemia (AML) patients ineligible for standard chemotherapy, with a reported overall response rate over 60% and a low early death rate, improving previous results obtained with HMA monotherapy (DiNardo CD, et al., NEJM 2020). Moreover, role of VenHMA is being explored in other clinical settings. In 2019 we introduced in our institution this regimen for both patients with newly-diagnosed AML (ND-AML) ineligible patients for standard chemotherapy and R/R AML without alternative salvage options.
Aims: Herein, we present the outcome of the patients treated with VenHMA, focusing on the analysis of possible predictors of clinically meaningful benefit.
Methods: We analyzed the overall response and follow-up of 51 patients diagnosed with AML and mixed-phenotype acute leukaemia (MPAL, n=2) who received a combination of off-label venetoclax (400mg/24h; initial ramp-up 100-200-400mg in 3 consecutive days, with dose adjustment in patients who also received CYP3A4 inhibitors), with standard-dose azacytidine (75mg/m^2) or decitabine (20mg/m^2) from March 2019. Response to treatment was evaluated following the European LeukaemiaNet 2017 criteria. Effect of response in overall survival was evaluated as a time-dependent variable (Mantel-Byar method, Simon-Makuch survival plot). Event was defined as death, progressive disease or refractoriness to treatment.
Results: Characteristics of our cohort are described in table 1. Notably, our cohort was enriched with high-risk ELN subtypes, in two thirds of patients. Median number of VenHMA cycles received was two (range 1-11), with on-going treatment in 14 patients. Early mortality in the first 30 days was only 2% (1 patient). Response rate (Complete response (CR) + complete response without haematological recovery (CRi) + partial response (PR)) was 54% in ND-AML (CR= 23%) and 29% in R/R AML (CR= 12%) with a median of one cycle to achieve the best response (range: 1-5). Four patients were treated in a molecular-MRD positive status, 3 of them achieving a molecular response (3/3 *NPM1*mut AML). Four patients proceeded to an allogeneic haematopoietic cell transplantation (alloHSCT). Median overall survival in the cohort was 6.9 months (1.52). Median overall survival was respectively 10 months (2.78) in ND-AML patients and 6.7 months (1.8) in R/R AML patients. 6-month overall survival was 56.2% (14.9) and event-free survival was 6.6 months. Response to treatment after two cycles, estimated with Mantel-Byar method, segregated two groups of patients, with an overall survival of 12 months in patients who achieved a CR/CRi versus 5 months in non-responders (p<0.0001). Furthermore, patients treated after alloHSCT relapse presented a dismal outcome (6.94 vs. 1.88 months, p<0.001). There were no other significant clinical or biological variables able to predict outcome.



Summary/Conclusion: VenHMA is a highly active low-intensity regimen associated to a relatively low toxicity profile, providing a meaningful antileukaemic effect in a subset of patients not considered appropriate for higher intensity regimens, including the possibility to bridge some patients to alloHSCT. Despite the precise subset of patients who can

benefit from this combination is still uncertain, especially in the R/R AML setting, its role in post-alloHSCT failure seems very limited. Early scope of response allows a rapid identification of those patients who benefit from continued treatment with VenHMA.

EP473 PROGNOSTIC SIGNIFICANCE OF ACHIEVING A COMPLETE REMISSION AFTER ONE OR TWO CYCLES OF INDUCTION CHEMOTHERAPY IN NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: ANALYSIS OF DATA FROM THE DATOOL-AML DATABASE

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Background: The achievement of a complete remission (CR) of acute myeloid leukemia (AML) after induction chemotherapy is an important factor for long-time survival. A good effect of the 1st induction cycle is a reduction of blast count to <5% in bone marrow on the day 15 or at the time of the blood count restitution. Otherwise, the patients receive the 2nd induction cycle, which can be based on the repeated 7+3 regimen as in the 1st induction cycle, or on a regimen with high-dose cytarabine. Resistant disease after the 2nd induction cycle has a poor prognosis. However, the prognosis of patients who achieved CR only after the 2nd induction cycle, compared to patients who achieved CR after the 1st induction cycle, is less clear.
Aims: First, to assess whether the relapse free survival (RFS) and the overall survival (OS) of patients who achieved CR only after the 2nd induction cycle differ from those who achieved CR after the 1st induction cycle. Second, to assess whether the type of regimen of the 2nd induction cycle (high-dose cytarabine regimens versus 7+3 regimen) correlates with CR rate, early death rate, RFS and OS of patients.
Methods: A retrospective analysis of real-world nationwide data from the database DATOOL-AML. Intensively treated adult patients with newly diagnosed AML (except AML M3) were included. The study period was 2007-2019.
Results: During the study period, 1010 patients (pts.) have initiated intensive induction chemotherapy; 631 (62.5%) pts. achieved CR after the 1st induction cycle (*CR I group*) and 191 (18.9%) pts. achieved CR only after the 2nd induction cycle (*CR II group*). The median age was 53 (18-74), the median follow-up was 24.7 months. There was a significantly higher proportion of intermediate I, intermediate II and adverse risk patients (ELN 2010 risk category) in the *CRII group*. On the contrary, the frequency of favorable risk patients in the *CR II group* was significantly lower, see Table 1. Allogeneic hematopoietic stem cell transplantation (HSCT) in the first CR was performed more frequently in *CR II group* and the difference was most evident in low and intermediate I risk categories, see Table 1. At 4 years, RFS of pts. in *CR I group* and in *CR II group* was 39.0% and 38.0%, respectively (p=0.179). At 4 years, OS of pts. in *CR I group* and *CR II group* was 52.6% and 46.2%, respectively (p=0.069). The high-dose cytarabine regimens administered during the 2nd induction cycle did not differ regarding the CR rate or early death rate in comparison to 7+3 regimen. CR rate after high-dose regimens versus 7+3 regimen was 62.4% and 69.8%, respectively (p=0.656), and early mortality rate was 6.6% and 4.7%, respectively (p=1.000). At 4 years, RFS of pts. treated by high-dose cytarabine regimens versus 7+3 regimen was 38.0% and 40.7% (p=0.449), and OS at 4 years was 43.3% and 68.8%, respectively (p=0.267).

	CR after the 1st induction cycle N (%)	CR after the 2nd induction cycle N (%)	P-value
Overall	631	191	x
ELN 2010 Category			
Favorable	216 (36.4)	19 (10.6)	<0.001
Intermediate I	221 (37.3)	82 (45.8)	0.049
Intermediate II	73 (12.3)	34 (19.0)	0.023
Adverse	83 (14.0)	44 (24.6)	0.001
Missing	38	12	x
Allo HSCT in 1st CR	245 (38.8)	128 (67.0)	0.001
Favorable	31 (14.4)	11 (57.9)	<0.001
Intermediate I	107 (48.4)	55 (67.1)	0.004
Intermediate II	38 (52.1)	23 (67.6)	0.147
Adverse	45 (54.2)	33 (75.0)	0.023

Summary/Conclusion: We did not demonstrate any difference in RFS in patients who achieved CR after the 2nd induction cycle compared to patients who achieved CR after the 1st induction cycle. There was a trend in inferior OS of patients who achieved CR after the 2nd induction cycle, but it was not statistically relevant. The results might be explained by the significantly higher number of allogeneic HSCT performed in the first remission in patients who achieved CR after the 2nd induction cycle. High-dose cytarabine reinduction regimens did not result in a substantial prolongation of RFS or OS compared to standard 7+3 regimen.

EP474 SORAFENIB IN COMBINATION WITH INTENSIVE CHEMOTHERAPY FOR RELAPSED OR REFRACTORY FLT3-ITD POSITIVE ACUTE MYELOID LEUKEMIA: A SINGLE-INSTITUTION EXPERIENCE

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Background: patients (pts) with relapsed/refractory (R/R) FMS-like tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML) have a poor prognosis. In this setting, response to salvage chemotherapy (CHT) alone has been unsatisfactory and first generation FLT3-inhibitors have shown limited activity in monotherapy. New selective and strong inhibitors, including the recently approved gilteritinib, are rapidly changing the treatment paradigm, being able to induce remission in a significant proportion of pts with limited toxicities. However, little is known about the efficacy and safety of intensive CHT combined with FLT3-inhibitors in R/R AML population.
Aims: we assessed the safety and efficacy of salvage chemotherapy in combination with the FLT3-inhibitor sorafenib in R/R AML pts.
Methods: we retrospectively analyzed R/R *FLT3*-ITD AML patients aged ≥ 18 years treated with intensive chemotherapy and sorafenib at our institution from July 2015 to December 2020. All patients had received a 3+7-like induction regimen with or without a FLT3 inhibitor. In case of refractoriness to induction or relapse, patients were treated with fludarabine and high-dose cytarabine-based chemotherapy plus sorafenib, at the dose of 400 mg BID for 14 days continuously after the end of CHT. The dose of sorafenib could be reduced in frailer patients.
Results: twenty-two pts were included, (male 59%), with a median age of 50 years (21-73). Eight pts (36%) harbored a *NPM1* mutation, 6 pts other molecular anomalies (*MLL*-PTD in 5, *IDH1* and *IDH2* in 1 each) and in 4 cases cytogenetic alterations were identified (+6, +8; -7; del7q). Sixty-four per cent of the pts (n=14) were refractory to induction, while 36% (n=8) relapsed after having achieved a remission. Complete remissions (CR) plus CR with incomplete hematologic recovery (CRi) after salvage CHT combined with sorafenib was of 63% (64% in refractory cases vs. 62.5% in relapsed ones). Patients with *NPM1* mutation had a CR/CRi rate of 88% vs. 50% in the remaining ones. After a median follow up of 45 months, median overall survival (OS) after salvage therapy was of 13 months, with 4-year OS of 35.9%. For the 14 patients achieving CR/CRi, median relapse-free survival (RFS) was of 5 months, with 4-year RFS of 35.7%. Consolidation with allogeneic stem cell transplantation (HSCT) was performed in 13 pts (59%), 4 of them with active disease. Median OS of transplanted pts was not reached, with 4-year OS of 50.4%. The most common toxicities of CHT plus sorafenib were neutropenic fevers (95%), gastrointestinal (54%) and hepatic (54%) and cutaneous (27%) toxicities, pneumonia (27%) and cardiac complications (18%). Grade 4 toxicities were observed in 3 pts (1 pneumonia, 1 neutropenic enterocolitis, 1 QTc prolongation).
Summary/Conclusion: sorafenib in association with high-dose CHT represented a feasible second line option for the treatment of *FLT3*-ITD positive R/R AML, with encouraging rates of CR/CRi, especially in *NPM1*-mutated cases, and roughly 50% of transplanted patients experiencing long-term survival. Toxicities were not negligible, but in line with those expected after intensive CHT in this population. The potential benefit of combining FLT3 inhibitors with intensive chemotherapy should be further explored in this setting for fit patients, and this strategy is currently under investigation in clinical trials testing new FLT3 inhibitors.

EP475 RISK FACTORS AND MANAGEMENT OF CATHETER-RELATED THROMBOSIS IN ADULT PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA

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Background: Newly-diagnosed acute myeloid leukemia (NDAML) patients (pts) frequently develop catheter-related thrombosis (CRT) despite concurrent thrombocytopenia. The risk of symptomatic CRT in these pts varies between 5%>10%. While risk factors for CRT occurrence in pts with solid tumors are well-established, such data in NDAML are scarce. CRT treatment in NDAML is challenging due to concomitant severe thrombocytopenia and high bleeding risk. Current treatment strategies include catheter removal and full/low dose anticoagulation supported by platelet transfusion. Modification of anticoagulant therapy is based on platelet counts, with predetermined cutoffs for dose adjustment (25-50x10^9) and treatment cessation (<25x10^9).
Aims: We aimed to identify risk factors for CRT development in NDAML and to assess the efficacy of anticoagulation [low molecular weight heparin (LMWH)] along with its complications.
Methods: This retrospective analysis included all consecutive pts treated at the Rambam Health Care Campus between 2006-2019 for NDAML using a central venous catheter (CVC). Data on patient demographics, clinical characteristics, lab results and vital signs at diagnosis were automatically collected using a designated big-data platform (MDClone, Beer-Sheba, Israel). Intensity of CRT treatment and related bleeding complications were recorded along with the rate of venous thromboembolism (VTE) recurrence. Rates or proportions were compared using t-test or Wilcoxon test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. A multivariable logistic regression analysis was performed.
Results: Out of 632 evaluable NDAML pts 64 (10.1%) developed CRT. In a univariate analysis, the following CRT risk factors were identified: AML subtype [non-acute promyelocytic leukemia (non-APL) vs. APL, OR 0.39; 95%CI 0.17-0.86; p=0.02)], BMI (OR 1.05; 95%CI 1.01-1.10; p=0.01), heart rate at diagnosis (OR 0.76; 95%CI 0.63-0.91; p=0.003), and history of prior VTE (OR 16.87; 95%CI 5.33-53.41; p<0.001). In multivariate analysis, BMI, heart rate and history of prior VTE provided a good prediction model (C-Statistic 71.6%) (Table 1). While pts with CRT had lower platelet levels at diagnosis (107000; SD 148000 vs. 146000; SD 139; p=0.003), this parameter was found to be a poor CRT predictor (ROC curve area-under-curve 61.4%; 95%CI 54.1%>68.7%). The CVC was removed in 51 (80%) of 64 pts, which was in most cases associated with catheter-related bloodstream infection (p=0.050). Pts treated with full-dose LMWH were more likely to suffer from gastrointestinal bleed than those receiving reduced dose or no anticoagulant at all (p=0.003). There was no significant difference in blood products use before or after CRT-related anticoagulant treatment initiation (blood product per week per each patient). The lack of correlation between CRT or anticoagulation and blood product use could be explained by other medical conditions requiring blood transfusion (e.g., symptomatic anemia, severe thrombocytopenia).
At a mean follow-up of 2.9 years, CRT recurrence was recorded in 8 pts (12.5%). There was no difference in CRT recurrence between pts treated with different anticoagulant doses (p=0.40).

Table 1: Multivariate logistic regression analysis of CRT risk factors

	Adj. OR	95%CI		P-value
		Low	High	
BMI	1.086	1.034	1.140	0.0009
Heart rate ¥	0.756	0.622	0.919	0.0050
Prior VTE	16.034	5.852	43.932	<.0001

¥ For 10 unit increase; Adj. OR = adjusted odds ratio
Hosmer and Lemeshow Goodness of fit p=0.5717; C-statistics = 71.6%

Summary/Conclusion: In this large cohort of NDAML patients treated at a tertiary care center, BMI, heart rate and history of prior VTE emerged as significant CRT risk factors. Neither complete blood count nor platelet levels were found to be reliable CRT predictors. Importantly, platelet count-based modification of anticoagulation dose appeared to be efficacious and relatively safe.

EP476 INVESTIGATING THE INCIDENCE OF SECONDARY PRIMARY CANCER IN ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS

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Background: With the advance of diagnostic tools, standard of cares and therapeutic strategies, there is an obvious improvement in terms of overall survival and clinical responses in patients with acute promyelocytic leukemia (APL). In comparison with other hematological malignancy, APL has been now considered a highly curable disease, with 2-year event-free survival rates of 75–84%. Most cases achieved complete remission status after induction and consolidative therapies, which only required regular follow-up in outpatient department. In line with this, the incidence of second primary malignancies (SPMs) among APL survivors would be expected and investigated further.
Aims: Despite the fact two studies have reported the incidence and cancer types of SPM in APL patients, the data still remain unclear in Asia APL patients. We aim to investigate the incidence, types and possible risk factor of SPM comprehensively through a national wide database.
Methods: Through a longitudinal and nationwide database- the National Health Insurance database (NHIRD), totally 492 APL cases were enrolled into this retrospective analysis. SPM was investigated in different APL populations undergoing ATRA (vesanoid) alone or ATRA and ATO (arsenic trioxide) with/without chemotherapy. Additionally, in order to deciphering molecular association behind this notion, a public genomic database (GSE 155779) was utilized for further analysis the effect of these therapeutic agents in APL cases.
Results: Two different study groups were identified, which included the patients with APL undergoing ATO/ATRA or ATRA alone. In APL patients under ATO/ATRA or ATRA alone, SPM was identified in 30 out of 246 cases and 40 cases out of 246 cases in these study cohorts, respectively. Looking into detailed distribution of cancer types, SPM included malignant melanoma, breast, pancreatic, liver, lung, bladder and hematopoietic malignancy in both APL group. Intriguingly, the majority of SPM is acute lymphocytic leukemia in both study cohorts. GSEA analysis demonstrated gene signatures in terms of cytokine response, NF-kB inflammatory signaling and angiogenesis pathways are enriched positively in NB4 cells undergoing ATRA treatment compared to NB4 control groups. Surprisingly, MLL-AF4 fusion target gene signatures are also enriched in NB4 cells with ATRA treatment group, which indirectly unveiled a possible explanation regarding an increased incidence of ALL among APL patients treated with ATRA or ATRA/ATO in our study.
Summary/Conclusion: In the current study, our results raised a consideration regarding the incidence and detailed cancer types of SPM in APL cases. Otherwise, this study demonstrated a distinctive distribution of SPM compared to previous studies.

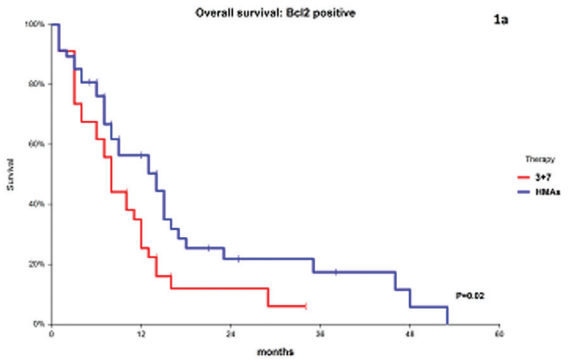
EP477 BCL-2 EXPRESSION IN ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS AND IMPACT ON OUTCOMES ACCORDING TO DIFFERENT THERAPEUTIC STRATEGIES

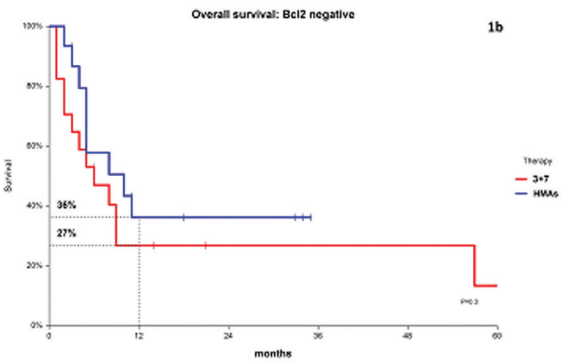
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Background: Bcl-2 overexpression has been associated with resistance to chemotherapy and reduced survival in acute myeloid leukemia (AML), but few data are available in elderly patients, a subset accounting for majority of AML cases and with dismal prognosis. Promising results have been reported with the use of bcl-2 inhibitor venetoclax.
Aims: We aimed to elucidate the prognostic role of bcl2 expression in elderly AML and its impact on outcomes across different therapeutic strategies, i.e. conventional 3+7 chemotherapy or hypomethylating agents (HMAs).

Methods: We retrospectively analyzed 114 AML patients aged >65 years treated with induction 3+7 chemotherapy (n=51) or HMAs decitabine or azacytidine (n=62) at the Division of Hematology of the University of Udine from 2010 to 2019. Bcl-2 expression on leukemic blasts was tested by flow cytometry, results were expressed as the mean fluorescence index (MFI) and bcl-2 was considered overexpressed for an MFI ≥17). Complete remission (CR) was defined according to conventional ELN 2017 criteria after one 3+7 course or 3-4 HMAs cycles; overall survival (OS) probability was estimated by the KM method.
Results: The characteristics of the 114 patients at diagnosis were: median age 68 years (range: 65-85); de novo AML n=49 (43%) and secondary AML n=65 (57%); leukocytes >30x10^9/L n=27 (24%); CD34-positive n=91 (80%); CD56-positive n=36 (32%); ELN 2017 genetic risk: favorable n=17 (15%), intermediate n=48 (42%), adverse n=49 (43%). Fifty-one patients (45%) received 3+7 induction chemotherapy while 62 patients (55%) were treated with HMAs.
Bcl-2 was expressed in 81 patients (71%), without differences according to clinical and biological variables in bcl-2 positive and negative AML. CR was achieved in 36%, being equal in bcl-2+ and bcl-2- patients; in bcl-2 positive cases, CR rate was higher with HMAs (20/44, 45.5%) than with 3+7 (8/34, 23.5%; p=0.04). One-year OS in the entire population was 39%, without differences among bcl-2+ (42%) and bcl-2- (32%) cases and with a trend toward a superior 1-year OS in patients treated with HMAs compared to 3+7 (51% vs 26%, p=0.07). The only factors affecting survival in multivariable analysis were WBC count (OR=3.2) and ELN risk (OR=3.0 for intermediate risk and OR=15.8 for adverse risk). While bcl-2 expression and induction therapy per se had no impact on OS in the whole cohort, when analyzing patients according to bcl-2 expression we found a significant better survival with HMAs than chemotherapy in bcl-2 positive cases (1-year OS 56% vs 25%, p=0.02, OR=1.8 – figure 1a) while no differences were found in bcl-2 negative ones (1-year OS 36% with HMAs and 27% with 3+7, p=0.3 – figure 1b).





Summary/Conclusion: Bcl-2 overexpression was not associated with inferior CR rate or survival in elderly AML, but bcl-2 positivity, that is preeminent among patients over 65 years, seems to be associated with a more favorable response to HMAs compared to conventional chemotherapy. Thus, the combination of HMAs with venetoclax appears to be particularly appealing in bcl-2 overexpressing patients.

EP478 ABERRANT CD7 EXPRESSION IN PEDIATRIC ACUTE MYELOID LEUKEMIA: SIGNIFICANCE AND CLINICAL IMPLICATIONS

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Background: CD7 is a lymphoid marker that can be aberrantly expressed in Acute Myeloid Leukemia (AML). Several studies have investigated the significance of this marker in adult AML, but the significance is still unclear.
Aims: We investigated CD7 expression in newly diagnosed pediatric AML and correlated with clinical and genetic features and outcomes.
Methods: We retrospectively reviewed data from 55 pediatric patients diagnosed with *de novo* AML from January 2010 to December 2020. AML diagnosis was assessed according to World Health Organization (WHO) criteria. All patients were enrolled in the Italian Association of Pediatric Hematology Oncology (AIEOP) AML 2002/01 and AML 2013/01 protocol. They were risk stratified and treated according to their respectively assigned protocol.
Induction chemotherapy was similar for the two clinical trials, while consolidation was based on risk stratification (standard vs high) for the first protocol and on risk stratification (standard, intermediate and high) and donor availability in the second. Patients with Down Syndrome AML underwent specific treatment. One CD7+ patient initially with ALL features was treated on the AIEOP LLA 2000R protocol, then was treated with AML-directed protocol (IDA FLA) since they were refractory to first line.
Results: Patients, disease and transplant characteristics are summarized in the Table. Thirty-five (64%) and 20 (36%) patients presented with CD7- and CD7+AML, respectively, four CD7+AML patients were with Down Syndrome (p=0.006).
Eleven/20 (55%) and 17/35 (49%) were male and median age was 7 and 8 years, among the CD7- and CD7+ subgroups, respectively.
Twenty-three (66%) and 8 (40%) patients underwent Allogenic Hematopoietic Stem Cell Transplantation (allo-HSCT) in the CD7+ and CD7- subgroups.
Measurable Residual Disease (MRD) on day +33, +78 (first and second time-points) and before transplant was negative in 22 (63%), 23 (66%), 17 (74%) and 12 (60%), 13 (65%), 5 (62%) in CD7- and CD7+ subgroups, respectively. Cytogenetic abnormalities, usually associated to a favorable outcome such as t (8;21), inv (16) or t (16;16) were less frequent in CD7+ compared to CD7- subgroup (5% vs 29%; p=0.042). No difference in median OS was noted between the 2 subgroups as described in Table.

	Total Cohort	CD7$^+$AML	CD7$^-$AML
N (%)	55 (100)	20 (36)	35 (64)
Median Age, years (range)	8 (0-17)	7 (1-17)	8 (0-17)
Sex, Male (%)	28 (51)	11 (55)	17 (49)
Down syndrome, n (%)	4 (7)	4 (20)	0
1st line chemotherapy, n (%)			
AIEOP 2002/01	31 (56)	6 (30)	25 (71)
AIEOP 2002/01 Down	4 (7)	4 (20)	0
AIEOP 2013/01	19 (35)	9 (45)	10 (29)
AIEOP LLA 2006R	1 (2)	1 (5)	0
HSCT	31 (56)	8 (40)	23 (66)
MRD-negative, n (%)			
+ 33	34 (62)	12 (60)	22 (63)
+ 78	36 (65)	13 (65)	23 (66)
Pre-HSCT	22 (71)	5 (62)	17 (74)
Median OS, months (range)	NR (2-141)	NR (4-141)	NR (2-139)
2-year OS %	81	85	79
5-year OS %	74	79	72
Cytogenetic risk, except Down S., n (%)			
Standard	11 (20)	2 (10)	9 (26)
Intermediate	25 (55)	11(55)	14 (40)
High	14 (25)	2 (10)	12 (34)
No metaphases	1 (2)	1 (2)	0
Cytogenetic features, n (%)			
Diploid	12 (22)	6 (30)	6 (18)
t (6;9)	1 (2)	1 (5)	0
t (1;22)	2 (4)	1 (5)	1 (3)
t (8;21)	6 (11)	0	6 (18)
Inv (16) or t (16;16)	5 (9)	1 (5)	4 (12)
Complex karyotype	9 (16)	3 (15)	6 (17)
No Metaphases	1 (2)	1 (5)	0

Summary/Conclusion: Aberrant expression of the lymphoid CD7 antigen is associated with pediatric Down Syndrome AML. In contrast to early T-cell precursor lymphoblastic leukemias, where the expression of a myeloid marker is predictive of a worse outcome, the expression of this lymphoid marker in myeloid leukemias was not correlated with prognosis in terms of response to treatment, MRD or transplant outcomes.

EP479 ENASIDENIB IN PATIENTS WITH IDH2-MUTATED ACUTE MYELOID LEUKEMIA (AML). A "REAL LIFE" MULTI-CENTER EXPERIENCE FROM SPANISH HOSPITALS

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Background: Enasidenib (ENA), an oral inhibitor of mutated IDH2 (IDH2mut), has recently been approved by the FDA in monotherapy based on a phase 2 clinical trial in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) (Stein et al Blood 2019). To date, as far as we know there are no studies reporting enasidenib efficacy and safety outside of Clinical trial.
Aims: To analyze the characteristics of the population that has received this treatment and the effectiveness and tolerance of ENA used outside of clinical trial.
Methods: Multicenter retrospective study including patients with IDH2-mut AML and MDS treated in Spain (2017-2020) with ENA outside of Clinical trial (compassionate use).
Results: ENA was requested for 25 patients in 11 Spanish centers. Three patients died before starting ENA due to disease progression. Of the remaining 22, 3 did not complete the first course of ENA due to disease progression. We analyzed 19 patients for effectiveness and toxicity, 17 were AMLs, 1 AREB II and 1 CMML. Median age was 71 years (44-89) other baseline characteristics detailed in Table 1. The disease stage and treatment received prior to ENA were: 4 patients were refractory to intensive treatment (IT), 3 refractory after non-intensive treatment (NIT), 9 relapsed [5 after NIT and 4 after IT (3 of them post-allotransplant)] and 3 patients received ENA in the first line (1L). Most (11 patients) had received a previous line of treatment, 5 patients ≥ 2 lines.
The overall response rate (ORR) was 47% (N=9), 6 patients (31%) achieved complete response (CR). One patient performed a subsequent allogeneic transplant. The median number of cycles to best response was 3 (extremes 1-8). There were no differences in ORR according to disease or patient characteristics. Four (30%) of the 13 transfusion-dependent patients achieved transfusion independence.
With a median follow-up of 10.3 months (m) (3.4-19.8), median overall survival (OS) was 8.7m, with an OS at 1 year (1y-OS) of 47%±24%. Excluding the 3 patients treated in 1L there was no difference in OS depending on disease status/previous treatment. 1y-OS was significantly better in patients who achieved ORR (83%±30% vs 12%±22%; p<0.001). The median event-free survival (EFS) was 6.9 m (95%CI 2.01-11.78), being significantly better in the group that achieved ORR compared to the rest (1y-OS:74%±32% vs 10%±18%; p<0.001) and better in those who achieved CR (1y-OS: 100% vs 11%±20%; p=0.001). Remarkable the three patients treated after alloSCT are alive and disease free at time of reporting.
There were no treatment related deaths. Regarding specific toxicities of ENA 4(21%) cases presented leukocytosis, 3 (15%) differentiation syndrome, 6 (31%) hyperbilirubinemia. There were 3 admissions due to toxicity and in 2 patients ENA was definitively discontinued due to toxicity.

Demographic and disease characteristics at baseline	
Median age (range) years	71(44-89)
Gender (male) n (%)	10(53%)
ECOG n (%)	
0	1(5%)
1	14(74%)
2	4(21%)
Leukocytes median (range)x109/L	2.4 (0.65-25)
Platelets median (range) x109/L	40 (9-244)
Hemoglobin median (range) g/dL	8.8 (7.8-110)
Bone marrow blast median % (range)	25 (0-77)
Transfusion dependency n(%)	13(68%)
WHO classification n (%)	
AML myelodysplasia related	9(47%)
changes	6(32%)
AML NOS	1(5%)
AML NPM1 mut	1(5%)
Myeloid sarcoma	1(5%)
AREB II	1(5%)
Chronic myelomonocytic leukemia	
Cytogenetics risk status MRC n(%)	
Favorable	0
Intermediate	15(79%)
Unfavorable	2(10.5%)
Information not available n	2(10.5%)
ELN risk category (%)	
Favorable	1(6%)
Intermediate	8(47%)
Unfavorable	6(35%)
Information not available n	2(12%)
IDH2 mutant allele n (%)	
R140	13(68%)
R172	6(32%)
Number of previous treatments	
n(%)	3(16%)
0	11(58%)
1	3(16%)
2	2(10%)
3	
Outcomes of prior AML therapy n	
(%)	4(21%)
Refractory to intensive treatment	3(16%)
Refractory after non-intensive	9(47%)
treatment	3(16%)
Relapsed after any treatment	
First line	
Time from diagnosis to start of	8.9
Enasidenib median (range) months	(1.4-86.7)

Summary/Conclusion: The results of this study confirm both the effectiveness and the good drug tolerability reported with ENA in the Phase II study
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EP480 CLI120-001 PHASE1B STUDY OF SEL120/RVU120 IN PATIENTS WITH AML OR HIGH RISK MDS: PRELIMINARY CLINICAL AND PK RESULTS FROM INITIAL DOSE ESCALATION COHORTS

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Background: SEL120/RVU120, a novel CDK8/CDK19 kinase inhibitor has shown significant efficacy in preclinical AML models. The First in Human phase Ib clinical trial with SEL120 in patients with relapsed/refractory (R/R) AML or HRMDS is currently open for enrollment at 6 sites in the US (NCT04021368). Here we present the preliminary safety, efficacy and pharmacokinetic (PK) data of the first 4 dose escalation single patient cohorts.
Aims: The primary objective of the study is to determine preliminary safety profile, dose limiting toxicities (DLTs), maximum tolerated dose (MTD) and the recommended phase 2 dose of SEL120 as a single agent. Secondary objectives include the characterization of PK, antitumor activity and exploratory pharmacodynamic effects.
Methods: All pts signed the informed consent. The study comprises at least 8 dose escalating cohorts. The first four cohorts followed an accelerated scheme, 1 patient enrolled/cohort, with the following cohorts switching to a modified Fibonacci 3+3 design. Data from each cohort was evaluated by a study data review committee (DRC). SEL120 was administered orally every other day, for a total of 7 doses, in a 3-week treatment cycle until disease progression/unacceptable toxicity. Adverse events were graded according to NCI-CTCAE v.5.0. DLTs were assessed at completion of C1. Disease evaluation was performed according to Dohner 2017 and Cheson 2006 response criteria for AML and MDS respectively. Plasma PK parameters were calculated by non-compartmental analysis
Results: Cohorts 1 to 4, each enrolled 1 DLT evaluable patient who received SEL120 at dose levels from 10 to 75mg. 3 patients had a diagnosis of R/R AML, 1 patient had persistent HR-MDS. The median age of patients was 74 years and the number of median prior lines of treatment was 3. No DLTs were observed, 4 Serious Adverse Events were reported and assessed by the investigator, as unlikely related to study drug (G3: pseudomonas sepsis; urinary tract infection; febrile neutropenia; lung infection). Cohort 1 patient, at 10mg dose level, and cohort 2 patient, at 25mg showed stable disease (SD) and progressive disease, respectively at C1. Cohort 3 patient, who started at 50mg dose level, is an 81-year-old male with HRMDS who showed evidence of an Erythroid Response at C5D8. He is now in C8, at 75mg, following to a dose escalation during C7. Cohort 4 patient, at 75mg dose level, is a 62-year-old male with persistent AML and extramedullary skin leukemia, who failed prior venetoclax/decitabine. This patient achieved a complete hematological recovery at C2 and absence of bone marrow blasts and continuous improvement of skin leukemia, now ongoing in C5, however, the profound post ven/dec pancytopenia complicates assessments of magnitude of the contribution of SEL120 to this response. PK parameters of these 4 patients, were similar across all dose levels. SEL120 absorption was relatively rapid with Tmax 4 -8hr after drug administration. Exposure, based on Cmax and AUC, was linear with doses between 10 and 75mg, both after single and repeat dosing. SEL120 elimination half-life in plasma was 22 to 40hr with low accumulation (1.3 to 1.8-fold). Within patient variability of plasma concentrations of SEL120, over at least 6 cycles, was low.
Summary/Conclusion: Preliminary results of the first four single patient dose escalation cohorts have shown a favorable safety and a linear PK profile of SEL120. The first signal of activity is observed at doses 50 to 75mg. Enrollment is currently ongoing, with switching to 3+3 design.

EP481 A HOME CARE PROGRAMME FOR THE RAMP-UP AND FIRST COURSES OF TREATMENT WITH VENETOCLAX AND HYPOMETHYLATING AGENTS IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA

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Background: The combination of venetoclax (Ven) with hypomethylating agents (VenHMA) has shown promising results both in newly diagnosed and relapsed or refractory acute myeloid leukaemia (AML) patients, ineligible for intensive chemotherapy. Due to our expertise acquired in at-home management of diverse complex haematological procedures, we initiated in February 2020 an at-home (AH) programme for the VenHMA regimen. This AH-VenHMA programme included the initial dose ramp-up to prevent tumour lysis syndrome (TLS), a phase usually recommended to be performed as an inpatient hospital admission.
Aims: Herein we present preliminary results of our AH experience during the first two cycles of VenHMA treatment for AML patients.
Methods: Before implementation of AH-VenH programme, ramp-up was performed during a hospital admission (n=29, reference cohort). In Feb 2020, we initiated the VenH programme; outcome of in this patient cohort are compared with the reference cohort.
In AH programme, prior to VenHMA initiation, medical evaluation is performed by a haematologist and a liaison nurse. Medical history, potential drug interactions and TLS risk are thoroughly evaluated. Laboratory tests (LT) including blood count and biochemistry are completed. Extensive health education is provided to patient and caregiver before the first cycle. A peripheral insertion intravenous catheter (PICC) is placed to all patients before starting ramp-up. Intravenous (IV) fluids by a portable pump (PP) are started 24hrs before the beginning of VenHMA, as well as uricosurics agents; patients are advised to maintain oral hydration. Daily morning visits during ramp-up are performed by trained nurses who complete vital sign, obtain LT, review therapeutic compliance, replaced PP and administer hypomethylating agent. Patients are started on Ven in an escalation schedule of 100mg on day 1, 200mg on day 2, and 400mg on day 3 of the cycle, they are advised to take Ven after dinner, following an explicit indication of our team given after daily LT review. An appropriate dose reduction is performed in patients receiving concomitantly CYP3A4 inhibitors. After achieving planned Ven full dose, IV fluids are ceased (Image 1). Patients are followed throughout the whole cycle by the AH team. Platelet transfusions are administered at-home while red cell concentrates are administered at the hospital, due to our transfusion policy.
Results: Between February 2020 and January 2021, 22 AML patients (40 cycles) received VenHMA at-home. Fourteen patients were men (63.6%), with a median age of 73 years (23-83). Main characteristics were well balance in both patient cohorts.
Neutropenia (86.3%), thrombocytopenia (90.9%) and anaemia (86.4%) were the most frequent adverse events (AEs). A trend to a lower proportion of febrile episodes was observed in the AH program (19/29 *vs.* 8/22, p=0.074). Hospital readmission rate after ramp-up was markedly low in the AH cohort, significantly lower than in the reference cohort (4/22 vs. 19/29, p = 0.001). TLS was not observed in any group. Main AEs are shown in table 1. Median days of at-home treatment were 49 (19-187). Discontinuation was due to refractoriness in 5 (22.7%) patients. Two patients presented SARS-CoV-2 infection in early March 2020, resulting in death in both cases.

Table 1. Adverse Events during the first two cycles of VenHMA treatment

Adverse Events during the first two cycles of treatment	All patients (N = 51)	Hospitalized (n=29)	At-home (n=22)	P
Any Adverse Event, no. (%)	50 (98)	29 (100)	21 (95.5)	NS
Neutropenia, no. (%)	48 (94.1)	29 (100)	19 (86.3)	NS
Grade 3	5 (9.8)	5 (17.2)	0 (0)	
Grade 4	43 (84.3)	24 (82.8)	19 (86.3)	
Thrombocytopenia, no. (%)	45 (88.2)	25 (86.2)	20 (90.9)	NS
Grade 2	4 (7.8)	1 (3.4)	3 (13.6)	
Grade 3	3 (5.9)	0 (0)	3 (13.6)	
Grade 4	38 (74.5)	24 (82.8)	14 (63.6)	
Anaemia, no. (%)	45 (88.2)	27 (93.1)	19 (86.4)	NS
Grade 2	22 (43.1)	14 (48.3)	9 (40.9)	
Grade 3	21 (41.1)	12 (41.4)	9 (40.9)	
Grade 4	2 (3.9)	1 (3.4)	1 (4.5)	
Fever, no. (%)	27 (52.9)	19 (65.5)	8 (36.4)	0.074
Fever in neutropenia	13 (25.5)	9 (31)	4 (18.2)	NS
Bacterial infection	12 (23.5)	9 (31)	3 (13.6)	NS
Viral infection	5 (9.8)	3 (10.3)	2 (9.1)	
Fungal infection	4 (7.8)	3 (10.3)	1 (4.5)	NS
SARS-Cov-2 infection	2 (3.9)	0 (0)	2 (9.1)	
Sepsis, no. (%)	3 (5.9)	2 (6.9)	1 (4.5)	NS
Acute bleeding, no. (%)	3 (5.9)	2 (6.9)	1 (4.5)	NS
Deep vein thrombosis, no. (%)	2 (3.9)	2 (6.9)	0 (0)	NS
Hospital admissions, median (range)	0 (0-4)	1 (0-4)	0 (0-1)	NS
Hospital admission after ramp-up, no. (%)	25 (49)	19 (71.4)	4 (21.7)	0.001
Hospitalization days after ramp-up, median (range)	0 (0-63)	8 (0-63)	0 (0-14)	0.23

Summary/Conclusion: Home care during the ramp-up and early phase of VenHEM regimen is a feasible and safe option. An AH programme was followed by a low readmission rate and offers diverse benefits such as optimization of health resources and increase of the comfort and well-being of patients and their caregivers.

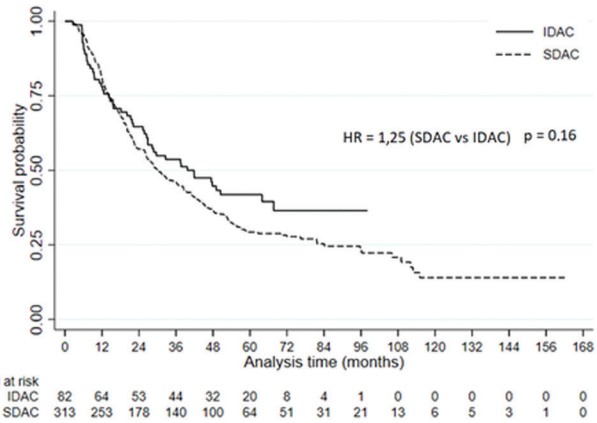
EP482 INTERMEDIATE OR STANDARD DOSE CYTARABINE AS POST REMISSION THERAPY IN OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA: IMPACTS ON OUTCOMES AND HEALTH CARE RESOURCE CONSUMPTION

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Background: High-dose cytarabine is currently a well accepted post remission therapy for younger patients with acute myeloid leukemia (AML) in first complete remission (CR1). No standard exists for older (≥ 60 years) patients. Although intermediate-dose cytarabine (IDAC) delivered every 12 hours for three days is regularly used in older fit patients, several academic groups also apply an outpatient schedule by standard dose cytarabine associated with single-dose anthracycline in monthly courses (SDAC).
Aims: To compare outcome of elderly patients with AML in CR1 receiving post-remission therapy, either with SDAC and anthracycline or with IDAC as single agent
Methods: Patients ≥ 60 years-old with non-M3 AML in CR1 after intensive chemotherapy included in French DATAML registry (Bordeaux and Toulouse) between 2007 and 2017 were retrospectively reviewed for study specific data collection. Patients had to receive at least one course of post-remission chemotherapy, either with SDAC or with IDAC. SDAC regimen consisted of six to seven 28-days courses of idarubicine (8mg/m^2) D1 plus cytarabine (50mg/m^2 BID in sub-cutaneous injection) D1-D5. IDAC regimen consisted of three 35-days course of cytarabine (1,5g/m^2 in 2 hours infusion) every 12h for a total of 6 injections. Allogeneic stem cell transplantation (alloSCT) was performed at the physician's discretion.
Results: Population: 395 patients were included. Median age was 68 years. 82 patients received IDAC regimen and 313 received SDAC regimen. IDAC patients were younger (median age 65 versus 69, p <0.001), but have more adverse cytogenetics risk (31% *vs* 11%, p < 0.001) and were more likely secondary (35% *vs* 18%) or therapy related (18% *vs* 3%) (p < 0.001). Median course of post-remission therapy was 3 for IDAC and 5 for SDAC regimen. AlloSCT has been performed in 62 patients. **Outcome:** After a median follow up of 72 months, median OS was 40 months for IDAC *vs* 30 months for SDAC patients (p = 0.16), and median LFS was 21 months vs 17.5 months, respectively (p = 0.187). In multivariate analysis, factors associated with better OS were only Charlsons comobirdity index < 2, favorable ELN2010 category and alloSCT in CR1 (with an HR = 0.5). Post remission schedule was not independently associated to outcome. **Tolerance:** 1 year non relapse mortality was 10% for the whole cohort, without statistical difference between IDAC and SDAC patients. Deaths in remission during treatment were unfrequent (< 5%) in both groups. The rate of infectious events needing parenteral antibiotic was significantly lower with SDAC compared to IDAC (36.1% *vs* 74.4%) (*p* < 0.01) as well as the rate of documented bacteremia (15.7% *vs* 41.5%, p < 0.001). Median red blood cell transfusion requirement per cure was 1 (IQR 0,3 – 2) for SDAC *vs* 3 (IQR 2 – 4) for IDAC, and median platelet transfusion requirement per cure was 0,8 (IQR 0,2 – 1,4) *vs* 2,5 (IQR 1,6 – 3,3), respectively (p < 0.001 for both). Duration of hospitalization for the whole post-remission program was shorter with SDAC (12 days, IQR 7 – 19) compared to IDAC (32.5 days, IQR 22.5 – 38.5) (p < 0.001).

Figure 1: overall survival of study population



Summary/Conclusion: Although IDAC is feasible in fit AML patients over 60, the outpatient SDAC regimen induced low myelosuppression, decreased rate of infections and transfusions, and therefore significantly reduced the length of hospital stay without affecting outcomes.

EP483 APPLICATION OF MACHINE LEARNING IN STRATIFYING MINIMAL RESIDUAL DISEASE LEVEL WITH FLOW CYTOMETRY IN ACUTE MYELOID LEUKEMIA

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Background: Residual disease detection and monitoring by flow cytometry guides clinical physicians to modify treatment strategies according to patient's risk profile. Current flow cytometry analysis approach is based on manual interpretation, which is relatively labor-intensive and time-consuming.
Aims: We propose to use machine learning algorithm for residual disease percentage (RDP) classification by using clinical flow cytometry (FC) data.
Methods: Retrospective clinical FC data of AML patients, as well as demographic data (age & gender) were collected from National Taiwan University Hospital. From 2013 to 2016, a total of 487 FC data positive for residual disease from 249 AML patients were enrolled in this study. There are 81 FC data with RDP within 0.01 to less than 1%, and 406 FC data with RDP greater than or equal to 1%. The median age at flow cytometry test performed was 51.8 years old.
Our proposed machine learning framework includes a phenotype representation learning paradigm and a classification model. To derive the phenotype representation, we trained a multivariate Gaussian Mixture Model (GMM) on the 38-dimension FC data to capture the training data distribution and characteristics in a probabilistic unsupervised manner. Then, a Fisher-scoring method derived from the differential of the learned GMM parameters was used to vectorize each sample as a high dimensional representation. This Fisher vectorization method transformed samples to a high dimensional feature space as phenotype vectors, which were finally fed into the random forest (RF) classifier. To alleviate the negative effects of imbalance classes in RDP identification tasks, we applied synthetic minority oversampling technique (SMOTE) algorithm which augmented the minority class by linearly interpolating synthetic samples from existing samples in the minority class. We train RF models for original fisher vectorization feature set and oversampled set separately to discriminate the RDP classes. The algorithm is evaluated by randomly divided 5-fold cross validation which separates 80% data for training and 20% for testing.
Results: The accuracy (ACC) and area under the ROC curve (AUC) of RDP prediction models achieved 0.897 and 0.934, respectively (Table 1a). Around 91.9% of those FC data with RDP greater than or equal to 1%, and 79.0% of those FC data with RDP within 0.01 to less than 1% are correctly classified when using oversampled set (Table 1b).

Table 1a. RDP Classification with and without Oversampling Performance Using RF Model

	ACC (%)	AUC
Original fisher vectorization set	86.9	0.909
Oversampled fisher vectorization set	98.7	0.934

Abbreviations: ACC: accuracy; AUC: area under the ROC curve; RF: random forest.

Table 1b. Confusion Matrix of RDP Classification Model Using Oversampled Set

Predicted class / True class		0.01% ≤ RDP ≤ 1%	RDP ≥ 1%	Total
		n (%)	n (%)	
0.01% ≤ RDP ≤ 1%	n (%)	64 (79.0)	17 (21.0)	81 (100)
RDP ≥ 1%	n (%)	33 (8.1)	373 (91.9)	406 (100)

Abbreviations: RDP: residual disease percentage.

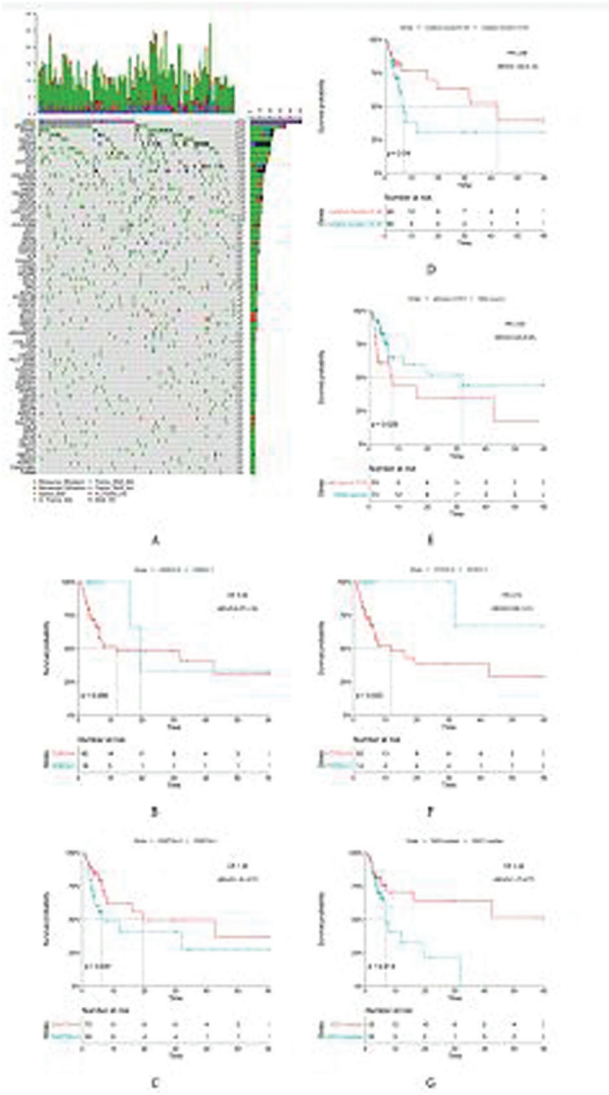
Summary/Conclusion: This study demonstrated the potential of machine learning algorithm used in RDP prediction in patient with AML. Further study with larger cohorts or different data sources are needed to validate this machine learning based prediction model as a clinical support tool to assist physicians in clinical decision making.

EP484 THE PROGNOSTIC SIGNIFICANCE OF FLT3 INTERNAL TANDEM DUPLICATIONS' CHARACTERISTICS AND CO-MUTATIONS IN ACUTE MYELOID LEUKEMIA

L.-M. Cao [1,*], L.-X. Wu [1], Y.-L. Zhou [1], Z.-L. Wang [1], J.-L. Li [1], Q.-Y. Sun [1], L.-X. Liu [2], C.-C. Wang [2], H. Jiang [1], Q. Jiang [1], L.-P. Xu [1], X.-H. Zhang [1], K.-Y. Liu [1], X.-J. Huang [1,3,4], G.-R. Ruan [1]

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Background: About 25% of newly diagnosed adult AML patients(pts) with normal cytogenetics have Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD). And it confers unfavorable prognosis, however, factors associated with clinical outcomes of FLT3-ITD$^+$ mutations are still controversial.
Aims: To find out the variables associated with the different outcomes of ITD+ patients(pts).
Methods: We evaluated 106 adult AML pts with this genotype who were diagnosed at Peking University People's Hospital and achieved histological complete remission within two cycles of induction therapy. And we analysis the status of mutations for all pts based on next-generation sequencing.
Results: In our cohort, we totally found 171 ITDs(1 ITD: 60 pts, 2 ITDs: 31 pts, 3 ITDs: 11 pts and 4 ITDs: 4 pts). Of the 171 ITDs, 102(59.6%) located in the juxtamembrane domain(JMD); 24(14.0%) located in the tyrosine kinase domain-1(TKD1); 25(14.6%) located in the hinge region(HR) and 20 (18.7%) located in the other region of FLT3 receptor. Median of insert lengths was 65 bp[range,18-259 bp], median of variant allele frequency (VAF) was 0.45[range,0.04-0.78]. We founded that a better prognosis could be noticed if the inserted sequence is derived from wild type FLT3 gene fragment sequence[p=0.026 for leukemia-free survival (LFS) with transplant censored, p=0.039 for overall survival (OS) with transplant censored].We also focused on the co-mutated genes of FLT3-ITD and noticed pts with CEBPA$^{bi\text{-}mut}$[n=16, p=0.066 for LFS, p=0.092 for OS],and POTEH[n=14, p=0.023 for LFS, p=0.2 for OS] showed an advantage in survival. However, high mutation burden[VAF> 0.45(established by using the ROC curve for maximum LFS), p=0.04 for LFS, p=0.077 for (OS)]; the mutation of DNMT3A [n=36, p=0.041 for LFS, p=0.13 for OS]; high WBC[> 29.83*10^9cells/L(median), p=0.014 for LFS, p=0.015 for OS] predicted worse survival. In addition, there were no obvious correlation of the insert site, the lengths of ITDs and the insert ITD number with the unfavorable prognosis of FLT3-ITD$^+$ pts.



Summary/Conclusion: In this study, we revealed that POTEH^{mut}, CEBPA$^{bi\text{-}mut}$ and ITDs which were derived from wild type FLT3 gene fragment always had a better survival, however, DNMT3A^{mut}, high mutation burden and high WBC had a worse survival. Our study was beneficial to in-depth understanding of the FLT3-ITD's characteristics and the genes combined with it. It also had guiding significance for clinical risk stratification of FLT3-ITD$^+$ AML patients with normal cytogenetics.

EP485 SURVIVAL OUCOMES IN PATIENTS WITH ACUTE MYELOID LEUKEMIA PRESENTING WITH HYPERLEUCOCYTOSIS

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Background: Approximately 10% to 20% of patients with acute myeloid leukemia (AML) present with hyperleukocytosis. Hyperleukocytosis can result in leukostasis leading to end organ dysfunction and critical illness requiring admission to intensive care unit (ICU) admission. Institutional practices vary on the management of patients with hyperleukocytosis and leukostasis including location of chemotherapy administration and thresholds for ICU admission. There is paucity of data on the short- and long- term outcomes of

these patients, particularly across those managed on in-patient wards compared to ICU.
Aims: To describe the characteristics of patients with hyperleukocytosis and factors associate with ICU admission and 60 day mortality.
Methods: We conducted a retrospective cohort study of consecutive admissions to Princess Margaret (PM) Cancer Center or Mount Sinai Hospital ICU between 2014-2019. All adult patients with a white blood cell count (WBC) >50x10^9/L and a new diagnosis of AML were included. Their clinical and laboratory data were evaluated across the first 5 days after presentation with hyperleukocytosis. Our primary outcome was ICU admission and our secondary outcome was 60 day mortality.
Results: One-hundred and sixty-nine patients were admitted with a diagnosis of AML and hyperleukocytosis. Mean age was 58 (SD 15) and 59% were male with 43% having greater than 2 comorbidities. Median WBC on the first day of hyperleukocytosis was 103 x 10^9/L (IQR 67-152), with 55% having a WBC >100x10^9/L and 15% having a WBC >200x10^9/L. On the first day of hyperleukocytosis, 63% had hypoxemic respiratory failure, 25% had biochemical tumor lysis syndrome, and 49% were diagnosed with acute kidney injury (8% requiring dialysis) (*Table 1*). ICU admission was required in 44% of the cohort and the median time to ICU was 1 (IQR 0-3) day. Across entire cohort, median change in WBC from day 1 to 2 was – 17x10^9/L (IQR -31 - -1), the median greatest decrease in WBC over a 24 hour period was 58x10^9/L (31-88). Drop in WBC in first 5 days was higher in those not admitted to ICU and across survivors (Table 1). Across the ICU cohort, 59% required invasive mechanical ventilation, 76% had acute kidney injury and 48% require vasopressors. Across those admitted to the ICU, 81% were admitted within 4 days of hyperleukocytosis. Sixty-day mortality across the whole cohort was 30% (57% across the ICU cohort and 8% across the non-ICU exposed). ICU mortality was 82% across those who required invasive mechanical ventilation during the first 5 days post diagnosis of hyperleukocytosis. Hospital admission factors associated with ICU admission included hypoxia on day 1 of hyperleukocytosis (PaO2/FiO2 OR 0.97 (95% CI 0.96-0.98, p<0.001) and acute kidney injury (OR 12.2 95% CI 1.8-83, p 0.011). Factors associated with 60 day mortality included male sex, WBC >100x10^9/L, lower PaO2/FiO2, any invasive mechanical ventilation and a lower drop over a 24 hour period in the WBC across the first 5 days.

TABLE 1	Entire Cohort (N=169)	ICU Cohort (N=75)	No ICU (N=94)	60-day Mortality (N=50)
DEMOGRAPHIC VARIABLES				
Age	58 SD 15	59 (15)	58 (14)	59 (16)
Comorbidities	1 (IQR 0-2)	2 (IQR 1-3)	1 (IQR 0-2)	2 (IQR 1-3)
Sex-Male	100 (59%)	48 (64%)	52 (55%)	38 (76%)
WBC DETAILS				
WBC >100 on presentation	92 (55%)	44 (59%)	48 (52%)	31 (65%)
WBC >200	25 (15%)	16 (21%)	9 (10%)	12 (24%)
WBC day 1	103 (67-152)	106 (61-187)	102 (69-143)	114 (71-195)
Greatest decrease in 24 hours over first 5 days*	58 (31-88)	48 (18-91)	62 (37-87)	48 (21-80)
CLINICAL VARIABLES				
ICU admission	75 (44%)	N/A	N/A	43 (86%)
PaO2/FiO2 Day 1	280 (IQR 140-450)	168 (112-251)	452 (442-461)	145 (108-206)
Any hypoxia day 1	80 (63%)	71 (96%)	9 (11%)	
AKI day 1	82 (49%)	54 (72%)	28 (31%)	39 (79%)
Dialysis day 1	14 (8%)	14 (19%)	0	10 (20%)
OUTCOMES				
60-day mortality	50 (30%)	43 (57%)	7 (8%)	N/A
Death within 24 hours	11 (7%)	11 (15%)	0	11 (22%)

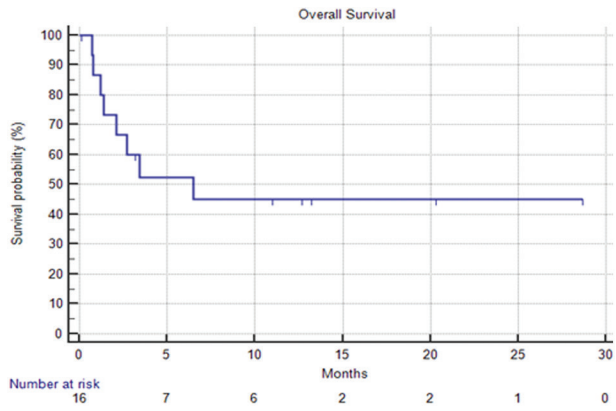
Summary/Conclusion: Patients with hyperleukocytosis managed on the inpatient wards had a mortality rate of 8%. Patients admitted to ICU and particularly those requiring invasive mechanical ventilation on admission had inferior survival.

EP486 GLASDEGIB IN COMBINATION WITH LOW DOSE CYTARABINE FOR ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS FAILING HYPOMETHYLATING AGENTS

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Background: The prognosis of relapsed or refractory acute myeloid leukemia (R/R AML) in elderly and unfit patients who fail hypomethylating agents remains very poor. Glasdegib is a novel small-molecule inhibitor of the Smoothened (SMO) receptor and its efficacy is based on down-regulation of the Hedgehog signaling pathway which is involved in the resistance of AML cells. Glasdegib combined with low dose Cytarabine (LDAraC) is currently approved for newly diagnosed unfit AML patients, however data in the R/R AML setting are lacking. Here, we present data on 16 elderly and unfit R/R AML patients who had previously failed Decitabine or Azacitidine based therapies and were treated with outpatient Glasdegib + LDAraC.
Aims: The aim of our study was to evaluate the efficacy and toxicity of Glasdegib + LDAraC therapy in R/R AML patients with prior exposure to hypomethylating agents.
Methods: We retrospectively collected clinical data on AML patients who had R/R AML and failed Decitabine or Azacitidine based therapies at Vilnius University Hospital Santaros Klinikos in 2018-2020. Glasdegib was kindly provided by Pfizer via the compassionate use program and the treatment was approved by the institutional Ethics Committee. The data collection was approved by Vilnius Regional Biomedical Research Ethics Committee. The treatment cycles consisted of self-administered Cytarabine 20mg/m^2 s/c Day 1-10 and Glasdegib 100mg p/o daily on outpatient basis. The cycles were repeated every 28-35 days, longer interruptions were allowed in case of toxicity or social reasons. Glasdegib was continued after Day 28 even if the start of the next cycle was postponed. Indications for stopping the treatment were progressive disease with no further clinical benefit observed, excessive toxicity or availability of alternative treatment strategies.
Results: 16 patients (11 female) were enrolled. The median age was 77 (71-86) years. The median ECOG performance status was 2 (1-3). Extramedullary involvement was confirmed in 12% (2/16) of cases. 14 (88%) patients had previously received 1 treatment line, whereas 2 (12%) patients failed two therapies. All patients had previously received low intensity frontline therapies with Decitabine or Azacitidine, 4 (25%) patients had Venetoclax exposure. Adverse cytogenetics were identified in 38% (6/16) of patients. Based on the ELN2017 risk group stratification criteria, 12% (2/16), 50% (8/16) and 38% (6/16) of patients were stratified to favorable, intermediate and adverse risk groups, respectively. A median of 2 (1-17) treatment cycles were administered, 5 patients (31%) received at least 4 cycles. Responses were evaluated in 13 cases. Four patients achieved CR, one patient achieved CRp and one PR was confirmed. The composite CR+CRp rate was 39% (5/13) and the overall response rate (CR+CRp+PR) was 46% (6/13). The median response duration was 2 months (0.3-6) Stable disease was confirmed in 23% (3/13), whereas 31% (4/13) were diagnosed with progressive disease. After the median observation time of 13.2 months, the median overall survival was 6.5 months (95% CI 2.1-6.5). The most common grade III-V adverse events of Glasdegib + LDAraC were infections (57%, 9/16). Grade 3 QT prolongation was confirmed in 1 case (6%), no episodes of life-threatening arrhythmias were observed. Day 30 and day 60 mortality rates were 12% (2/16) and 19% (3/16), respectively.



Summary/Conclusion: Glasdegib + LDAraC is a fairly safe, non-intensive outpatient regimen that may achieve disease stabilization and induce responses in elderly and unfit R/R AML patients after unsuccesful therapy with hypomethylating agents.

EP487 GEMTUZUMAB OZOGAMICIN ADDED TO HIDAC CONSOLIDATION THERAPY FOR STANDARD-RISK ACUTE MYELOID LEUKEMIA IS SAFE AND EFFICACIOUS

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Background: Patients (pts) with standard-risk acute myeloid leukemia (AML) are not regularly planned for up-front allogeneic stem cell transplantation (allo-SCT). Yet, some of these pts fail reaching minimal residual disease (MRD) negativity with standard chemotherapy and are allocated to allo-SCT during 1st complete remission. Gemtuzumab ozogamicin (GO), an antibody-toxin conjugate targeting $CD33^+$ cells, is associated with overall survival (OS) benefit and reduced relapse rate in standard-risk AML. The FDA approval of GO use as an addition to intensive chemotherapy relies on results of the French ALFA-0701 trial where pts were assigned to receive GO (3mg/m^2 on days 1,4,7) combined with the 7+3 regimen as induction and combined with daunorubicin/cytarabine (GO: 3mg/m^2 on day 1) for 2 courses as consolidation. However, in many countries, reimbursement issues preclude the use of GO as part of induction.
Aims: The Israeli Leukemia Group recommended including GO (capped at 4.5mg total on day 1) in any consolidation therapy comprising high-dose cytarabine (HIDAC) for standard-risk AML pts, even if GO was not applied as part of induction. The present study aimed to evaluate outcomes of pts who received GO+HIDAC as consolidation, in terms of MRD clearance and toxicities.
Methods: Electronic medical records of 4 Israeli tertiary care centers were retrospectively reviewed to identify standard-risk AML pts treated with 7+3 induction and HIDAC consolidation. Pts were then grouped into two cohorts based on GO use in combination with HIDAC (GO vs No-GO). The cohorts were compared in terms of OS, progression-free survival (PFS) and MRD clearance after 2 intensive chemotherapy cycles. For toxicity evaluation, the number of infectious events, blood products used, hemorrhage events, mucositis (≥grade 3) events, veno-occlusive disease (VOD) events and occurrence of prolonged thrombocytopenia (platelet count <100 at 30 days post-treatment) were analyzed. The dose intensity per unit time was also assessed. Of note, hospitalization duration was not included in the final analysis due to inter-hospital admission policy differences.
Results: The GO and No-GO cohorts included 22 and 21 pts, respectively. They were comparable in terms of age, sex and specific driver mutations other than the combination of *NPM1*+ low allelic ratio-*FLT3-ITD* that was less prevalent in the GO cohort (5% vs 27%; p=0.046). The majority of pts (77% vs 57%; p=0.2) received intensified induction (daunorubicin 90mg/m^2 or its equal). Among the pts whose MRD data were available, MRD clearance was reached in all those who received GO and only in two thirds of the No-GO cohort (12/12 vs 7/11; p=0.037). No VOD or treatment-related death occurred. A total of 113 consolidation cycles were given: 55 HIDAC+GO and 58 HIDAC cycles (Table 1). The GO+HIDAC regimen was associated with higher rates of platelet transfusion (median 3.5 vs 1 of pooled or apheresis platelets) and prolonged thrombocytopenia (42.3% vs 5.2%; p<0.001). Only 7 bleeding events occurred (5 after GO injection). No life threatening bleeds were recorded. GO administration did not entail higher neutropenic fever rates (74.5% vs 60%; p=0.12), excessive use of packed cell units (p=0.44), treatment delays or therapy-related death.

Table 1. Consolidation treatment-associated toxicity

	HIDAC + GO (n=55)	HIDAC only (n=58)	P-value
Neutropenic fever events	41 (74.5%)	35 (60%)	0.12
Packed red blood cell administration (mean)	2.44±2.08	2.14±1.59	0.44
Platelet (pooled or apheresis) administration (median)	3.5 (1.75-6.0)	1 (1-3)	0.004
Prolonged thrombocytopenia (platelet count <100K on day 30)	22 (42.3%)	3 (5.2%)	<0.001
Hemorrhage	47/52(90%)	55/57 (96%)	0.25
Mucositis (≥grade 3)	5 (9%)	6 (10%)	1.00
Days between each cycle (mean)	42.6±16.6; N=37	40.2±14.9; N=33	0.54

Summary/Conclusion: While associated with high bleeding risk attributed to severe and prolonged thrombocytopenia, consolidation with HIDAC+GO is safe and provides high rates of MRD eradication. Standard-risk AML patients who do not receive GO in induction may benefit from its addition to consolidation regimens.

EP488 INDUCTION CHEMOTHERAPY WITH CYTARABINE, DAUNORRUBICIN AND ETOPOSIDE VERSUS STANDARD-DOSE CYTARABINE AND DAUNORRUBICIN IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Intensive induction chemotherapy is the standard approach in patients (pts) with acute myeloid leukaemia (AML) for achieving complete remission (CR), enabling the delivery of consolidation treatment. Since achievement of CR is a strong predictor of survival, it is important to optimize the induction chemotherapy protocol.
Aims: Comparison induction regimen for AML with standard-dose 7+3 versus 10+3+etoposide.
Methods: Unicentric retrospective review of pts diagnosed with AML (excluding M3) from January 2012 to June 2020 treated with standard-dose 7+3 (cytarabine 200mg/m^2 day 1-7 + daunorubicin 60mg/m^2 day 1-3) and 10+3+E (cytarabine 100mg/m^2 day 1-10 + daunorubicin 50mg/m^2 day 1, 3, 5 + etoposide 50mg/m^2 day 1-5).
Results: Identified 173 pts - median age 50 years (19-70y), 53% women. Secondary AML was diagnosed in 18.5% and according to the European Leukemia Net (ELN) risk stratification 38% had favourable risk, 43% intermediate and 19% unfavourable. Median leukocyte at diagnosis was 10.56x10^9/L and bone marrow blast 52%. Age (median 53y in 7+3 vs 48y in 10+3+E; p<0.001) was the only characteristic that differed between treatment (tt) arms. From the pts identified, 61 received 7+3 and 112 received 10+3+E. A total of 78% achieved CR after one cycle of induction tt – 77% in 7+3 vs 78.6% in 10+3+E, without statistically significant difference (p=0.817). Only ELN risk had statistical impact on CR - 94% in favourable vs 77% in intermediate vs 48% in unfavourable (p<0.001). Partial remission and refractory disease were both obtained in 8%, without statistically significant difference. 10 pts died before evaluation of response, all of them as a consequence of bone marrow aplasia, with no difference between tt arms. Median neutrophil-recovery time was different between tt [27days (10-74d) in 7+3 vs 31days (10-65d) in 10+3+E; p=0.02]. Median myelosuppression-recovery time (Hb>8g/dL; Leuk>1.5x10^9/L; Plaq>20x10^9/L) wasn't statistically significant between tt (median 28days in 7+3 vs 30days in 10+3+E; p=0.216). Also the number of febrile neutropenia wasn't different, with a median 2 episodes/patient. 16 pts required ICU admission, with no difference between tt.
Early relapse rate (≤6 months after induction tt) was 6.4%, lower in 10+3+E arm (3.6% vs 11.5%; p=0.047), regardless ELN risk. Overall relapse rate was 47% with statistically difference according to ELN risk (61% vs 50% vs 38% in unfavourable, intermediate and favourable risk; p<0.001) but no difference by tt arm (p=0.296). Median overall survival (OS) was 20months (95%CI 16-24months), without difference by tt (p=0.651).
At univariate analysis, several factors were associated with poor OS: ELN risk (p<0.001; HR 2.166), myelosuppression ≥50days (p=0.005; HR 18.717), neutropenia ≥60days (p<0.001; HR 17.711), ICU admission (p<0.001; HR 3.152) and disease relapse (p<0.001; HR 1.029). CR after induction was a protective factor (p<0.001; HR 0.389). At multivariate analysis factors that remained significant were: ELN risk (p<0.033; HR 2.148), myelosuppression ≥50days (p=0.003; HR 5.302), ICU admission (p=0.015; HR 2.706) and disease relapse (p<0.001; HR 13.937).
Summary/Conclusion: Outcomes were similar, with both induction regimens increased CR rates without increasing mortality in patients with AML fit for intensive treatment.
The only identified difference was that addiction of etoposide to 7+3 regimen had a lower early relapse rate but with slightly increased haematological toxicity. No difference was observed in overall relapse rate. Thus, both induction regimens are effective and tolerated in fit adult patients with AML.

EP489 NEXT STEP AFTER COMPLETE REMISSION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: patients with Acute Myeloid Leukemia (AML) who achieve Complete Remission (CR) after 1 or 2 courses of chemotherapy need consolidation treatment to avoid relapse. We do not know what is the most effective chemotherapy scheme just after CR.
Aims: to analyse the impact of the first consolidation treatment (HDAC based, more intensive regimens including anthracyclines or directly transplant (HSCT) in terms of Relapse-Free Survival (RFS) and OS (OS) in patients with AML in CR after induction.
Methods: we reviewed retrospectively 190 patients with AML who were diagnosed between 2011 and 2020. We analysed 114 who achieve CR after 1 or 2 courses of intensive chemotherapy and received at least 1 cycle of consolidation or were directly transplanted after induction. We consider CR <5% blast by cytology and MRD+ ≥0.1% by Multiparameter Flow Cytometry (MFC). We divided the cohort according to the first consolidation treatment: Group 1 HDAC based consolidation, Group 2 intensive regimen including anthracyclines, and Group 3 HSCT directly HSCT. The decision on the first consolidation chemotherapy treatment (HDAC vs anthracyclines-based) was at the discretion of the prescribing physician. In table 1 are reflected the baselines characteristics of our cohort.
Results: we didn't find differences among the groups, except Group 3 had more percentage of secondary AML and adverse risk profile and they needed more frequently 2 cycles to achieve CR. With a median follow up of 19 months (12-47.5), the 3year (3y) EFS was 35%, the 3y-OS 45% and the 3y Cumulative Incidence of Relapse (3y-CIR) 43%. The 3y-EFS according to the first consolidation was 49% in Group 1 vs 30% Group 2 vs 39% in Group 3 (HR 1.2, p=0.2) and the 3y-OS was 54% Group1 vs 43% Group 2 vs 45% in Group 3 (HR 1.3, p=0.3). The CIR was 27% vs 49% vs 34% respectively (Grey test 3.2,p=0.2). Differences remained not significant after patients who received HSCT in CR were censored at the time of infusion for the EFS (HR 1.4, p=0.4). The response by both cytology and MFC before and after first consolidation were available in 21 HDAC-based first consolidation patients (9 MRD- after induction and 12 MRD+) and in 50 anthracycline-based first consolidation patients (25 MRD- and 25 MRD+). In patients with MRD- after induction, 1/9 patients had MRD+ and 1/9 patients had Active Disease (AD) after consolidation with HDAC and 1/25 patients had MRD+ and 1/25 AD after the consolidation with anthracyclines-based regimen (p=0.5). In patients with MRD+ after induction we found than in HDAC group, 3/12 patients achieve MRD- after the consolidation, 7/12 maintained MRD+ and 2/12 had AD while in anthracyclines-based first consolidation group, 13/25 patients achieved MRD-, 7/25 maintained MRD+ and 5/25 had AD (p=0.2). We analysed the impact of the first consolidation stratifying patients according to the MRD after induction (MRD+ and MRD-), the number of cycles (1 or 2) to achieve complete remission, the ELN at diagnosis (Favorable Intermediate and Adverse). We did not find statistical differences for EFS and OS according to the first consolidation in any of these subgroups.

	HDAC n=25	Intensive regimen including anthracyclines n=74	TPH n=15
Sex M (%)	17 (68%)	44 (59.5%)	7 (46.7%)
Age, median	57 (43.5-62)	56.5 (44-62)	59 (40-62)
Hb median	9.6 (8.1-11.3)	9.6 (7.9-11.3)	9.7 (8.3-11.3)
Platelets	75550 (33750-151000)	75550 (35250-152000)	73600 (19000-122250)
WBC	3910 (2035-24340)	6390 (2070-24780)	2415 (1347-18225)
Median blasts	54% (43.5%-62%)	53% (33.3%-81.2%)	54% (29%-70%)
Secondary AML	13 (52%)	28 (38.4%)	11 (73.3%)
ELN classification			
Favorable Risk	5 (20%)	15 (20.3%)	0 (0%)
Intermediate Risk	16 (64%)	42 (56.8%)	6 (42.9%)
Adverse Risk	4 (16%)	17 (23%)	8 (57.1%)
Nº induction cycles to achieve CR			
1	22 (88%)	69 (93.2%)	8 (53.3%)
2	3 (12%)	5 (6.8%)	7 (46.7%)
Best response after induction			
MRD- by flow cytometry	9 (36%)	34 (45.9%)	7 (46.7%)
MRD+ by flow cytometry	15 (60%)	36 (48.6%)	8 (53.3%)
Unknown	1 (4%)	4 (5.4%)	0 (0%)
Received HSCT, yes n(%)	19 (76%)	59 (79.7%)	15 (100%)
Patients transplanted in 1RC	15 (78.9%)	38 (64.4%)	13 (86.7%)
Type of HSCT, n (%)			
AloTPH	19 (100%)	54 (91.5%)	15 (100%)
AutoTPH	0 (0%)	5 (8.5%)	0 (0%)
Conditioning intensity			
Myeloablative	12 (63.2%)	33 (55.9%)	9 (60%)
Reduce Intensity	6 (31.6%)	23 (39%)	6 (40%)
Sequential conditioning	1 (5.3%)	3 (5.1%)	0 (0%)
PreHSCT disease state, n(%)			
MRD- by flow cytometry	13 (68.4%)	41 (69.5%)	10 (66.7%)
MRD+ by flow cytometry	6 (31.6%)	10 (16.9%)	4 (26.7%)
Active disease	0 (0%)	5 (8.5%)	1 (6.6%)
Unknown	0 (0%)	3 (5%)	0 (0%)
Number chemotherapy cycles, median (range)	3 (3-5)	3 (2-3)	1 (1-2)
Days since diagnosis to HSCT, median (range)	190 (146-245)	182 (141-236)	113

Summary/Conclusion: the EFS and OS was not better using a first consolidation anthracycline-based compare to HDAC or patients that consolidate directly with HSCT regardless the MRD by flow cytometry after induction, the number of cycles to achieve CR or the cytogenetic risk. In patients with MRD+ after induction the first consolidation with another cycle of intensive chemotherapy based in anthracyclines did not significantly improve the depth of the response compare to standard HDAC regimen.

EP490 ROLE OF EXTRACELLULAR VESICLE-INDUCED MYELOID-DERIVED SUPPRESSOR CELLS IN ACUTE MYELOID LEUKEMIA

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Background: Acute myeloid leukemia (AML) is the most common malignant of the hematopoietic system. Allogeneic hematopoietic stem cell transplantation not only improves the prognosis of patients, but also emphasizes the role of immunity in the development of AML. Myeloid-derived suppressor cells (MDSCs) are immunosuppressive cell populations derived from myeloid cells, However, their role in AML has not been extensively elucidated in bone marrow (BM) or peripheral blood (PB). Furthermore, it remains unclear whether the percentage of MDSCs derived from BM and PB of patients with AML are consistent. Extracellular vesicles (EVs) as mediator in intercellular communication and play an important role in tumor immunity. However, the role of EVs derived from AML (AML-EVs) in MDSCs expansion is not well understood.
Aims: This study aimed to investigate the role of MDSCs in patients with newly diagnosed AMLand evaluate the role of extracellular vesicle-induced MDSCs in AML.
Methods: Collected BM or PB from newly diagnosed AML patients and healthy donors (HD) to extract mononuclear cells (MNCs), and the percentage of MDSCs and its subpopulation was determined by flow cytometry. Analyzed the relationship between MDSCs and clinicopathological characters, MICM classification, survival. In addition, extracted and identified the EVs in the serums from HDs and AML patients. AML-EVs and HD-EVs were incubated with peripheral blood mononuclear cells (PBMCs) or MNCs from hematopoietic stem cell (HSCs) suspension. And the percentage of MDSCs were detected by flow cytometry.
Results: The MDSCs and its subpopulation percentage was significantly higher in patients with AML than in HDs, with no significant difference between PB and BM. The MDSCs percentage in AML patients was positively correlated with WBC, β-MG, LDH, ferritin, and negatively correlated with PLT. However, MDSCs percentage was not correlated with RBC, HGB, PB blasts cells and BM blasts cells. The MDSCs percentage was positively correlated with AML risk stratification which the higher risk displayed the elevated MDSCs. The MDSCs percentage varied among those with different fusion genes and gene mutations, with higher frequency observed in those with *FLT3- ITD* mutation and *NUP98- HOXA9* fusion genes. The MDSCs percentage at the time of diagnosis was not significant different among the CR, PR, and NR groups, and was also no significantly differ between the MRD positive and negative group. Further categorized into low- and high-MDSC groups based on the median MDSCs percentage of 3.07% at the time of diagnosis, and the OS was significantly longer in the low-MDSC group than in the high-MDSC group. EVs entered into MNCs was observed by fluorescence microscopy. The MDSCs frequency was significantly higher in myeloid cells incubated with AML-EVs, but the MDSCs frequency was no significant change in PBMCs incubated with AML-EVs.
Summary/Conclusion: The MDSCs percentage was significantly elevated in both the BM and PB of AML patients, and there was no statistical difference in PB and BM. The percentage of MDSCs was positively correlated with AML risk stratification which the higher risk displayed the elevated MDSCs. The OS was significantly longer in the low-MDSCs group than in the high-MDSCs group. Taken together, MDSCs level at the time of diagnosis could predict AML prognosis. AML-EVs could promote the transformation of myeloid cells into MDSCs, and the role of AML-EVs in inducing MDSCs was stronger in myeloid cells than in PBMCs.

EP491 MULTICENTER OBSERVATIONAL RETROSPECTIVE STUDY ON BACTERIAL/FUNGAL/VIRAL INFECTIONS IN PATIENTS WITH SECONDARY ACUTE MYELOID LEUKEMIA TREATED WITH CPX-351 IN "REAL-LIFE"

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Background: CPX-351, a dual-drug liposomal encapsulation of cytarabine and daunorubicin has been approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
Aims: The primary endpoint of this study was to evaluate the absolute infectious risk in the real-life setting of AML patients (pts) treated with CPX-351. Secondary endpoints were the evaluation of the type, incidence and outcome of infections and to assess the infection-related mortality rate.
Methods: This retrospective, multicentre, observational study includes all consecutive AML pts receiving at least 1 CPX-351 course in 26 Italian hematological centers belonging to the SEIFEM (Sorveglianza Epidemiologica Infezioni nelle Emopatie) group from July 2018 to June 2020.
Results: Overall 152 pts [M/F 77/75; median age 64.5 y.o. (range 49-73)] have been included in this study: 110 with AML-MRC and 42 with t-AML. Overall, 253 courses of CPX-351 had been administered: all 152 pts received first induction course, 12 pts (8%) received second CPX induction, whereas 62 pts (41%) proceeded with the first CPX-351 consolidation course with 27 (43.5%) of them receiving also the second consolidation course.
A total of 179 (71%) febrile events were recorded: 141 (79%) during first or second induction, 25 (14%) and 12 (7%) after first and second consolidation respectively.
After a diagnostic workup in 55 cases (31%) the event has been defined as febrile neutropenia of unknown origin (FUO); the remaining 124 events were classified as microbiologically documented in 99 cases (55%) and clinically documented in 25 cases (14%).
The type of clinically documented infections was 11 pneumonia, 7 cellulitis/ abscesses, 3 arthritis, 2 colitis, 1 sinusitis, 1 cystitis.
Most microbiologically documented infections were of bacterial origin (91/99, 92%) with Gram-positive bacteria detected in 49 cases (54%) and Gram-negative in 42 (46%). Among bacterial infections, sepsis occurred in most cases (80/91) associated with pneumonia in 8 cases; other types of infections were pneumonia (3), abscesses (2), cystitis (4), discitis (1), sinusitis 1.
Overall, a fungal infection due to *Aspergillus spp* was diagnosed in 9 cases (in 1 case associated with bacterial sepsis) classified as proven 1 case, probable 7 cases, possible 1 case. Sites of aspergillosis were lung in 8 cases and orbital in 1 case.
Only 1 case of CMV reactivation associated with bacterial sepsis occurred.
Stratifying infections according to the treatment phase 141 events (79%) occurred during induction and 38 (21%) during consolidation. Interestingly all *Aspergillus* infections were diagnosed during the induction phase.
All pts were deeply neutropenic during infections [median duration of neutrophils count< 100 /mL and <500/mL was 12 days (range 1-42) and 16 days (range 2-60) respectively].
The overall 30-days mortality rate was 14% (22/152); most of the deaths (18/22) occurred during the induction phase. Causes of death were infection in 8 pts, AML progression in 8 pts, cerebral hemorrhage 3 pts, cardiac complication 3 pts.
Attributable mortality-infection rate resulted therefore 5.2% (8/152, 7 bacterial and 1 fungal). Notably, all infection-related deaths occurred in pts refractory to CPX-351 treatment.
Summary/Conclusion: Our data compared to those of previous registered studies show similar results in terms of infection incidence during CPX-351 induction treatment. Despite prolonged neutropenia infection-related mortality rate resulted relatively low.

EP492 DELAY IN THE DIAGNOSIS OF ACUTE MYELOID LEUKEMIA, COMPARISON BEFORE AND AFTER SARS-COV-2: A SINGLE CENTRE STUDY

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Background: Since the first case of severe acute respiratory infection by coronavirus 2 (SARS-CoV-2), Coronavirus Disease 2019 (COVID-19) has been the priority in any centre. This situation has produced collateral damage in patients with other acute diseases, with a delay in diagnosis and associated poorer outcomes. Acute myeloid leukemia (AML) is considered a hematologic emergency and delayed induction chemotherapy can harm these patients.
Aims: To analyse the impact of the COVID-19 epidemic outbreak on patients diagnosed with AML. We examined the impact on the times from symptom onset to hospital admission, performance status, possibility of administrating treatment and short-term outcome.
Methods: Patients diagnosed with AML between January 1, 2019 and December 31, 2020 were included. Cases were grouped into two periods, depending on the year. Demographic and clinical data were recorded including age, sex, detection of symptoms to diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, diagnoses using World Health Organization (WHO) classification, treatment administered, overall survival, and mortality. Comparisons between groups were made using chi-square tests to compare categorical variables and the Student test for continuous variables; with Kaplan-Meier estimates and Log-Rank test for survival analysis.
Results: In total 17 patients with AML were studied (male 9; 52.94%; median age 66; interquartile range (IQR) 59-74). Table 1 shows the comparison of baseline characteristics of the patients between the two years. In 2020 there was an increase in the time until the admission to the hospital (30.55 days vs 11.55 days, p=0.0419), with a worsening in ECOG punctuation on arrival statistically significant (Xi2=7.8254, p=0.020). In 2019, all the patients received treatment; and in 2020, 3 patients due to their status; did not received treatment, just best supportive care. Overall survival time was inferior in the cohort of 2020 (3.064 vs 14.028 months; p=0.045).

	2019 N=8	2020 N=9
Sex (n, %)		
Male	5, 62.50%	3, 33.33%
Female	3, 37.50%	6, 66.67%
Age (median, IQR)	62, (58.5-75)	66 (64-82)
ECOG (n, %)		
0-1	6, 75%	1, 11.11%
1-2	2, 25%	5, 55.56%
>3	0, 0%	3, 33.33%
Days before medical attention (median, IQR)	6.5, (4-22.5)	16 (8-55)
Classification according to WHO criteria (n, %)		
AML with recurrent genetic abnormalities	1, 12.50%	1, 11.11%
AML with myelodysplasia-related-changes	3, 37.50%	4, 44.44-%
Therapy-related myeloid neoplasms	3, 37.50%	2, 22.22%
Acute leukaemia of ambiguous lineage	0, 0%	1, 11.11%
AML, not otherwise specified	1, 12.50%	1, 11.11%
Treatment		
Cytarabine plus idarubicin (3+7)	2, 25%	2, 22.22%
Fludarabine plus cytarabine (FLUGA)	3, 37.50%	0, 0%
Fludarabine plus cytarabine plus idarubicin and granulocyte-colony stimulating factor (FLAG-Ida)	1, 12.50%	1, 11.11%
3+7 plus midostarin	1, 12.50%	0, 0%
3+7 plus quizartinib or placebo	0, 0%	1, 1.11%
Azacitidine	1, 12.50%	1, 1.11%
Azacitidine plus Venetoclax	0, 0%	1, 1.11%
No treatment	0, 0%	3, 33.33%
Overall survival (Median, IQR, months)	15.5 (6.5-21.66)	1 (0.56-4.43)

Summary/Conclusion: This retrospective study realized in our centre illustrates the collateral damage caused by the COVID-19 pandemic. Delay in seeking medical attention in a time-course-dependent pathology such as AML; it is followed by an increase in morbidity and mortality.

EP493 AN UPDATE ANALYSIS OF PROGNOSTIC SIGNIFICANCE OF PERIPHERAL BLOOD BLASTS ON DAY 7 OF INDUCTION CHEMOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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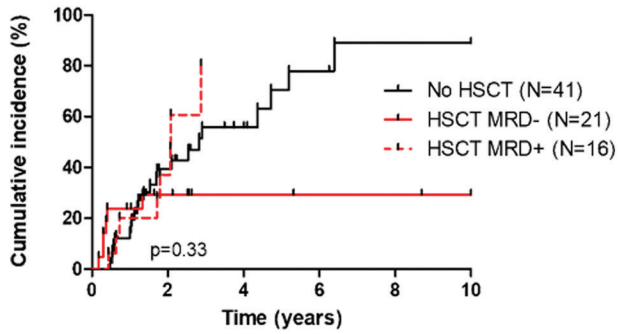
Background: In previous study, we found that peripheral blood blast percentages on day 7 (D7PBBP) of induction chemotherapy significantly associated with remission and long-term outcomes of patients with acute myeloid leukemia (AML). Moreover, D7PBB7 was proven to be an independent indicator for unfavorable prognosis.
Aims: The aim of this study was to assess the prognostic significance of D7PBBP for AML patients with a larger patient sample.
Methods: A retrospective analysis was performed with 137 AML (excluding those with acute promyelocytic leukemia) patients enrolled in this study between October 1, 2015 to October 31, 2018. D7PBBP was determined by flow cytometry. The previous patient cohort in our published study was used as training set, and patients of the present study were regarded as validation set.
Results: Of the 137 patients received one course of standard induction chemotherapy, 100 cases (73.0%) achieved complete remission (CR). With the cut-off value of 0.945% used in training set, the significant association between D7PBBP and achieving CR after one course of chemotherapy also could be observed in validation set (CR rates of patients with D7PBBP ≥0.945% *vs*. <0.945% were 38.2% *vs*. 84.5%; $P < 0.001$). Furthermore, D7PBBP was significantly related with levels of minimal residual disease (MRD) in the bone marrow (negative MRD rates were 17.7% and 40.8% in patients with D7PBBP ≥0.945% and <0.945%, respectively; $P = 0.014$). Similar to our training set, the cutoff value of 0.43% could be used to re-stratify prognosis of patients with AML. Patients with low D7PBBP (<0.43%) had significantly superior relapse-free survival (RFS) and overall survival (OS) compared with those with high levels of D7PBBP (≥0.43%). Additionally, we found that D7PBBP was potential marker for prognostic re-stratification in AML patients with low and intermediate cytogenetic karyotypes.
Summary/Conclusion: In summary, these results indicated that D7PBBP could predict treatment responses and long-term outcomes for patients with AML. Furthermore, D7PBBP was potential index to be integrated into cytogenetics-based risk adapted prognostic system for AML patients in low and intermediate risk group.

EP494 IMPACT OF TREATMENT INTENSITY, MRD AND HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ELDERLY R/R AML PATIENTS: A MONOCENTRIC RETROSPECTIVE STUDY

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Background: The management of acute myeloid leukemia (AML) in patients older than 60 years remains a major challenge as it is still rather unclear which patients will benefit or not from intensive chemotherapy compared to low intensity regimens according to clinical, molecular or cytogenetic markers. In relapse/refractory (R/r) settings, outcome in the elderly is usually very poor and there is currently no standard of care regarding second line or salvage therapy.
Aims: In this study, we aimed to investigate retrospectively the impact on the outcome of salvage/second line of treatment in R/r AML patients aged over 60 years old.
Methods: In this monocentric study, we analyzed 236 patients who were refractory to intensive (N=182) or semi-intensive (LIC) (low dose cytarabine/hypomethylating agents) (N=54) first line of treatment for newly diagnosed AML. Flow cytometry minimal residual disease (MRD) after intensive salvage chemotherapy was available in 42 patients and based on leukemia-associated immunophenotype (LAIP) using ELN recommendations (bulk lyses, and at least 500 000 live cells to achieve a sensitivity of 0.1%). MRD flow was performed in bone marrow samples using 8-color panel.
Results: Overall, 50%, 24.6% and 25.4% of patients received either intensive (3+7 based), LIC or best supportive care (BSC) respectively. With a median follow-up of 15.2 months (range: 1.1-190), median overall survival (OS) of the entire cohort was 15.3 months. Median OS was 19.2, 21.6 and 14 months in patients receiving intensive salvage (N=118), LIC (N=58) and BSC (N=59) respectively (p=0.02). Regarding baseline characteristics at R/r, duration of 1st complete remission (CR) ELN 2013 classification and NPM1/FLT3-ITD status were predictive for long term survival. Median OS for NPM1+FLT3-, NPM1+FLT3-ITD and NPM1-FLT3-ITD was 25.4, 14.3 and 7 months respectively (p<0.001). Next generation sequencing at diagnosis was available in 83/237 patients. Median OS was higher in IDH1/2 mutated cases (46.8 months) compared to TP53, ASXL1/RUNX1 and MAPK/RTK mutated cases (p<0.001). Late relapse (LR) (defined as relapse occurring after 12 months after 1st CR) was associated with a better outcome independently of the treatment intensity compared to early relapse (ER)/refractory status. For intensively salvaged patients, CR and CRi/MLFS (according to ELN definition) was 21.2% and 23.7% respectively. Median OS was 34.9 and 21.2 months for CR and CRi/MLFS compared to 12.8 months in refractory patients (p<0.001). Post-induction MRD1 negativity (defined positive when ≥ 0.1%) for patients in CR2 was reached in 60.9% of cases. Among intensively salvaged patients, 20 received GO-based regimen. Sixty percent (12/20) of them reached CR2 (compared to 44.9% in non-GO based salvage, p=0.06). Cumulative incidence of relapse at 3 years was 49.1% and 77.5% in MRD1- and MRD1+ patients respectively. For those who underwent HSCT in CR2 (N=38), pre-HSCT MRD positivity was associated with a high rate of relapse which was similar to non-transplanted patients (figure). HSCT treatment related mortality was 31.5%.



Summary/Conclusion: These results suggest that intensive salvage chemotherapy might be preferred for patients eligible for HSCT in CR2. Post-intensive salvage MRD1 by flow cytometry might also identify patients with a more favorable outcome, even if HSCT seems to be detrimental for long term survival. Low intensive regimens might also be a suitable option in unfit and/or HSCT non-eligible patients, especially in the era of venetoclax and anti-IDH based regimens.

Aggressive Non-Hodgkin lymphoma - Clinical

EP495 PROPHYLACTIC CORTICOSTEROID USE WITH AXICABTAGENE CILOLEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

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Background: In Cohorts 1 + 2 (C1 + 2; N=101) of ZUMA-1, the pivotal Phase 1/2 study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B-cell lymphoma, rates of Grade ≥3 cytokine release syndrome (CRS) and neurologic events (NEs) were 13% and 28% at the 6-month primary analysis (*N Engl J Med*. 2017;377:2531), and the objective response rate (ORR) was 82% (54% complete response [CR] rate). With a median follow-up of 51.1 months, median overall survival (OS) was 25.8 months and the 4-year OS rate was 44% (*Blood*. 2020;136[suppl, abstr]:40-42). In safety management Cohort 4 (C4; N=41), with its earlier corticosteroid use than C1 + 2, rates of Grade ≥3 CRS and NEs were 2% and 17%, and the ORR was 73% (51% CR; *Blood*. 2019;134[suppl, abstr]:243). In Cohort 6 (C6), the effect of prophylactic corticosteroid use on CRS and NEs was evaluated.
Aims: To present the primary analysis of C6, alongside those of C4 and C1 + 2 for context.
Methods: Eligible patients were leukapheresed, could receive optional bridging chemotherapy (in C4 and C6 but not C1 + 2), and received conditioning chemotherapy before axi-cel (target dose, 2×10^6 chimeric antigen receptor [CAR] T cells/kg). Patients in C6 received dexamethasone 10 mg orally on Days 0 (before axi-cel), 1, and 2 and earlier intervention with corticosteroids and tocilizumab. Primary endpoints were incidence and severity of CRS and NEs.
Results: As of 6/16/20, 40 C6 patients had received axi-cel, with median follow-up of 8.9 months. The median age was 64 years (50%, ≥65 years); 58% of patients were male; 55% had Eastern Cooperative Oncology Group performance status of 1; 65% had disease stage III/IV, and 53% received bridging. C6 patients had median tumor burden (by sum of product diameters post-bridging, if given, but before conditioning) lower than C1 + 2 and C4 (C6, 1184 mm^2; C1 + 2, 3723 mm^2; C4, 2100 mm^2). Median baseline lactate dehydrogenase level was similar in C6 and C4 but lower than C1 + 2 (C6, 236 U/L; C4, 262 U/L; C1 + 2, 356 U/L).
Among patients who received corticosteroids, median cumulative corticosteroid use (cortisone-equivalent dose) in C6 (1252 mg [n=40]) was greater than that in C4 (939 mg [n=30]) but less than that in C1 + 2 (6388 mg [n=24]). In C6, there was no Grade ≥3 CRS; 13% of patients had Grade ≥3 NEs, and there were no Grade 5 CRS or NEs. Onset of CRS appeared to be delayed in C6 (median, 5 versus 2 days in C4 and C1 + 2), and 68% of patients had no NEs or CRS within 72 hours of axi-cel. ORR was 95% (80% CR), and 63% of patients had ongoing responses at the data cutoff.
Median peak CAR T-cell levels trended higher in C6 versus C1 + 2 and C4 (C6, 64 cells/μL; C1 + 2, 42 cells/μL; C4, 53 cells/μL), which was corroborated by median CAR area under the curve in blood (C6, 526 cells/μL × day; C1 + 2, 462 cells/μL × day; C4, 511 cells/μL × day). Median peak serum levels of biomarkers associated with CAR T-cell treatment-related adverse events (eg, C-reactive protein, interferon-γ, granulocyte-macrophage colony-stimulating factor, interleukin-2) were lower in C6 versus C4 and C1 + 2.
Summary/Conclusion: Prophylactic corticosteroid use appears to reduce the rate of severe CRS and NEs and delay onset of CRS, without affecting median peak CAR T-cell levels or responses. Differences in cohort sizes and baseline characteristics should be considered when comparing cohorts. Longer follow-up is required to determine the impact on duration of response and survival.

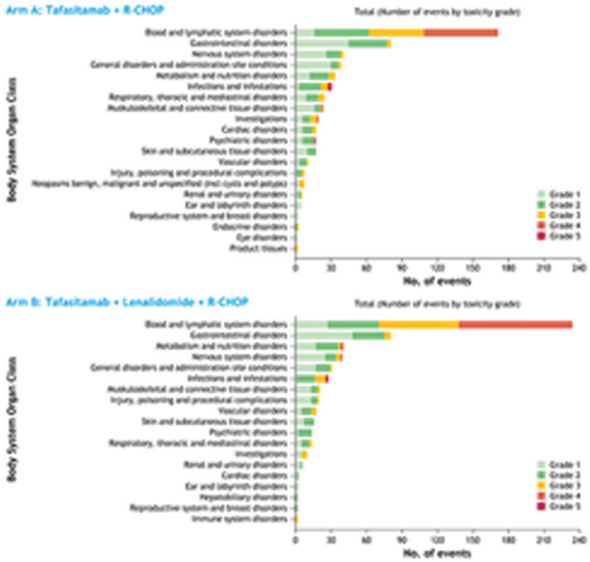
EP496 FIRST-MIND: A PHASE IB, OPEN-LABEL, RANDOMIZED STUDY TO ASSESS SAFETY OF TAFASITAMAB OR TAFASITAMAB + LENALIDOMIDE IN ADDITION TO R-CHOP IN PATIENTS WITH NEWLY DIAGNOSED DLBCL

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Background: Tafasitamab is a humanized, Fc-modified anti-CD19 monoclonal antibody that enhances antibody-dependent cellular cytotoxicity and phagocytosis. It is FDA-approved in combination with lenalidomide for adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), including arising from low-grade lymphoma, who are ineligible for autologous stem cell transplant (ASCT).
Aims: First-MIND (NCT04134936) is a Phase Ib, open-label, randomized study to assess the safety and preliminary efficacy of tafasitamab + R-CHOP or tafasitamab + lenalidomide + R-CHOP in patients with newly diagnosed DLBCL.
Methods: Eligible patients were aged ≥18 years, treatment-naïve, with DLBCL, international prognostic index (IPI) 2–5 and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2. Patients with known double- or triple-hit and transformed lymphoma were excluded. Treatment comprised six 21-day cycles of R-CHOP + tafasitamab (12 mg/kg IV, Day [D] 1, 8 and 15) (arm A) or R-CHOP + tafasitamab (12 mg/kg IV, D1, 8 and 15) + lenalidomide (25 mg orally, D1–10) (arm B). G-CSF and VTE prophylaxis was mandatory. Primary objective is safety; secondary objectives include overall response rate (ORR) and PET-CR rate at end of treatment, progression-free survival, long-term safety, pharmacokinetics and immunogenicity.
Results: From Dec 2019 to Aug 2020, 83 patients were screened in nine countries across Europe and the US; 66 were randomized (arm A: n=33; arm B, n=33). Data cut-off: 9 Dec 2020; the study is ongoing. Median age was 64.5 years (range 20–86 years). Overall, 30% of patients (20/66) were ≥70 years and many had high-risk disease: IPI 2 28.8%, IPI 3 45.5%, IPI 4 25.8%. ECOG PS: 47.0% of patients were ECOG PS 0, 43.9% PS 1, 9.1% PS 2. Most patients had stage III/IV disease (92%); 45.5% had bulky disease.
All patients experienced a treatment-emergent adverse event (TEAE); 555 events occurred in arm A and 570 in arm B. Grade ≥3 neutropenia was observed in 54.5% (arm A) and 66.7% (arm B) of patients. Grade ≥3 thrombocytopenia was observed in 12.1% (arm A) and 30.3% (arm B) of patients. Six patients in each arm experienced febrile neutropenia. Diarrhea, fatigue and vomiting were comparable between the two arms. Grade ≥3 nervous system disorders were experienced by 6.1% of patients in arm A and 12.1% in arm B (the majority of events were polyneuropathies related to vincristine). Infusion-related reactions to both rituximab and tafasitamab occurred in 12.1% (arm A) and 18.2% (arm B) of patients, and 21.2% (arm A) and 27.3% (arm B) of patients had a grade ≥3 infection and/or infestation (TEAEs by system organ class [SOC] shown in Figure 1). Serious TEAEs occurred in 42.4% (arm A) and 51.5% (arm B) of patients. There were three deaths unrelated to tafasitamab and/or lenalidomide (sepsis, urosepsis and COVID-19 pneumonia). Dose intensity of R-CHOP was maintained in both treatment arms.
Among 60 patients who completed tumor assessments after cycle 3, ORR was 89.7% (arm A) and 93.5% (arm B).

Figure 1: TEAEs by system organ class and toxicity grade



Summary/Conclusion: These data suggest that R-CHOP + tafasitamab or tafasitamab + lenalidomide is tolerable in patients with treatment-naïve DLBCL. Dosing and scheduling of R-CHOP is not affected by the addition of tafasitamab. Toxicities are similar to those expected with R-CHOP alone or R-CHOP + lenalidomide. Updated safety and early efficacy data will be presented at the conference.

EP497 EARLY RESPONSE AT ONE MONTH IS PREDICTIVE OF THE OUTCOME OF THE PATIENTS WITH RELAPSE/ REFRACTORY LARGE B-CELL LYMPHOMA AFTER CAR T-CELL

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Background: Anti-CD19 CAR T-cells, Tisagenleuclecel (Tisa-cel) and Axicabtagene ciloleucel (Axi-cel), have been approved for pts with relapsed or refractory aggressive large B-cell lymphomas (R/R LBCL) after 2 lines of therapy, with durable remissions observed in 30% to 40% of the pts, and median progression-free survival (PFS) at 2.9 and 5.9 months (M), respectively. Predictive value of early response assessments at M1 and M3 on patient outcome has not been described.
Aims: To evaluate the predictive value of early response at M1 and M3 after CAR T-cells infusion in R/R LBCL, using clinical evaluation and visual and semi-quantitative PET approach analysis.
Methods: Clinical, biological and metabolic characteristics, including, SUVmax, SUVpeak and total metabolic tumor volume (TMTV) before CART infusion (baseline), at M1 and at M3 were retrospectively collected. Complete metabolic response (CMR) was defined by a Deauville Score (DS) 1,2,3. Conversion rate from partial response (PR)/stable disease (SD) at M1 to complete response (CR) at M3 were assessed. Optimal ΔSUVmax at M1 or M3 able to predict PFS events were identified using time-ROC. Survivals were estimated by the Kaplan-Meier method. Cox models were used to select prognostic covariates based on landmark at M1 or M3.
Results: 151 patients with R/R DLBCL (n= 122), transformed follicular lymphoma (tFL) (n= 19) or PMBL (n=10) were treated with Tisa-cel (n= 61) or Axi-cel (n=90). Median age was 63 (21-77). At time of decision, 131 (87%) patients were PS 0-1, 86 (57%) were IPI low or intermediate risks, 84 (56%) had abnormal LDH levels. Median number of prior lines was 3 (2-7). PFS at 6 and 12 months for the whole cohort were 48% and 42% respectively, and overall survival (OS) were 80% and 64%, respectively. Median time from infusion to progression was estimated at 3.7 months (95%CI, 3.0 to 16.7). At baseline: median SUVmax was 21.5 and median TMTV was 54ml. 66 (44%) patients presented a high TMTV (>80ml). At M1: 61/151 (40%) patients are in CR, 37/151 (24.5%) in PR and 10/151 (7%) in SD. Among 128 patients evaluable with DS, 52 (41%) are in CMR with DS 1-3, 32 (25%) have DS-4 and 44 (34%) have DS-5, with 6-month PFS and OS rates (from M1) at 78% and 95% for DS1-3, 76% and 97% for DS-4, 10% and 63% for DS-5, respectively. At M3: 64/108 (59%) were in CR and 14/108 (13%) were in PR or SD. 13 PR patients at M1 converted to CR at M3, while 13 stayed in PR/SD, and 11 progressed. 9/10 SD progressed. Among 103 patients evaluable with DS, 53 (51%) are in CMR with DS 1-3, 17 (17%) have DS-4 and 33 (32%) have DS-5, with 6-month PFS and OS rates (from M3) at 87% and 92% for DS1-3, 97% and 100% for DS-4, 9% and 71% for DS-5, respectively. ΔSUVmax cutoffs identifying good responder patients were a decrease of at least 73% at M1 and 85% at M3 with 51.6% and 51.6% of the patients who reached these cutoffs, respectively. Patients below the 73% threshold at M1 had decreased PFS (HR 3.96, p<0.001) and OS (HR=4.45, p<0.001). By contrast, patients below the 85% threshold at M3 had a decreased PFS (HR=4.18, p<0.001) but no different OS (HR=1.34, p=0.55), probably because early progressor with the poorest outcome have been excluded from this analysis.
Summary/Conclusion: Early metabolic response at M1 is strongly associated with better outcome. These data argue for an early monitoring of patients using functional imaging, and innovative strategies for very high-risk patients.

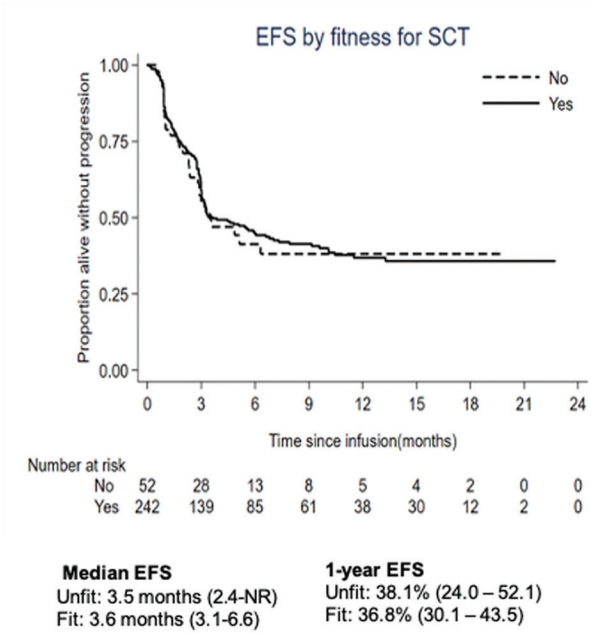
EP498 CD19 CAR-T IN LESS FIT PATIENTS WITH R/R HIGH-GRADE LYMPHOMA

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Background: Relapsed/refractory (r/r) lymphoma patients with comorbidities and/or advanced age are increasingly considered for treatment with CD19 CAR-T. However, there are no clear criteria to define fitness and limited data on the clinical benefit of CAR-T in the less fit patient population.
Aims: To analyse the outcomes of lymphoma patients approved for licenced CD19 CAR-T in the UK who were deemed unfit for autologous stem cell transplant (ASCT).
Methods: We analysed 400 consecutive r/r high-grade lymphoma patients approved for treatment with axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between Dec 2018 and Nov 2020 across 10 UK centres. Data on patients' fitness and comorbidities were retrospectively collected. Fitness for ASCT was defined by the treating team based on physical suitability irrespective of disease status.
Results: 80/400 (20%) of patients approved for CAR-T were deemed unfit for ASCT (40 for age alone, 10 frailty, 11 cardiac function, 6 kidney function, 13 other/multiple comorbidities).
52/80 (65%) of patients in the ASCT-unfit cohort underwent CAR-T infusion; Reasons for not proceeding with treatment were as follows: 20 progressive disease (PD), 2 manufacturing failures, 1 cardiac failure, 1 diagnosis of dementia, 3 deaths. The drop-out rate from approval to infusion in the ASCT-unfit vs. ASCT-fit group was 34% vs. 24% (p=0.062). 27/52 (52%) patients received tisa-cel, 25 (48%) axi-cel (vs. 20% tisa-cel in fit patients; p‹0.0001). Patients' median age was 71 years (range 47-78) vs. 56 years (range 18-72) in the ASCT-fit cohort (p‹0.0001). ASCT-unfit patients were more likely to have ECOG PS 1 at baseline (65% vs. 46%; p=0.02), high-risk IPI (24% vs. 9%; p=0.005), HCT-CI comorbidity score of 3+ (17% vs. 5%; p=0.005), lower GFR (‹50ml/min: 25% vs. 5%; p‹0.0001), and lower LVEF (‹50%: 18% vs. 6%; p=0.01). No other significant difference in baseline characteristics was observed.

The ongoing 6-months ORR was 31% (all CR). With a median follow-up of 10.5 months, the median EFS/OS were 3.5/10.6 months and the 12-months EFS/OS 38/42%. There was no significant difference in efficacy outcomes between the ASCT-unfit and -fit cohorts. Moreover, no evidence of a difference between groups who were unfit due to age or comorbidities, nor evidence of worse prognosis for patients with impaired kidney- or cardiac function or high HCT-CI.
Among 52 ASCT-unfit patients, there was one case with G3 CRS (2%), and 6 patients (11%) with G3+ ICANS. No significant difference was observed in the incidence of any grade/G3+ CRS or ICANS, the use of tocilizumab or steroids, ICU admission rate, and the incidence of G3+ cytopenias post CAR-T compared to the ASCT-fit cohort.



Summary/Conclusion: Results from our large, prospective real-world cohort demonstrate that CD19 CAR-T can be safely delivered in carefully selected older patients and patients with comorbidities who are not deemed suitable for transplant. There was a trend towards a higher drop-out rate in less fit patients, but patients who successfully undergo infusion appear to have the same long-term benefit from CD19 CAR-T as ASCT-fit patients and should be considered for this potentially curative treatment.

EP499 SUBCUTANEOUS EPCORITAMAB IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA: SAFETY PROFILE AND ANTI-TUMOR ACTIVITY

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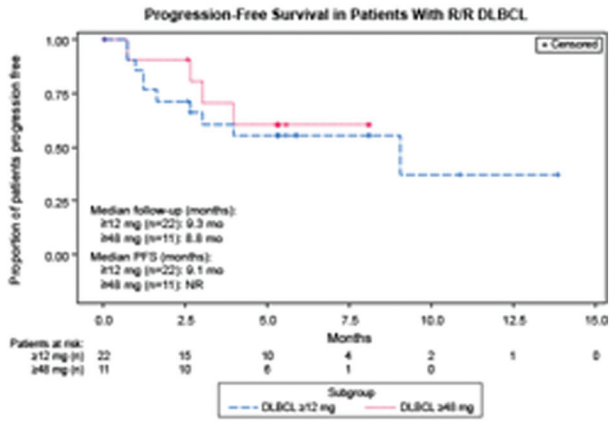
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Background: Epcoritamab is a CD20xCD3 bispecific antibody that induces T-cell–mediated killing of CD20–positive malignant B-cells.

Aims: To present updated data, including progression-free survival (PFS) from the dose escalation part of the first-in-human phase 1/2 study of epcoritamab in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL; NCT03625037).

Methods: Adults with R/R CD20+ B-NHL received flat-dose 1 mL SC epcoritamab (step-up dosing approach) in 28-day cycles (q1w: cycles 1–2; q2w: cycles 3–6; q4w thereafter) until disease progression or unacceptable toxicity. Step-up dosing and standard prophylaxis were used to mitigate severity of cytokine release syndrome (CRS). Informed consent was obtained from all patients prior to trial enrollment.

Results: At data cut off (31 January 2021), 68 patients with B-NHL were enrolled across histologies including diffuse large B-cell lymphoma (DLBCL; n=46 [67.6%]; de novo and transformed), follicular lymphoma (FL; 12 [17.6%]), mantle cell lymphoma (MCL; 4 [5.9%]), and others (6 [8.8%]). The majority of patients were heavily pretreated (median [range] prior lines: DLBCL, 3 [1–6]; FL, 4.5 [1–18]); including prior CAR-T (n=6) and prior ASCT (n=10). At median follow-up of 14.1 months (DLBCL, 10.2 months; FL, 15.2 months), treatment was ongoing in 15 (22%) patients. The most common treatment-emergent adverse events (AEs) were pyrexia (69%), CRS (59%), and injection site reaction (47%). CRS events were all grade 1 or 2 and most occurred in cycle 1; neurotoxicity was limited (6%; grade 1: 3%; grade 3: 3%; all transient). One case of tumor lysis syndrome was observed (1.5%; grade 3); there were no cases of febrile neutropenia or treatment-related death. Overall response rates (ORRs) for patients with DLBCL at doses ≥12 mg (n=22) and ≥48 mg (n=11) were 68% (CR=46%; PR=23%) and 91% (CR=55%; PR=36%), respectively. The ORR for patients with FL at doses ≥12 mg (n=5) was 80% (CR=60%; PR=20%); the ORR for patients with MCL at doses ≥0.76 mg (n=4) was 50% (CR=25%; PR=25%). Responses deepened over time (PR converted to CR: DLBCL, 6 patients; FL, 3 patients). For patients with DLBCL, median (range) time to response was 1.4 (1.0–4.0) months; median (range) time to CR was 2.7 (1.1–3.9) months. For patients with FL, median (range) time to response was 1.9 (1.0–4.0) months. Among DLBCL patients achieving CR with doses ≥6 mg (n=11), none relapsed while on treatment. The median PFS for patients with DLBCL ≥12 mg (n=22) was 9.1 months (95% CI: 1.6, NE; median follow-up 9.3 months) and for patients with DLBCL ≥48 mg (n=11) median PFS was not reached (median follow-up 8.8 months) (Figure). Updated analyses will be presented.



Summary/Conclusion: With longer follow-up, SC epcoritamab demonstrated substantial single-agent activity, inducing deep and durable clinically meaningful responses, with a consistent safety profile. Notably no severe (grade ≥3) CRS events, no febrile neutropenia, and limited neurotoxicity was observed.

EP500 PIRTOBRUTINIB (LOXO-305), A NEXT GENERATION, HIGHLY SELECTIVE, NON-COVALENT BTK INHIBITOR IN PREVIOUSLY TREATED MCL, WM AND OTHER NHLS: RESULTS FROM THE PHASE 1/2 BRUIN STUDY

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Background: Despite the marked efficacy of covalent BTK inhibitors (BTKi) in MCL, WM, and MZL, the development of resistance and discontinuation for adverse events can lead to treatment failure. Moreover, pharmacological liabilities of these agents such as low oral bioavailability or short half-life, can lead to suboptimal BTK target coverage and ultimately result in acquired resistance in some patients (pts). To address these limitations, pirtobrutinib (LOXO-305), a highly selective, non-covalent BTKi that inhibits both WT and C481-mutated BTK with equal low nM potency was developed.
Aims: To evaluate safety and efficacy of pirtobrutinib in previously treated MCL and other NHLs.
Methods: BRUIN is a multicenter phase 1/2 trial (NCT03740529) enrolling pts with advanced B-cell malignancies who have received ≥2 prior therapies. Oral pirtobrutinib was dose escalated in a standard 3+3 design in 28-day cycles. The primary endpoint was MTD/RP2D identification. Efficacy evaluable pts included all dosed pts who underwent their first response evaluation or discontinued therapy. Safety was assessed in all pts (n=323). Response was assessed according to Lugano Classification or iWWM.
Results: As of 27 September 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, and 66 other B-cell lymphomas) were treated on 7 dose levels (25-300mg QD). Median age was 69 (range 50-87) years for MCL pts, 68 (42-84) for WM pts, and 68 (27-86) for other NHLs pts. Median number of prior lines of therapy was 3 (range, 1-8) for MCL, 3 (2-11) for WM, and 4 (2-10) for other NHLs. 93% of MCL, 70% of WM and 36% other NHL pts had received a prior BTKi. Pirtobrutinib demonstrated high oral exposures, with doses ≥100mg QD exceeding the BTK IC90 for the entirety of the dosing interval. No DLTs occurred. Consistent with pirtobrutinib's selectivity, the only treatment emergent adverse events regardless of attribution or grade in ≥10% of pts (n=323) were fatigue (20%), diarrhea (17%) and contusion (13%). Grade 3 atrial fibrillation/flutter was not observed; 1 pt had grade 3 hemorrhage in the setting of mechanical trauma. Responses were observed at the first dose level of 25mg QD. A RP2D of 200mg QD was selected. At the efficacy cutoff date, 35 (57%) MCL pts, 18 (69%) WM pts and 34 (52%) other NHL pts remained on therapy. Among the 52 efficacy evaluable prior BTKi treated MCL pts, the ORR was 52% with 13 CR, 14 PR and 9 SD. Median follow up was 6 months (range 0.7-18.3+) for MCL. Responses in MCL were observed in 9/14 pts (64%) with prior autologous or allogeneic transplant, and 2 of 2 with prior CAR-T cell therapy. Among the 19 efficacy-evaluable pts with WM, the ORR was 68% (9 PR, 4 MR, 3 SD), and 69% in prior BTKi treated pts. 10 of 13 WM responders were ongoing (follow-up time from initial response: 0.8-9.2 months). For the 55 efficacy-evaluable other NHL pts, best response was as follows: DLBCL - 24% ORR (4 CR, 2 PR, 2 SD, 12 PD, 5 NE), FL - 50% ORR (2 CR, 2 PR, 1 SD, 3 PD), MZL - 22% ORR (2 PR, 7 SD), Richter's transformation - 75% ORR (6 PR, 1 SD, 1 NE) and Other (2 B-PLL, 3 Low grade transformation) 1 SD, 2 PD, 2 NE.
Summary/Conclusion: Pirtobrutinib demonstrated promising efficacy in MCL pts following multiple prior lines of therapy, including a covalent BTKi. Pirtobrutinib also showed efficacy in previously treated other NHLs. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index.

EP501 GLOFITAMAB STEP-UP DOSING (SUD): UPDATED EFFICACY DATA SHOW HIGH COMPLETE RESPONSE RATES IN HEAVILY PRETREATED RELAPSED/REFRACTORY (R/R) NON-HODGKIN LYMPHOMA (NHL) PATIENTS (PTS)

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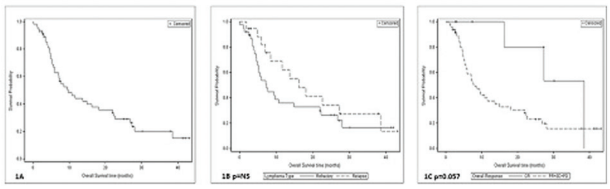
Background: Glofitamab (RG6026), a T-cell-engaging, bispecific, full-length antibody, allows bivalent binding to CD20 (B-cells), and monovalent binding to CD3 (T-cells). In NP30179 (NCT03075696), an ongoing multicenter, Phase I dose-escalation and expansion study, 0.6–25mg glofitamab fixed-dosing with obinutuzumab pretreatment (Gpt), showed high, durable complete responses and manageable safety in heavily pretreated R/R NHL (Dickinson, et al. EHA 2020). Glofitamab SUD, in addition to Gpt, allowed dose escalation up to 30mg to maximize efficacy, while mitigating cytokine release syndrome (CRS) (Hutchings, et al. J Clin Oncol 2021).
Aims: To present updated efficacy data from glofitamab monotherapy SUD cohorts.
Methods: Gpt (1000mg) was given to pts 7 days pre-glofitamab initial dose. Intravenous SUD of glofitamab was given on Day (D) 1 and 8 of Cycle (C) 1 and then at the target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg); treatment continued for up to 12 cycles, every 21 days. Response rates were based on the Lugano criteria (Cheson, et al. J Clin Oncol 2014).
Results: Fifty-two pts received glofitamab SUD; 17 and 35 pts received 2.5/10/16mg and 2.5/10/30mg, respectively. Twenty-eight pts (53.8%) had aggressive NHL (aNHL) and 24 pts had indolent NHL (iNHL). Pts had a median age of 68 (44–85) years and received a median of 3 (1–12) prior lines of therapy. Forty (76.9%) and 38 (73.1%) pts were refractory to their most recent and any prior CD20 therapy, respectively.
After a median follow-up of 6.3 months, an updated efficacy analysis was conducted on December 1, 2020. For pts with aNHL (N=28), the best overall response (OR) and complete metabolic response (CMR) rates were 64.3% and 57.1%, respectively; a trend of improved response was observed with increased target dose, with a CMR rate of 71.4% at 2.5/10/30mg (N=14). Notably, 4/5 pts (80%) with mantle cell lymphoma (2.5/10/16mg, n=2; 2.5/10/30mg, n=2) had CMR. For aNHL, 13/16 CMRs are ongoing, with 8 CMRs lasting >3 months. For pts with iNHL (N=24), OR and CMR rates were 79.2% and 70.8%, respectively; 14/17 CMRs are ongoing, with 10 CMRs lasting >3 months.
As of August 3, 2020, common adverse events (52 pts) were CRS (63.5%), neutropenia (38.5%), and pyrexia (32.7%). CRS was mostly confined to C1: 24/50 pts had CRS after 2.5mg; 20/49 pts after 10mg; 2/16 and 8/32 pts had CRS after 16 and 30mg (C2D1), respectively. Grade [Gr] 1 and 2 CRS was reported in 18 (34.6%) and 12 (23%) pts, respectively; 3 pts had Gr 3 CRS; none had Gr 4/5 events (ASTCT 2019). Updated data, including biomarker data on baseline CD20 expression and CD8 levels in the tumor, will be presented.
Summary/Conclusion: Updated data for glofitamab monotherapy SUD show higher preliminary response rates than previously reported in pts with R/R NHL who have failed multiple lines of therapy. CRS was mostly manageable, of low grade, and confined to the first cycle of treatment.
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EP502 IBRUTINIB, BENDAMUSTINE, RITUXIMAB FOR RELAPSED AND REFRACTORY AGGRESSIVE B CELL LYMPHOMA – FINAL ANALYSIS OF PHASE II CLINICAL TRIAL

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Background: Ibrutinib is a first-in-class, potent, orally-administered covalently-binding small molecule, an inhibitor of Bruton's tyrosine kinase (BTK). It was found to be effective in Diffuse large B cell lymphoma Lymphoma (DLBCL) specifically of the Activated (ABC) type. Ibrutinib, bendamustine, and rituximab (IBR) combination was found to be effective for the treatment of B cell lymphomas, including DLBCL in phase I clinical trial.
Aims: To explore the efficacy of the IBR regimen in relapse & refractory (RR) DLBCL.
Methods: We performed a phase II single-center trial. Patients (pts) with RR DLBCL and transformed low-grade lymphoma were eligible. Patients with CNS lymphoma, inadequate bone marrow function or previous exposure to bendamustine or ibrutinib were excluded. FDG/PET-CT's were interpreted according to the Lugano criteria. Rituximab and bendamustine were given in a 28 days cycle in their standard dose. Ibrutinib 560mg, was administered continuously from day 1. FDG/PET-CT was repeated afters cycles 3 and 6, and then every 16 weeks. Patients who achieved response after 3 cycles and were eligible were reffered to stem cell transplantation (SCT). For the time of this analysis, 62 pts were screened, and 56 were treated.
Results: Thiry pts (54%) were male. Median age was 69.7 years (28-94). Lymphoma subtype which was defined by the Hans criteria was as follows: GCB in 7 (12.5%), non GCB in 21 (37.5%), double/triple hit in 9 (16.1%), follicular grade 3B in 2 (3.6%), mediastinal in 3 (5.4%) transformed low grade in 4 (7.1%) and NA in 10 (17.9%). Thirty eight pts had refractory disease (67.9%). Thirty patiens (53%) had stage IV disease at screening. Sixteen pts received the therapy as second line and 40 as third line. Nine pts (16.1%) had previous autologous stem cell transplantation. ORR was 27.2% for the entire cohort and 36.1% for the pts that completed 3 cycles of therapy (n=36). Only 19% of the non-GCB pts responded to treatment. Thiry nine pts died during follow-up, 36 of them due to disease progression, the others due to stroke, myocardial infarction and allogeneic stem cell transplantation complications. Median follow-up was 7.9 months. Median OS of the entire cohort was 9.7 months (figure 1A). Refractoy pts had median OS of 7.3 months, while relapsed pts had 16.2 (figure 1B p=NS).Patients who achieved CR had median OS of 38.5 months while those who did not had 7.7 (p=0.057 figure 1C).Median PFS of the enitre chorot was 5 months and for the pts that completed at least 3 cycles of therapy 7 months. Patients that achieved response had significantly longer PFS than others (p<0.0001). Five pts underwent either autologous or allogeneic SCT after 3 cycles of treatment, all of them are alive and 4 in remission. Altogether 37 serious adverse event (SAE) were recorded in 20 pts (35.7%). Fifteen of them were related to ibrutinib, and the most common were infections.



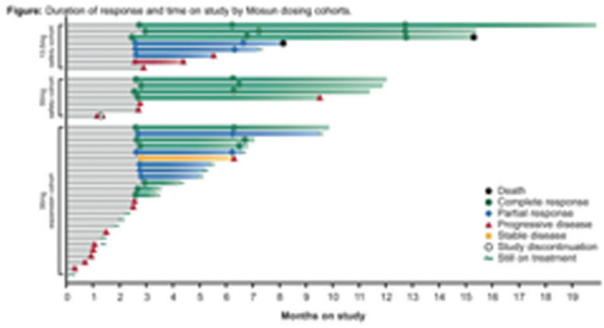
Summary/Conclusion: The IBR protocol is a conveniently administered ambulatory regimen. The regimen was found to be safe and effective in this cohort of elderly pts whose disease was mostly refractory to previous lines of treatment. Patients that achieved response had significantly better PFS and OS than those who did not. Response rate in the non-GCB group was not better than all other subtypes. Although the median OS of the entire cohort is short, pts who achieved remission and underwent SCT survived so far. We conclude that the IBR regimen should be considered for the treatment of R/R DLBCL pts and can also serve as a bridge to transplant.

EP503 MOSUNETUZUMAB (MOSUN) MONOTHERAPY FOR ELDERLY/UNFIT PATIENTS (PTS) WITH FIRST-LINE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) CONTINUES TO SHOW PROMISING SAFETY AND EFFICACY WITH DURABLE COMPLETE RESPONSES

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Background: Elderly/unfit pts with DLBCL who are ineligible for standard first-line (1L) chemoimmunotherapy (CIT) due to frailty and comorbidities often receive either no treatment, reduced-dose R-CHOP, or therapies such as R-CVP and R-bendamustine: outcomes are often poor (Shewade, et al. ASH 2020). Mosun, a full-length, humanized, IgG1 CD20xCD3 bispecific antibody, has promising efficacy and tolerable safety in relapsed/refractory DLBCL (ongoing Phase I study NCT02500407; Schuster, et al. ASH 2019). Preliminary data from the Phase I/II, multicenter GO40554 study (NCT03677154) show notable efficacy and tolerability with Mosun monotherapy for elderly/unfit pts with 1L DLBCL who cannot tolerate full-dose CIT (Olszewski, et al. ASH 2020).
Aims: To describe updated clinical data from the GO40554 study.
Methods: Two safety-evaluation cohorts were assessed (Mosun 13.5mg and 30mg), followed by an expansion phase (Mosun 30mg). Pts were aged ≥80 years, or 60–79 years with impairment in ≥1 activity of daily living (ADL) or instrumental ADL, or impaired cardiac, renal or liver function precluding full-dose CIT. Pts received optional pre-treatment with prednisone (+/- vincristine), followed by intravenous Mosun in step-up doses on Days (D) 1 (1mg), 8 (2mg) and 15 (full dose: 13.5/30mg) of Cycle (C) 1 and full (C1D15) dose Mosun on D1 of each subsequent 21-day cycle. Pts with a complete response (CR) stop Mosun after 8 cycles; pts with a partial response (PR) or stable disease can continue Mosun for a total of 17 cycles.
Results: As of January 15, 2021, 40 pts had received Mosun (13.5mg safety cohort, n=8; 30mg safety cohort, n=7; 30mg expansion, n=25). Median age was 84 (67–100) years, 27 (67.5%) pts were female, 27 (67.5%) had ECOG performance status 0–1, 20 (50%) had Ann Arbor Stage III–IV and 32 (80%) had an IPI score ≥2. Pts received a median of 6 (range: 1–13) Mosun cycles; 2 pts in PR continued Mosun after 8 cycles. Of 40 pts, 35 (87.5%) had ≥1 adverse event (AE), 27 (67.5%) had ≥1 Mosun-related AE; 15 (37.5%) pts had a grade (Gr) 3–4 AE, 8 of which were Mosun-related. The most common (>10%) treatment-emergent AEs were cytokine release syndrome (CRS; n=9, 22.5%), abdominal pain (n=7, 17.5%), rash (n=5, 12.5%) and neutropenia (n=5, 12.5%); one pt had febrile neutropenia. Six (15%) pts had Gr 1 CRS per ASTCT (Lee, et al. 2019). Three (7.5%) pts had Gr 2 CRS events, all were managed with supportive care and fluids for hypotension, steroids and low-flow oxygen, as required (no tocilizumab, vasopressors, high-flow oxygen or intensive care required). One pt with Gr 1 CRS had Mosun-related Gr 2 neurotoxicity on C1D2 (inability to answer questions, drowsiness and weakness), which resolved after 2 days. One pt had a Gr 2 non-serious headache. No fatal AEs or Gr ≥3 neurologic AEs were observed. Between C1–C8, 14 (35%) pts discontinued Mosun due to progressive disease (PD); no pts discontinued due to AEs. For efficacy-evaluable pts (n=31), the overall response rate was 67.7% and CR rate was 41.9%. Responses after C8 (n [%]) with Mosun 13.5mg (N=8) were: CR: 3 (37.5); PR: 3 (37.5); PD: 2 (25); and after C4 or C8 with Mosun 30mg (N=23) were: CR: 10 (43.5); PR: 5 (21.7); PD: 3 (13). Of 13 pts with CR (11 ongoing), 4 durable responses have been observed ≥12 months from the start of therapy (**Figure**). Biomarker analyses are ongoing and will be provided.



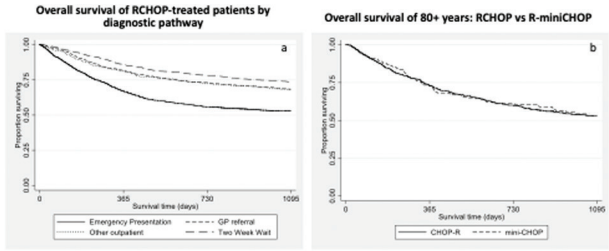
Summary/Conclusion: Mosun continues to show promising efficacy, including durable responses, and tolerable safety for elderly/unfit pts with 1L DLBCL and should be further evaluated as a chemotherapy-free backbone for pts unable to tolerate standard CIT.

EP504 DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) IN PATIENTS OLDER THAN 65 YEARS: ANALYSIS OF 3 YEAR REAL WORLD DATA OF PRACTICE PATTERNS AND OUTCOMES IN ENGLAND

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma. In the UK, the NHS Cancer Plan in the year 2000 announced the NHS urgent cancer referral pathway - the 'Two Week Wait' diagnosis pathway is an initiative for the implementation of all suspected cancer patients (pts). This national pathway is designed to expedite urgent specialist referral (within 2 weeks) for pts whose signs or symptoms were suggestive of cancer, with the aspiration to enable early diagnosis and improve patient outcomes.
Aims: We wished to examine real-world practice, treatment and outcome patterns in older pts, with a focus on the effect of route to initial diagnosis to outcome. No prior published analyses have examined the effect of the diagnostic pathway on pt survival with aggressive lymphoma.
Methods: Data were extracted from Public Health England's National Cancer Registration and Analysis Service between 2013-2015 which included route to initial diagnosis, disease characteristics, socio-economic deprivation quintiles, and survival. The Systemic Anti-Cancer Therapy dataset identified front-line regimens, cycle number and doses. Overall survival (OS) was defined from DLBCL diagnosis until time of death from any cause and differences in OS were determined by log-rank tests. Lymphoma-specific survival (LSS) was defined from DLBCL diagnosis until the time of death from DLBCL, with censoring occurring at the cause of death for causes other than DLBCL. To account for the impact of multiple variables on survival, a cox-regression model was implemented using the 'stcox' command. Differences in proportions for descriptive statistics were tested with a 2-sided Z-test. Data were interrogated to explore potential associations between route to diagnosis and baseline characteristics with OS and LSS.
Results: A total of 9186 DLBCL pts ≥65 years across a 3-year period (2013-2015) were identified. Median follow-up of the whole cohort was 2.1 years. 68% were aged 65-79 years. Gender distribution was equal. 4536 presented with stage III-IV (61%). Routes to initial diagnosis were emergency (34%), NHS urgent cancer referral pathway (29%) and standard GP referral (25%). The most common regimen was R-CHOP (n=4392), administered to 80.5% of those with a known regimen. 313 pts received R-miniCHOP (7% of all R-CHOP). For all pts, 3-year OS for those 65-79 years was 57% (95% confidence interval (CI) 56%>58%) and for ≥80 years was 32% (95% CI 30%>33%). 3-year OS for R-CHOP-treated pts diagnosed via emergency presentation (n=1160) was 54% (reference 1.00, GP referrals (Fig A): fully-adjusted hazard ratio (HR) 1.63 (95% CI:1.43-1.86, p<0.01) and 75% (fully-adjusted HR 0.81 (95% CI:0.71-0.93, p<0.01) on the NHS urgent cancer referral pathway (n=1635). NHS urgent cancer referral pathway retained its association with an improved LSS (HR 0.71, 95% CI 0.53-0.95, p=0.02), whilst pts with an emergency presentation had a significantly worse LSS by MVA (HR 1.95, 95% CI 1.49-2.54, p<0.01). 3-year OS was equivalent (54%) for both R-miniCHOP and R-CHOP in those ≥80 years (Fig B).



Summary/Conclusion: Our large, comprehensive real world practice analysis are the first to show that the NHS urgent cancer referral pathway leads to superior lymphoma-specific and overall survival in R-CHOP treated DLBCL pts even after adjusting for multiple confounders. Equivalent survival for R-CHOP and R-mini-CHOP in those ≥80 years supports the use of the latter in this setting.

EP505 HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH CONDITIONING INCLUDING ALLOGENEIC BISPECIFIC CAR-T CELLS TARGETING BOTH CD19 AND CD22 FOR REFRACTORY/RELAPSED B-CELL NON-HODGKIN LYMPHOMA

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Background: The prognosis of refractory/relapsed aggressive B-cell non-Hodgkin lymphoma (r/r B-NHL) is extremely poor, especially for the patients who failed to autologous chimeric antigen receptor-T (CAR-T) cells.
Aims: For r/r B-NHL, a clinical trial using haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) with conditioning including allogeneic bispecific CAR-T cells targeting both CD19 and CD22 from the same donor (allo-CD19/CD22 CAR-T) has been registered, and the safety and efficacy will be evaluated.
Methods: From September 2020 to January 2021, 7 patients with r/r B-NHL were enrolled. The median age was 43 (26-54) years old. The diagnosis included diffuse large B-cell lymphoma (DLBCL, n=6) and Burkitt lymphoma (n=1). Four cases were with TP53 mutations. All patients failed to multi-line therapies, including chemotherapy (n=7), autologous HSCT (n=1), autologous CAR-T (n=6), local irradiation (n=4) and anti-PD1 antibodies (n=2). The disease status before transplant was stable disease (SD) in 1 case, partial remission (PR) in 3 and progressive disease (PD) in 3. Before the trial, the expression of CD19 and/or CD22 antigen in tumor tissue of all patients was positive confirmed by pathology. Conditioning with busulfan, fludarabine-based regimen combined with allo-CD19/CD22 CAR-T was applied. Tacrolimus, mycophenolate mofetil, a short-term methotrexate and antithymocyte globulin were used for graft-versus-host disease (GVHD) prophylaxis. The kinetics and function of CAR-T cells was monitored by quantitative PCR and flow cytometry. The efficacy was evaluated by PET-CT at 60 days after CAR-T infusion.
Results: The median CAR-T cells infused were 3.6 (1.87-4.0)×10^6/kg. Cytokine release syndrome (CRS) occurred in all cases with 2 cases in grade I, 2 cases in grade II and 3 cases in grade III. No immune effector cell-associated neurotoxicity syndrome (ICANS) was noted. Three cases with grade III CRS were relieved with methylprednisolone. Granulocyte colony-stimulating factor–mobilized peripheral blood stem cells were infused 7 days after CAR-T with the median $CD34^+$ cells 6 (3-8.19)×10^6/kg. The neutrophil engraftment was achieved in all cases on median days 16 (11-24) post-transplant. Platelets were engrafted in 4 cases on median days 19 (16-65). No acute GVHD (aGVHD) was seen. CMV viremia occurred in 3 cases. Three patients developed grade I BKV hemorrhagic

cystitis. The highest proportion of CAR-T cells in vivo was 90.2 (0.096-502) % on median 7 (6-71) days after CAR-T cell infusion. CAR-T cells were detected persistently in vivo in 6/7 (85.7%) patients and the longest lasting time was 140 days post-transplant so far. B-cell aplasia was documented in all cases during the follow-up. With the median follow-up 62 (30-153) days, all patients survived. Four cases have been evaluated by PET-CT, one case with DLBCL achieved PR first and then progression, one case obtained PR, and two cases achieved complete remission. For the other 3 cases short than 60 days after CAR-T therapy, the tumor sizes have shrinked significantly measured by B ultrasound.

Summary/Conclusion: CRS is manageable and has no influence on hematopoiesis reconstitution. CAR-T cells still exist persistently post-transplant in majority of patients, which may contribute a long-term anti-lymphoma effect. With current protocol, no aGVHD was observed, viral reactivation was mild and encouraging disease control was found. Haplo-HSCT with conditioning including allo-CD19/CD22 CAR-T cells is a safe and effective strategy for r/r B-NHL. Long-term follow-up is needed.

EP506 ECHELON-2, (NCT01777152), 5-YEAR RESULTS OF A RANDOMISED, DOUBLE-BLIND, PHASE 3 STUDY OF FRONTLINE BRENTUXIMAB VEDOTIN + CHP VS CHOP IN PATIENTS WITH CD30-POSITIVE PERIPHERAL T-CELL LYMPHOMA

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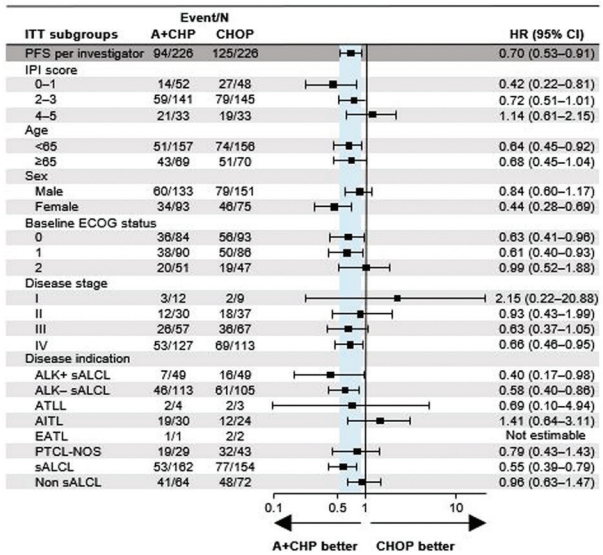
Background: ECHELON-2 (NCT01777152), a phase 3, randomised, double-blind, double-dummy, placebo-controlled, active-comparator, multicentre study, established the superiority of frontline brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (A+CHP) vs cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of patients (pts) with systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCLs) (Horwitz, Lancet 2019). Both risk of progression-free survival (PFS) per blinded independent central review (primary endpoint) and overall survival (OS) events favoured A+CHP over CHOP at the primary analysis. A+CHP was the first treatment regimen to increase OS compared with CHOP in this population.

Aims: We report the 5-year data from ECHELON-2, including PFS per investigator (INV) data and the following key secondary endpoints: OS, PFS in sALCL, complete remission (CR) rate, and objective response rate (ORR) in re-treated pts.

Methods: Adults with untreated CD30-positive PTCL (targeting 75% ± 5% with sALCL) were randomized 1:1 to receive 6–8 cycles of A+CHP or CHOP. Pts were stratified by histological subtype and international prognostic index (IPI) score. Brentuximab vedotin-based subsequent therapies were allowed.

Results: Of 452 pts enrolled, the majority had sALCL (n=316 [70%]; 218 [48%] anaplastic lymphoma kinase [ALK]-negative, and 98 pts [22%] ALK-positive) and had advanced disease (27% Stage III, 53% Stage IV; 78% IPI ≥2). At data cutoff, median follow-up was 47.6 months for PFS and 66.8 months for OS. A+CHP was favoured over CHOP with a hazard ratio (HR) for PFS per INV of 0.70 (95% confidence interval [CI]: 0.53, 0.91; p=0.0077) and OS HR of 0.72 (95% CI: 0.53, 0.99; p=0.0424). Median PFS was 62.3 months (95% CI: 42.0, not evaluable) for A+CHP, and 23.8 months (95% CI: 13.6, 60.8) for CHOP. Estimated 5-year PFS was 51.4% (95% CI: 42.8, 59.4) and 43.0% (95% CI: 35.8, 50.0) with A+CHP and CHOP, respectively. Median OS was not reached in either arm. Estimated 5-year OS was 70.1% (95% CI: 63.3, 75.9) for A+CHP vs 61.0% (95% CI: 54.0, 67.3) for CHOP. PFS in prespecified subgroups and overall PFS were generally consistent (Figure). The HR for PFS (0.55 [95% CI: 0.39, 0.79]) also favoured A+CHP over CHOP in pts with sALCL, with an estimated 5-year PFS of 60.6% (95% CI: 49.5, 69.9) for the A+CHP arm vs 48.4% (95% CI: 39.6, 56.7) for the CHOP arm. Subsequent systemic therapy with brentuximab vedotin was administered to a total of 29 pts (13%) in the A+CHP arm (sALCL [n=19]; PTCL not otherwise specified [n=5], angioimmunoblastic T-cell lymphoma [n=5]) and 54 pts (24%) in the CHOP arm. Median time to retreatment for pts in the A+CHP arm was 15.0 months (range, 3–64); 17 pts (ORR: 59%) had CR (n=11) or partial remission (n=6) after retreatment with brentuximab vedotin monotherapy (n=25) or a brentuximab vedotin-containing regimen (n=4). Of the treatment-emergent peripheral neuropathy (PN) in the A+CHP (n=117) and CHOP arms (n=124), 72% in the A+CHP arm and 78% in the CHOP arm had resolved or improved. In pts with ongoing events at last follow-up (A+CHP [n=47] vs CHOP [n=42]) PN was grade 1, 2 and 3 in 70% vs 71%, 28% vs 26% and 2% vs 2%, respectively.

Prespecified subset analyses: PFS



Summary/Conclusion: After 5 years' follow-up, frontline A+CHP continued to provide clinically meaningful improvements in PFS and OS vs CHOP, including sustained remission in 59% of re-treated pts with sALCL, as well as a manageable safety profile, including continued resolution or improvement of PN.

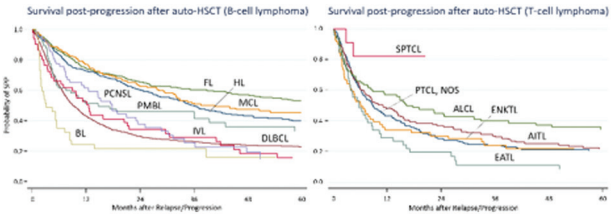
EP507 RELAPSE AND SURVIVAL POST-PROGRESSION IN LYMPHOMA PATIENTS AFTER STEM CELL TRANSPLANTATION

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Background: The prognosis of patients who relapsed after hematopoietic stem cell transplantation (HSCT) is generally poor. However, the survival post-progression (SPP) after HSCT in lymphoma patients has not been well evaluated.
Aims: The aim of this study is to evaluate and identify the prognostic factors for SPP.
Methods: Using the Japanese transplant registry, adult patients (> 15 years old) who underwent their first autologous (auto-HSCT) or allogeneic HSCT (allo-HSCT) for lymphoma in 1980–2018 were analyzed. SPP was defined as the time from progression or relapse after HSCT to death. To identify the prognostic factors for SPP, univariate and multivariate analyses were conducted. This study was approved by the Japan Society for Hematopoietic Cell Transplantation Ethical Committee.
Results: A total of 15,097 transplant cases, including 10,973 and 4,124 after auto-HSCT and allo-HSCT, respectively, were analyzed. In patients who underwent auto-HSCT, the major primary disease included diffuse large B-cell lymphoma (DLBCL) in 5,803 patients, Hodgkin lymphoma (HL) in 1,261, follicular lymphoma (FL) in 1,139, mantle cell lymphoma (MCL) in 659. In patients who underwent allo-HSCT, the primary disease included DLBCL in 1,201 patients, FL in 894, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) in 448, extranodal NK/T-cell lymphoma (ENKTL) in 334. Enteropathy associated T-cell lymphoma (EATL) patients had the highest relapse rate among patients after auto- and allo-HSCT (62% and 75%, respectively). Among patients after auto-HSCT, the median SPP was poor in patients with BL (3.1 months) and EATL (5.8 months). In contrast, the 2-year SPP was more than 60% in patients with HL, FL, MCL, and subcutaneous panniculitis like-T-cell lymphoma (SPTCL). In the univariate and multivariate analyses, patients' age, disease status at HSCT, HSCT year, time from HSCT to relapse or progression, subsequent HSCT, and lymphoma subtype were identified as risk factors. Chemo-resistant or relapsed disease was a risk factor for worse SPP [hazard ratio (HR) 1.5 (95% confidence interval (CI) 1.3-1.6), vs complete response (CR)]. Early relapse or progression [within 3 months (HR 3.0, 95% CI 2.7-3.3) and 6 months (HR 1.7, 95% CI 1.5-1.9) vs more than 1 year] was also significant prognostic factor. All lymphoma subtypes, except for MCL and SPTCL, were significantly associated with worse SPP compared with FL. Subsequent HSCT was associated with better SPP (HR 0.8, 95% CI 0.7-0.9). In the subgroup analyses by lymphoma subtypes, subsequent HSCT improved SPP in patients with HL, DLBCL, and most T-cell lymphomas. Among patients after allo-HSCT, the median SPP was shortest in patients with Burkitt lymphoma (BL) and aggressive NK-cell leukemia (ANKL) (both, 1.9 months), whereas it was longest in HL patients (13.6 months). In the univariate and multivariate analyses, age, disease status, time from HSCT to relapse or progression, and lymphoma subtype were identified as risk factors. Chemo-resistant disease was a prognostic factor for SPP (HR 2.0, 95%CI, 1.6-2.4). Majority of lymphoma subtypes, except for several subtypes including FL, MCL and ENTKL, were significantly associated with worse SPP compared with HL. The strongest association with poor SPP was observed in BL (HR 2.4, 95%CI 1.7-3.5) and ANKL (HR 3.3, 95%CI 2.1-5.1).



Summary/Conclusion: The lymphoma subtype, as well as age and disease status, were identified as risk factors. Subsequent HSCT after auto-HSCT play an important role in improving SPP in several lymphoma subtypes. For patients with poor SPP, an improvement of subsequent treatment strategy is warranted.

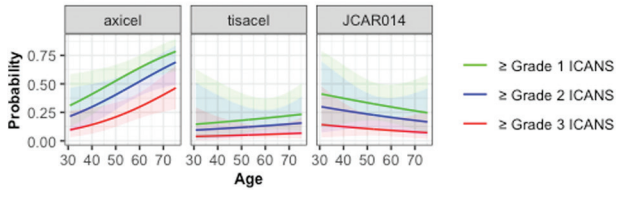
EP508 CRS AND ICANS RISK ACROSS THREE CD19 CAR-T CELL PRODUCTS IN PATIENTS WITH AGGRESSIVE NHL

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Background: CD19-targeted chimeric antigen receptor-engineered (CD19 CAR) T cells can achieve high response rates in patients (pts) with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL). Despite its promising efficacy, CD19 CAR T-cell therapy remains limited by two significant toxicities: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Varying incidence and severity of CRS and ICANS have been reported across distinct CD19 CAR T-cell products, but these observations could have been confounded by differences in pt and disease characteristics.
Aims: To estimate the independent effect of 3 CD19 CAR T-cell products (axicabtagene ciloleucel[axicel], tisagenlecleucel [tisacel], and JCAR014) on CRS and ICANS severity in pts with R/R aggressive NHL.
Methods: We retrospectively analyzed 136 aggressive NHL pts treated with cyclophosphamide and fludarabine lymphodepletion (LD) followed by CD19 CAR T-cell therapy. Axicel and tisacel pts were treated off trial using commercial products. JCAR014 (defined-composition 4-1BB-costimulated CD19 CAR T cells) was administered in all pts at the dose of $2x10^6$/kg on a phase I/II clinical trial (NCT01865617). CRS and ICANS were graded according to the ASTCT criteria and CTCAE 4.03, respectively. We used multivariable proportional odds logistic regression to model CRS and ICANS grade. We used propensity score estimation to reduce confounding based on age, hematopoietic cell transplantation comorbidity (HCT-CI), preLD LDH, preLD albumin, lymphoma type.
Results: Lymphoma type was diffuse large B cell lymphoma non-otherwise specified in 74%, large B cell lymphoma transformed from indolent histologies in 15%, and other aggressive lymphoma types in 11% of pts. Pts received axicel, tisacel, or JCAR014 in 50%, 28%, and 22% of cases, respectively. Compared to axicel pts, we observed higher preLD LDH levels in tisacel and JCAR014 pts, and lower preLD albumin with tisacel ($p < 0.001$) with comparable age and HCT-CI across CAR T-cell products. Higher day-28 overall response rates by Lugano criteria were observed after axicel (71%) compared to tisacel (56%) and JCAR014 (53%).
Adjusting for age, HCT-CI, preLD LDH, preLD albumin, CAR T-cell product type remained associated with CRS severity (tisacel versus [vs] axicel, OR = 0.45, p = 0.05; JCAR014 vs axicel, OR = 0.29, p = 0.005;). Age had limited or no impact on CRS severity (OR 95%CI, 0.97-1.02), while the effect of HCT-CI was undetermined (OR 95%CI, 0.85-1.27).
In a multivariable model including the same covariates as above, CAR T-cell product type (tisacel vs axicel, OR = .14, p < .001; JCAR014 vs axicel, OR = 0.31, p = 0.009), preLD LDH (OR = 3.96 per log10 increase; p = 0.04) and age (OR =1.32 per 10-year increase; p = .06) were associated with ICANS severity. Interaction effect testing suggested effect modification of age by the CAR T-cell product type (tisacel/JCAR014 versus axicel, p = 0.06). Predictions of ICANS severity according to age and the CAR T-cell product type are shown in the Figure.
The independent impact of CAR T-cell product type on CRS and ICANS severity was confirmed after propensity score adjustment.

Figure



Summary/Conclusion: CAR T-cell product type was independently associated with CRS and ICANS severity in NHL pts. We observed higher ICANS severity in older patients treated with axicel; in contrast, age had limited impact on ICANS severity in those receiving tisacel or JCAR014. While further analyses comparing efficacy are warranted, our findings provide insights to guide CAR T-cell product selection in older patients.

EP509 EFFICACY AND SAFETY OF MOGAMULIZUMAB BY PATIENT BLOOD CLASSIFICATION

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Background: Cutaneous T-cell lymphomas (CTCL) are rare, serious and potentially life-threatening forms of non-Hodgkin lymphoma that primarily present in skin. Mycosis fungoides (MF) and Sézary syndrome (SS) are the classic subtypes and together account for around two-thirds of all CTCLs. Initial methods of disease staging in MF and SS built upon the tumour-node-metastasis (TNM) classification using disease-specific findings. Blood classification (B0–2) was added to staging in 2007 based upon the recognition of blood involvement as a prognostic factor; increasing blood tumour burden has previously been linked with worsening of overall survival (OS) and disease-specific survival (DSS), and an increased risk of disease progression (RDP) (Agar 2010, Am Soc J Clin Oncol), although this is a subject of debate and further study. Patients with B1 disease have previously been shown to have a median survival of just 3.2 years, similar to B2 for which it was 3.1 years (Agar 2010, Am Soc J Clin Oncol). The addition of blood classification allows for more specific disease staging which may inform clinical management strategy, whilst also contributing to a better understanding of prognostic factors and treatment response in MF and SS.
Aims: This post hoc analysis examined the efficacy and safety of mogamulizumab (MOGA) compared with vorinostat (VORI), stratified by patient blood classification.
Methods: MAVORIC (NCT01728805) was an open-label, phase 3 study where patients were randomized 1:1 to receive either intravenous MOGA 1.0 mg/kg weekly for the first 28 day cycle, then on days 1 and 15 of subsequent cycles, or oral VORI 400 mg once daily. VORI patients who experienced disease progression or intolerable toxicity could cross over to MOGA. The primary endpoint was investigator-assessed progression-free survival (PFS).
Results: In MAVORIC, investigator-assessed PFS was significantly greater for MOGA than VORI overall at 7.7 months and 3.1 months, respectively ($P<0.0001$). When data were stratified by blood classification, PFS was found to be significantly superior for MOGA as compared to VORI in patients with both B1 and B2 disease (**Table 1**). Overall response rate (ORR) was also significantly greater for MOGA than VORI in MAVORIC at 28.0% and 4.8% respectively ($P<0.0001$), and was found in this analysis to be significantly greater for MOGA than VORI in those patients with B2 disease (**Table 1**). ORR for B1 was not significant, but showed a trend (25.8% vs 6.5% for MOGA and VORI, respectively). Time-to-next-treatment (TTNT) was not significant for patients without blood involvement (B0), but was significantly greater for MOGA in patients with blood involvement (B1 or B2) with 13.70 and 3.30 months for MOGA and VORI respectively ($P<0.0001$) (**Table 1**). Drug-related treatment-emergent adverse events (TEAEs) were similar in patients regardless of blood involvement and were lower for MOGA than VORI at each blood classification level (**Table 1**).

Table 1. Investigator-assessed PFS, ORR and TTNT in the intent-to-treat set, and TEAEs by blood classification in safety analysis set

	VORI (N=186)	MOGA (N=186)	
PFS, median months (n)			***P*-value**
B0	4.37 (62)	4.7 (64)	0.9480
95% CI	2.87–6.80	2.90–5.97	
HR (95% CI)	1.05 (0.67–1.65)		
B1	2.53 (31)	8.63 (31)	**0.0142**
95% CI	1.40–3.07	3.97–15.03	
HR (95% CI)	0.32 (0.16–0.64)		
B2	3.30 (93)	11.17 (91)	**<0.0001**
95% CI	2.83–4.70	7.63–17.07	
HR (95% CI)	0.36 (0.24–0.53)		
ORR, % (n)			
B0	6.5 (62)	15.6 (64)	0.0549
95% CI	1.8–15.7	7.8–26.9	
Risk diff (95% CI)	9.2 (-2.4–21.2)		
B1	6.5 (31)	25.8 (31)	0.2758
95% CI	0.8–21.4	11.9–44.6	
Risk diff (95% CI)	19.4 (0.6–38.6)		
B2	3.2 (93)	37.4 (91)	**<0.0001**
95% CI	0.7–9.1	27.4–48.1	
Risk diff (95% CI)	34.1 (22.9–45.2)		
TTNT, median months (n)			
B0	4.13 (50)	6.77 (46)	0.0928
95% CI	3.00–5.60	4.87–8.80	
HR (95% CI)	0.68 (0.46–1.02)		
B1 and B2	3.30 (105)	13.07 (70)	**<0.0001**
95% CI	2.83–4.00	11.00–16.73	
HR (95% CI)	0.32 (0.23–0.44)		
Drug-related TEAEs (any grade), n (%)			
B0	58 (93.5)	51 (79.7)	
B1	30 (96.8)	25 (80.6)	
B2	90 (96.8)	80 (87.9)	
Drug-related TEAEs (≥Grade 3), n (%)			
B0	18 (29.0)	11 (17.2)	
B1	14 (45.2)	8 (25.8)	
B2	33 (35.5)	28 (30.8)	

MOGA, mogamulizumab; TEAE, treatment-emergent adverse event; VORI, vorinostat.
B0 = <15% CD4+CD26- or CD4+CD7- cells by flow cytometry.
B1 = ≥15% CD4+CD26- or CD4+CD7- cells by flow cytometry (not B2).
B2 = ≥1000/μL Sézary cells with positive clone, CD4:CD8 ≥ 10, CD4+CD7- cells ≥40%, or CD4+CD26- cells ≥ 30%.

Summary/Conclusion: MOGA is effective in patients with blood involvement (B1 and B2), including patients with MF. Drug safety is similar between patients irrespective of level of blood involvement.

EP510 COMPARATIVE EFFICACY OF TISAGENLECLEUCEL (TISA-CEL) AND LISOCABTAGENE MARALEUCEL (LISO-CEL) IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

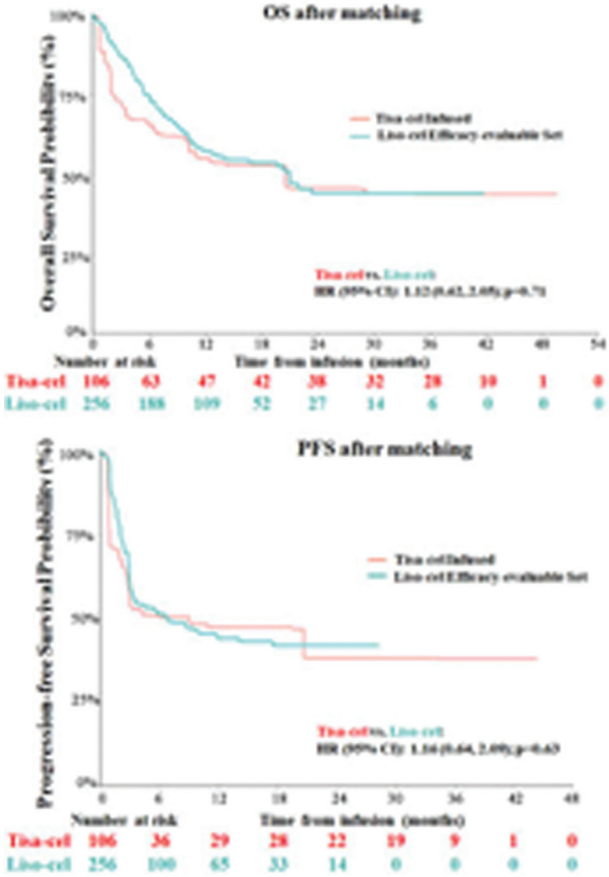
M. J. Kersten [1,*], J. Zhang [2], H. Yang [3], A. Agarwal [2], W. Tang [3], M. Martinez-Prieto [2], V. Bollu [2], D. Kuzan [2], S. Schuster [4], R. Maziarz [5]

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Background: The efficacy of chimeric antigen receptor T-cell therapies tisacel and liso-cel as effective treatments for r/r DLBCL was demonstrated in JULIET and TRANSCEND (Schuster 2019, Abramson 2020), respectively.
Aims: To compare efficacy outcomes of tisa-cel and liso-cel in r/r DLBCL using matching-adjusted indirect comparison (MAIC).
Methods: Individual patient-level data (IPD) from JULIET (tisa-cel; NCT02445248; 02/2020 datacut) were weighted to match the patient population in TRANSCEND (liso-cel; NCT02631044; 08/2019 datacut). Baseline prognostic factors available in both trials were adjusted for age, sex, histology, ECOG performance status (ECOG PS), left ventricular ejection fraction, radiologic sum of product diameters, lactate dehydrogenase, prior stem cell transplantation (SCT), use of bridging therapy, and number of and refractoriness to prior therapies in the MAIC. Overall survival (OS), progression-free survival (PFS), complete response (CR) rate, and overall response (OR) rate were compared. Primary analyses

compared infused patients in JULIET (N=106, excluding 8 without lymphodepleting chemotherapy [LDC] and 1 large cell neuroendocrine carcinoma) with the efficacy-evaluable set in TRANSCEND (N=256, infused patients). A scenario analysis compared JULIET infused to the TRANSCEND primary analysis set (PAS) (N=133, dose level 2, excluding those with ECOG PS 2, prior allogeneic SCT, primary mediastinal B-cell lymphoma, follicular lymphoma [FL] 3B, or transformation from indolent lymphoma besides FL). Sensitivity analyses included JULIET patients with only fludarabine-based LDC or only adjusted significantly different baseline prognostic factors. Safety outcomes were not compared because adverse event management has evolved and differed between the two trials; MAIC is unable to adjust for such differences.

Results: After adjusting for differences in baseline characteristics, no significant differences were observed in OS (hazard ratio [95% confidence interval (CI)]: 1.12 [0.62, 2.05], p=0.71) or PFS (1.16 [0.64, 2.09], p=0.63) between tisa-cel infused patients and the liso-cel efficacy-evaluable set (Figure). CR was also comparable (rate difference [95% CI]: -5.4% [-15.5%, 4.7%], p=0.29). The results comparing OS, PFS, and CR were consistent across all scenario and sensitivity analyses. The OR rate trended higher in the TRANSCEND efficacy-evaluable set (-9.7% [-20.0%, 0.6%], p=0.07) and was higher in the TRANSCEND PAS than in the respectively matched JULIET infused set (-13.5% [-25.6%, -1.5%], p<0.05).



Summary/Conclusion: The MAIC results indicate there is no evidence suggesting differences in OS, PFS, and CR between tisa-cel and liso-cel in r/r DLBCL. Analyses using IPD from both trials and/or real-world evidence are warranted to confirm these findings.

EP511 PROSPECTIVE EVALUATION OF LYMPHOMA RESPONSE TO IMMUNOMODULATORY THERAPY CRITERIA (LYRIC) IN GATA TRIAL FROM THE LYSA GROUP

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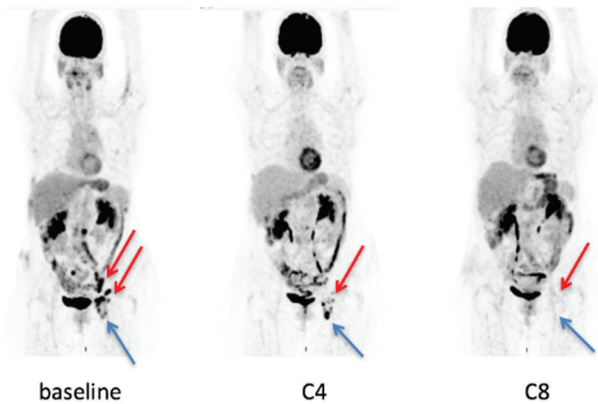
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Background: Checkpoint blockade may complicate response assessment by the development of a flare reaction or pseudoprogression (PP). To avoid the mistake of considering a new agent ineffective, it was proposed to add the category called "indeterminate response" (IR) to Lugano classification, in the LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC): 1/ increase in overall tumor burden in the first 12 weeks of therapy, without clinical deterioration (IR1), 2/ development of new lesions without overall progression (IR2), or 3/ increased F-fluorodeoxyglucose avidity despite no change in lesion size (IR3). These 3 patterns are defined as progressive metabolic disease (PMD) in the Lugano criteria. A PP was defined as an IR that became a partial or complete metabolic response (PMR or CMR) in comparison to baseline, at next evaluation.

Aims: The aim of this study is to assess in a practical and prospective manner the LYRIC criteria in relapsed/refractory diffuse large B cell lymphomas (DLBCL) and follicular lymphomas (FL) treated with atezolizumab, venetoclax and obinutuzumab (GATA trial), as well as measuring the incidence of PP.

Methods: The GATA study is a LYSA sponsored multicenter phase 2 trial (NCT03276468) evaluating the combination of atezolizumab, obinutuzumab and venetoclax in biopsy-confirmed R/R DLBCL and FL patients who failed at least one line of therapy (rituximab and anthracycline containing regimen). Local imaging practitioners were invited to use the LYRIC classification. Clinical investigators were warned of the possibility of PP, and a coordinating investigator's approval was required before stopping treatment. A centralized imaging review on Positron Emission Tomography (PET) and Computed Tomography (CT) scan was performed at three time points: baseline, cycle 4 (C4, 12 weeks) and cycle 8 (C8, 24 weeks), on Lugano and LYRIC criteria.

Results: Our study has included 116 patients (58 DLBCL and 58 FL) from GATA trial. With a median follow-up of 9 months the overall metabolic response rate (OMRR) at C8 was measured at 23.6% for DLBCL patients. With a median follow-up of 14.5 months the OMRR at C8 was measured at 53.6% for FL patients. Ninety-five patients had a centralized review at C4 and 57 at C8. Missing patients are those who progressed prior to the restaging by PET and CT scan. *Lugano criteria*: At C4, 84 reviewed responses (88.4%) were concordant with local response. At C8, 47 reviewed responses (82.5%) were concordant with local response. The differences were mainly between NMR (no MR) and PMR. *LYRIC criteria:* At C4, 9 PMD were classified as IR by both local reading and centralized review, 4 DLBCL and 5 FL. A discordance in the type of IR (1, 2 or 3) was seen in 6 out of 9 cases. During the follow-up, 4 cases turned out to be PP (1 DLBCL and 3 FL) and 5 cases real PD. One of the PP is illustrated on Figure 1, with IR3 at C4 (both locally and centrally), and CMR at C8. At C8, 7 PMD were classified as IR by centralized review (IR2 and IR3), only 2 of them were IR by local reading. During the follow-up, all of those cases turned-out to be real progressive diseases within 1 to 3 cycles of therapy.



Summary/Conclusion: We did observe 3.4% of PP, all classified as IR at C4. A high frequency of discrepancy between local and centralized

reading was observed with LYRIC criteria, probably due to the novelty of this classification. Interestingly, all IRs at C8 were found to be real progressions. Overall, these data are in favor of using the LYRIC classification, but only for early evaluation.

EP512 INTRAVENOUS HIGH DOSE METHOTREXATE FOR PREVENTION OF CNS RELAPSE IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): REAL-WORLD OUTCOMES AND PRACTICE PATTERNS FROM CHINESE INSTITUTION

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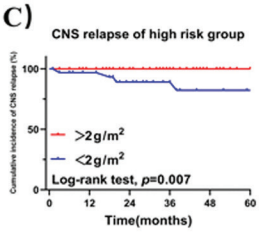
Background: Central nervous system (CNS) relapse occurs in 2-10% of DLBCL patients but carries a poor prognosis. Prophylactic intravenous high-dose methotrexate (HD-MTX) is recommended for patients with risk factors of CNS relapse, which requires hospital admission and increases the risk of treatment-related toxicity. However, there is limited evidence to guide whether it should be intercalated between cycles or given at the end of induction chemotherapy (EOI), and whether the optimal dosage of MTX is different between different risk groups.
Aims: To compare the toxicity and preventive efficacy on CNS relapse of intercalated HD-MTX with EOI delivery, and explore the optimal dosage of MTX for patients of different risk groups.
Methods: We conducted a retrospective analysis of 275 DLBCL patients from Sun Yat-sen University Cancer Center who received prophylactic HD-MTX with either intercalated (n=218) or EOI HD-MTX (n=57). We stratified the patients into two risk groups: patients with CNS-IPI 4-6, and/or testis involvement, and/or double hit lymphoma in the high risk group, and others in the low-intermediate risk group. Multivariable analyses (MVA) of risk factors for toxicity and delays were performed. The log-rank test and χ^2 test was applied to determine factors associated with CNS relapse, progression-free survival (PFS), and overall survival (OS).
Results: Figure 1A describes selected baseline characteristics. A total of 939 doses of intercalated HD-MTX and 127 doses of EOI HD-MTX was given. The treatment related adverse events were mainly hematological toxicity, including leucopenia (27%), neutropenia (20%) and thrombocytopenia (6%). Non-hematological toxicity mainly included gastrointestinal reactions (6%) and mucositis (3%). Nephrotoxicity was uncommon in this set (n=2, 1%). 197 (21%) intercalated HD-MTX cycles were associated with grade 3/4 toxicity, compared with 3 (2%) of EOI HD-MTX cycles (p<0.001). Intercalated HD-MTX was the only factor associated with grade 3/4 toxicity (HR 5.28(95% CI 2.11-13.23), p<0.001) and subsequent chemotherapy delays (HR 4.27(95% CI 2.45-7.45), p<0.001) on MVA. MVA also identified that intercalated HD-MTX delivery (HR 0.41 (95%CI 0.17-0.98), p=0.04) and induction therapy without rituximab (HR 0.37 (95%CI 0.16-0.88), p=0.03) were the significant factors negatively associated with complete remission (CR) rate of induction therapy. Overall, ten CNS relapses occurred (median time to relapse 17 months). The 3 year cumulative incidence of CNS relapse showed no significant difference between two kinds of MTX delivery either in all patients or in two risk groups (Figure 1B). There was no difference in PFS or OS either in all patients or in two risk groups (median follow-up 36.0 months). In addition, the optimal dosage of MTX was discussed. Relatively high MTX dose (≥2g/m^2) decreased CNS relapse(Figure 1C) and improved the PFS (p=0.001) and OS (p=0.009) in high risk patients significantly. However, there was no significant difference in CNS relapse(Figure 1D) and survival outcomes between different dosage groups in low-intermediate risk patients.

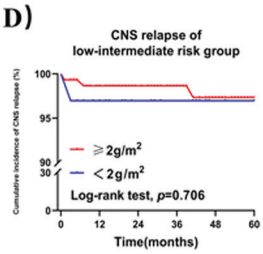
A)

Characteristic	All (n=275)	Intercalated (n=218)	End of treatment (n=57)	P
Age (median, range)	48 (13-75)	48 (13-75)	48 (21-73)	0.95
Male Sex	179(65%)	140(64%)	39(68%)	0.55
ECOG PS≥2	28(10%)	19(9%)	9(16%)	0.07
Stage III or IV	212(77%)	163(75%)	49(86%)	0.27
Testis involvement	52(19%)	46(21%)	6(11%)	0.07
Double/tripple hit	4(%)	3(%)	1(2%)	1.00
CNS-IPI	49(18%)	37(17%)	12(21%)	0.11
IT prophylaxis	200(73%)	163(75%)	37(65%)	0.14

B)

Group	CNS relapses	3-year cumulative incidence	95% CI	P
All (n=275)	10 (3.6%)	4.9%	1.4-5.9	
Intercalated (n=218)	7 (3.2%)	3.7%	0.9-5.6	0.29
EOI (n=57)	3 (5.7%)	8.8%	0.0-11.2	
High risk (n=90)	4 (4.4%)	5.7%	0.1-8.8	
Intercalated (n=72)	3 (4.2%)	4.9%	0.0-8.9	0.73
EOI (n=18)	1 (5.6%)	8.3%	-6.2-17.3	
Low-intermediate risk (n=185)	6 (3.2)	3.4%	0.7-5.8	
Intercalated (n=146)	4 (2.7%)	1.5%	0.1-5.4	0.15
EOI (n=39)	2 (5.1%)	9.1%	-2.1-12.4	





Summary/Conclusion: Intercalated HD-MTX was associated with increased toxicity and subsequent chemotherapy delays compared to EOI delivery, which may decrease the efficacy of induction therapy. However, there was no significant difference of CNS relapse and survival outcomes between two kinds of MTX delivery, even in high risk group. For low-intermediate risk patients, high dosage of MTX may not improve efficacy of CNS prophylaxis or bring additional survival benefit compared with low dosage.

EP513 COMPREHENSIVE GERIATRIC ASSESSMENT-DRIVEN TREATMENT DECISION VERSUS CLINICAL JUDGMENT IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN CHINA

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Background: Diffuse Large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in the elderly.some elderly patients can not tolerate the standard dose of R-CHOP due to age, poor physical condition, and severe complications. At present, the decision to treat a patient is made by clinical experience of clinicians, which is subjective. It is a major challenge to identify which patients can tolerate the standard dose of R-CHOP regimen in our clinical work. Comprehensive Geriatric Assessment (CGA) has been proposed as an objective tool for supporting treatment decision by age, evaluating activity of daily living, Instrumental activities of daily Living, and comorbidity score according to the Cumulative Illness Rating Score for Geriatrics (CIRS-G).However, It is still unknown whether comprehensive geriatric assessment or clinical judgment was more effective at guide the treatment in elderly patients with diffuse large B-cell lymphoma (DLBCL).
Aims: This prospective, observational, controlled cohort trial aims to investigate whether comprehensive geriatric assessment (CGA) is more effective than clinical judgment to guide the treatment in elderly patients with diffuse large B-cell lymphoma (DLBCL) in China.
Methods: 152 patients in Beijing Hospital were enrolled if they fulfilled the following inclusion criteria: 1)age ≥60 years; 2) newly diagnosed of DLBCL according to WHO classification by two independent pathologists; 3) no previous history of hematologic malignancies; 76 patients will received CGA-driven therapy at CGA-guided therapy group, and 76 patients will received therapy based on clinical judgement at clinical judgement-guided therapy group. the 2-year Overall Survival (OS), Progression Free Survival (PFS), Overall Response Rate (ORR) and toxicities were analyzed between the two group.
Results: according to CGA, 76 patients in the CGA-guided therapy group were classified into three groups: fit (41 patients, 53.9%), unfit(4 patients, 5.3%) and frail group (31 patients, 40.8%). patients assessed as unfit or frail group received a reduced dose of anthracycline of R-CHOP or R-miniCHOP or R-COP. the ORR was 94.7% (72/76), including CR rate was 73.7% (56/76). 2-year OS rates was 80.9%, 2-year PFS rates

was 72.7%. however, in the clinical judgement-guided therapy group, based on the CGA assessment, 41(53.9%) patients were assessed as fit group,including 36 patients received a standard dose of R-CHOP regimen.4(5.3%) as unfit group, 31(40.8%) as frail group including 4 patients in the frail group received a standard dose of R-CHOP regimen.the ORR was 81.6% (62/76), including CR rate was 57.9% (44/76). 2-year OS rates was 63.0%, 2-year PFS was 52.7%. there were significant difference between the two groups(ORR: x^2=5.104, p=0.024; CR:x^2=4.209, p=0.04; 2-year OS rates: x^2=7.348, p = 0.007; 2-year PFS: x^2=10.768, p = 0.001). Subgroup analysis showed that the complete remission rate in the fit group of patients in the CGA-guided therapy group was 82.9%(34/41), which was significantly higher than that in the clinical judgement-guided therapy group(58.5%, 24/41)(P = 0.015). The 2- year OS rate and 2-year PFS rate of patients in the CGA-guided therapy group were 86.9% and 76.5%, respectively, which were significantly higher than those in the clinical judgement-guided therapy group(62.1%, P = 0.000) and 62.9% (P = 0.000), respectively. the toxicity between two group was similar.
Summary/Conclusion: Using CGA to guide therapy for elderly patients with DLBCL can significantly improves the clinical efficacy and survival rate.

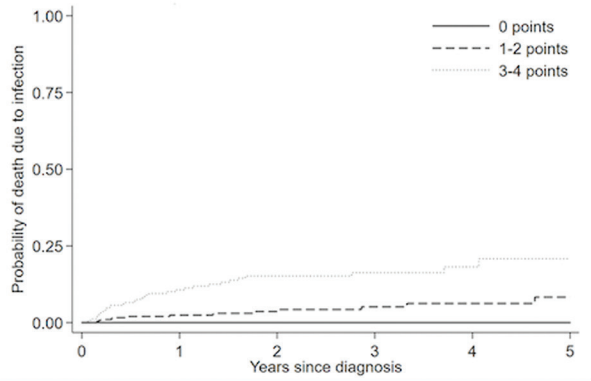
EP514 INFECTION-RELATED MORBIDITY AND MORTALITY FOR ELDERLY DLBCL PATIENTS TREATED WITH FULL OR ATTENUATED DOSE R-CHOP

T. Eyre [1,*], W. Wilson [2], A. Kirkwood [2], J. Wolf [3], C. Hildyard [4], H. Plaschkes [1], J. Griffith [3], P. Fields [5], A. Gunawan [5], R. Oliver [6], S. Booth [1], J. Kothari [1], C. Fox [7], N. Martinez-Calle [7], A. McMillan [7], M. Bishton [7], G. Collins [1], C. Hatton [1]

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Background: Infection-related morbidity and mortality are increased in elderly patients (pts) treated for DLBCL compared to population-matched controls. Key predictive factors for infection-related hospitalisation during R-CHOP and infective deaths in elderly pts during and following R-CHOP remain incompletely understood.
Aims: We aimed to examine the influence of baseline characteristics, presentation, comorbidities, and intended dose intensity (IDI; combined % dose: cyclophosphamide & doxorubicin at cycle 1) in a 690 consecutive elderly (≥70 years (ys)) DLBCL pts on the risk of both infection-related morbidity (i.e. single &/or multiple infective admissions), & infection-related mortality occurring on or following therapy
Methods: Pts receiving full or mini R-CHOP were analysed for risk of infection-related admission & infection-related death. Factors potentially related to such endpoints were analysed by standard & ordinal logistic regression.
Results: Median age was 77 ys. 34.4% were ≥80 ys. Median follow-up was 2.8 ys. Pt and baseline disease characteristics were assessed in addition to IDI. 17% received primary quinolone prophylaxis. 72% of pts were not hospitalised with infection. Across all ages, the mean rate per R-CHOP cycle of an admission due to neutropenic infection was 7.9% in those with an IDI ≥80% compared to 3.3% in those with an IDI <80% (rank-sum p<0.0001). Increased risk of infection-related admission was independently associated with IDI >80% across all pts. In 331 pts receiving an IDI ≥80%, 33% were hospitalised with ≥1 infection compared to 23.3% of 355 pts receiving IDI <80% (univariable OR:1.61 (95% CI 1.14-2.26), p=0.006; multivariable OR: 2.12 (1.38-3.25), p=0.001. Antibiotic prophylaxis was associated with lower risk of infection (univariable OR: 0.37 (0.22-0.64), p<0.001, multivariable OR: 0.29 (0.16-0.51), p<0.001). In those ≥80 ys, risk of ≥1 infection-related admission was 32.4% (11/34) in those with an IDI >80% versus 21.3% (43/202) in those with an IDI <80% (OR:1.77, 95% CI 0.80-3.91, p=0.16). In this same group ≥80 ys, mean rate of admission per cycle specifically with neutropenic fever was numerically higher at 7.4% for those with an IDI ≥80% versus 2.9% with an IDI <80% (rank-sum p=0.06). 51 pts (7.4%) died due to infection. 6-month, 12-month, 2-yr and 5-yr cumulative incidence of infection-related death was 3.3%, 5.0%, 7.2% and 11.1% respectively. Key independent factors associated with infection-related death were: IPI 3-5, CIRS-G ≥6 and low albumin; enabling production of a predictive risk score. CIRS-G ≥6 were assigned 2 points, IPI 3-5 were assigned 1 point and baseline albumin ≤36 were assigned 1 point. 3 distinct cohorts were defined. Risk groups included 106 pts (15.5%, score 0), 316 pts (46.4%, score 1-2) and 259 pts (38.0%, score 3-4) respectively. 2-yr cumulative incidence of infective mortality with a score of 0 was 0%, score 1-2 was 3.6% (95% CI 1.8%>6.9%) & score of 3-4 15.2% (95% CI 10.8%>21.1%). 5-yr cumulative incidence of infective mortality: score of 0 was 0%, score 1-2 was 8.3% (95% CI 4.3%>15.8%) & score 3-4 was 20.8% (95% CI 14.0%>30.3%) respectively.

Figure: Risk model for predicting infection-related mortality: cumulative incidence of death due to infection



Risk score	Events/N*	HR (95% CI)	P-value	Death due to infection rate	
				2-year	5-year
0	0/106	N/A		0%	0%
1-2	13/316	1.00	<0.001	3.6% (1.8%-6.9%)	8.3% (4.3%-15.8%)
3-4	34/259	3.52 (1.87-6.63)		15.2% (10.8%-21.1%)	20.8% (14.0%-30.3%)
All patients with risk score				7.2% (5.3%-9.8%)	11.1% (7.9%-15.5%)

*Only patients with data for all three variables included in risk score analysis. Log-rank test for trend – p<0.001, Log-rank 1-2 vs 0 – p=0.02, Log-rank 3-4 vs 0 – p<0.001, Log-rank 3-4 vs 1-2 – p<0.001

Summary/Conclusion: Increased risk of infection-related admission is independently associated with R-CHOP IDI>80% and no antibiotic prophylaxis in elderly DLBCL pts. Independent factors associated with infection-related death were IPI 3-5, CIRS-G ≥6 & low albumin, enabling a predictive risk score. Whether high risk pts could be targeted with enhanced anti-microbial prophylaxis remains unknown and requires a randomised trial.

EP515 POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER IN KIDNEY TRANSPLANT PATIENTS: A MULTICENTER REPORT IDENTIFYING THE IMPORTANCE OF ALLOGRAFT PRESENTATION

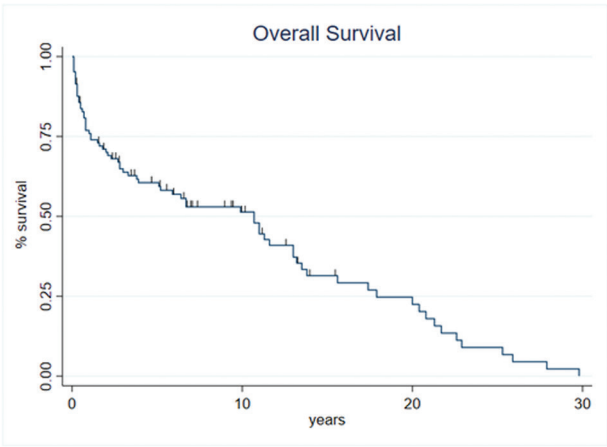
E. Chong [1,*], D. Tsai [2], M. Hughes [1], M. A. Lim [1], B. Besharatian [1], Y. El Kassiss [1], R. Bloom [1], D. Jagadeesh [3]

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Background: Post-Transplant Lymphoproliferative Disorder (PTLD) is a complication of transplantation that often arises due to reactivation of the Epstein-Barr Virus (EBV). Given the rarity of this disease, a full understanding of its presentation and optimal therapies has yet to be determined.
Aims: To describe the presentation, prognostic features, therapies, and outcomes of PTLD.
Methods: A multicenter retrospective analysis was performed utilizing data from kidney transplant patients (pts) who developed PTLD at the Hospital of the University of Pennsylvania and the Cleveland Clinic. The association between categorical variables and clinical response were assessed via Fisher's exact testing.
Results: 117 pts had diagnoses of PTLD after kidney transplantation. The median age at PTLD diagnosis was 52 yrs (range 17-89 yrs), and the median time from transplantation to diagnosis was 3.6 yrs (range: 7 days-36 yrs). Pt characteristics included: 84% Caucasian, 57% male, and 11% combined kidney and pancreas transplant patients. 68% pts had received unrelated donor transplants; 41% had prior rejection episodes. PTLD histology was 72% monomorphic and 28% polymorphic. Polymorphic PTLD was more likely to be EBV+ than monomorphic PTLD (81% vs. 54%, p=0.05). At diagnosis, immunosuppression included: steroids (95%), mycophenolate (44%), azathioprine (40%), sirolimus (30%), cyclosporine (46%), and/or tacrolimus (45%). Common PTLD symptoms included fever (34%), pain (38%), weight loss (30%), fatigue (30%), and/or mass (26%). The

most common sites of involvement were lymph nodes (64%), kidney allograft (22%), and/or GI tract (17%). At diagnosis, 61% of patients' tumors were EBV+ and 59% of patients had elevated serum LDH. Overall, the majority of pts responded to first-line PTLD therapy, with 61% CR and 14% PR. Reduction of immunosuppression (RI) alone (36% of pts) led to 48% CR and 12% PR; RI with rituximab (16%) led to 47% CR and 7% PR; and RI with chemotherapy (14%) resulted in 58% CR and 42% PR. Patients treated with RI as well as resection (n=18) of their limited stage disease had better outcomes (p=0.05). Overall survival for all patients was 10.7 years (95% CI: 5.1-13 years) (Figure), suggesting that a majority of patients achieve long term survival. PTLD patients <40 yrs were more likely to achieve CR after first line therapy (91% vs. 50%, p<0.001), have allograft involvement (43% vs. 14%, p=0.003), and have a polymorphic histology (52% vs. 17%, p=0.002).

Allograft involvement tended to occur sooner after transplant, occurring a median of 70 days (IQR: 29 days-2.6 yrs), whereas PTLD with no allograft involvement occurred a median of 5.4 yrs (IQR: 2.0-13.0 yrs, p=0.001). Allograft involvement was more likely to present with allograft failure (48% vs. 17%, p=0.003). PTLD with allograft involvement were more likely to achieve CR after first therapy than regular PTLD (88% vs. 54%, p=0.007) and often responded well to complete resection and RI.



Summary/Conclusion: Pts with PTLD may achieve a CR through different initial therapies. Younger patients and those able to undergo complete resection of disease and RI had better prognoses. Allograft involvement by PTLD carries a good prognosis and should be identified and treated differently from other presentations.

EP516 SAFETY AND EFFICACY OF TISAGENLECLEUCEL PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: UPDATED ANALYSIS OF THE PHASE 1B PORTIA STUDY

U. Jaeger [1,*], N. Worel [1], J. McGuirk [2], P. Riedell [3], I. Fleury [4], P. Borchmann [5], Y. Du [6], A. Abdelhady [7], X. Han [7], M. Martinez-Prieto [7], E. Waller [8]

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Background: Tisagenlecleucel showed durable responses and manageable safety in patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) in the phase 2 JULIET trial. High baseline programmed cell death 1 (PD-1) expression associated with higher probability of no response (Schuster et al. *NEJM* 2019).

Aims: To report an updated analysis of PORTIA, a phase 1b, multicenter, open-label study of tisagenlecleucel plus pembrolizumab in patients with r/r DLBCL.

Methods: Eligible patients (≥18 year) had r/r DLBCL after ≥2 lines of therapy and relapsed after or were not candidates for autologous stem cell transplant (autoSCT). Patients received a single tisagenlecleucel infusion on Day 1 and were enrolled in 1 of 3 cohorts that initiated pembrolizumab (200 mg q 21 days, for up to 6 doses) on either Days +15, +8, or –1. Primary endpoints were incidence of dose-limiting toxicities (DLTs) and overall response rate (ORR; complete response [CR] and partial response [PR]). Secondary endpoints included duration of response, progression-free survival, overall survival, safety, and cellular kinetics.

Results: As of November 9, 2020, 15 patients were enrolled and 12 received tisagenlecleucel (n=4 patients for each Days +15, +8, and –1 cohorts; median follow-up, 4 mo). At study entry, the median age among treated patients was 62 year (range, 35-79), 100% had an International Prognostic Index score ≥2, 67% had ≥3 prior lines of therapy, 58% had stage IV disease, 58% had lactate dehydrogenase greater than upper limit of normal, and 42% had prior autoSCT. All 12 patients had ≥1 adverse events (AE). Grade ≥3 AEs suspected to be related to tisagenlecleucel and/or pembrolizumab were neutropenia (n=4); neutrophil count decreased (n=3); febrile neutropenia, lymphocyte count decreased, malnutrition (each n=2); anemia, leukopenia, diarrhea, white blood count decreased, liver function tests increased, thrombocytopenia, hepatitis, and cytokine release syndrome (CRS; each n=1). No neurotoxicity or DLTs were observed. Among the Day +15, +8, and –1 cohorts (each n=4), the ORR was 50% (2/4; CR n=0, PR n=2), 25% (1/4; CR n=1, PR n=0), and 25% (1/4; CR n=1, PR n=0; longer follow-up is needed for n=2 patients), respectively. Tisagenlecleucel exposure and peak expansion were consistent with JULIET, with a trend toward delayed expansion in the Day –1 cohort (n=4). There was no sign of secondary expansion following pembrolizumab administration regardless of the number of doses. Compared with JULIET, lower CRS severity and frequency and lower cytokine profiles were observed for all 3 cohorts.

Summary/Conclusion: The combination of tisagenlecleucel plus pembrolizumab was feasible and showed manageable safety. The lack of improved efficacy in PORTIA with the addition of pembrolizumab compared with tisagenlecleucel alone may be related to more patients with ≥3 prior lines of therapy (67% vs 51%, respectively), and/or patients with more advanced disease in PORTIA. Additional studies with larger patient cohorts are needed to determine the value of adding PD-1 inhibitors to CAR-T cell therapy in patients with r/r DLBCL.

Clinical trial information: NCT03630159

EP517 INTERIM-PET IS NOT PREDICTIVE OF OUTCOME IN DLBCL PATIENTS WITH MYC REARRANGEMENTS DUE TO ABERRANT RESPONSE PATTERNS

J. J. Eertink [1,*], A. I. Arens [2], J. E. Huijbregts [3], F. Celik [4], B. de Keizer [5], S. Stroobants [6], D. de Jong [7], S. E. Wiegers [1], G. J. Zwezerijnen [8], C. N. Burggraaff [1], R. Boellaard [8], H. C. de Vet [9], O. S. Hoekstra [8], P. J. Lugtenburg [10], M. E. Chamuleau [1], J. M. Zijlstra [1]

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma with a large spread in outcome. Part of the heterogeneity can be explained by genetic abnormalities, such as *MYC* oncogene rearrangements. *MYC* rearrangements are often accompanied by *BCL2* and/or *BCL6* rearrangements and occur in approximately 10-15% of patients and has been associated with poor prognosis.

Aims: The aim of this study was to analyse the patterns of ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography (^{18}F-FDG PET/CT) response in DLBCL patients with *MYC* rearrangements (*MYC*+) compared to the response patterns of DLBCL patients without *MYC* rearrangements (*MYC*-).

Methods: 80 *MYC*+ DLBCL patients included in the HOVON-130 study, and 126 *MYC*- DLBCL patients in the HOVON-84 study were analysed. *MYC*, *BCL2* and *BCL6* positivity was assessed by Fluorescence In Situ Hybridization. For the *MYC*+ patients, 25% of patients had a single hit, and 75% a double or triple hit lymphoma. *MYC*+ patients were treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP21) combined with lenalidomide, followed by 2 gifts of rituximab. *MYC*- patients were randomized between 6-8 cycles of R-CHOP14 with or without rituximab intensification. ^{18}F-FDG PET/CT scans were performed at baseline, after 3-4 cycles of treatment (I-PET) and at end of treatment (EoT-PET). All scans were centrally reviewed and evaluated according to the Deauville 5-point scale (DS). DS 1-3 was regarded as PET-negative and DS 4-5 as PET-positive. I-PET and EoT-PET positivity rates were compared between *MYC*+ and *MYC*- groups using the chi-square test for independence. Positive predictive value (PPV) and negative predictive value (NPV) of I-PET and EoT-PET were calculated for 2-year overall survival, defined as date of registration to death, as outcome. Metabolic tumour volume was calculated at baseline, I-PET and EoT-PET using the ACCURATE tool.

Results: As expected, *MYC*+ DLBCL patients had significantly more positive EoT-PET scans compared to MYC- patients (33% (26/79) vs 15% (18/118), p=0.004, Table 1). I-PET response rates were comparable between *MYC*+ and *MYC*- DLBCL patients. Of the I-PET negative patients 23% (13/56) of the *MYC*+ patients turned out positive at EoT-PET, compared to 2% (2/91) for the MYC- patients. In total, 81% (21/26) of EoT-PET positive *MYC*+ patients presented with new nodal and/or extranodal lesions compared to I-PET, and 35% of EoT-PET positive *MYC*+ patients showed new lesions at EoT-PET in regions that were not initially involved at baseline. For the *MYC*- patients, 22% (4/18) of the EoT-positive patients presented with new nodal and/or extranodal lesions compared to I-PET, and 5.6% of the EoT-PET positive patients had new lesions in regions that were not initially involved at baseline. Out of the *MYC*+ patients that were positive at I-PET and EoT-PET, 60% showed enhancement of tumor volume at EoT-PET, this was the case of 38% of the *MYC*- DLBCL patients. 50% (13/26) of the EoT-PET positive *MYC*+ patients had negative I-PET assessment, compared to 11% (2/18) of the EoT-PET positive *MYC*- patients. Positive predictive values of I-PET and EoT-PET were higher for the *MYC*+ DLBCL patients compared to *MYC*- DLBCL patients (range: 31.6%>61.5%), whereas negative predictive values were higher for *MYC*- DLBCL patients (range: 81.8%>94.1%).

Table 1. Response rates of *MYC*+ and *MYC*- DLBCL Patients on interim PET and end of Treatment PET

		EoT-	EoT+	No EoT
MYC+	**I-PET-**	43	13	1
(n=80)	**I-PET+**	10	13	
MYC-	**I-PET-**	89	2	5
(n=126)	**I-PET+**	11	16	3

Abbreviations: I-PET: interim PET, EoT: End of Treatment PET
PET-: Deauville score 1-3, PET+: Deauville score 4-5

Summary/Conclusion: *MYC*+ DLBCL patients demonstrate specific response patterns, therefore I-PET is less predictive in *MYC*+ DLBCL patients.

EP518 DURATION OF RESPONSE TO LONCASTUXIMAB TESIRINE IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA BY DEMOGRAPHIC AND CLINICAL CHARACTERISTICS: SUBGROUP ANALYSES FROM LOTIS-2

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Background: Outcomes for patients with refractory/relapsed diffuse large B-cell lymphoma (R/R DLBCL) are poor, particularly for those with high-risk clinical characteristics. There remains an unmet need for new treatment options for these patients. Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin. LOTIS-2 was a pivotal Phase 2 study that demonstrated substantial single-agent anti-cancer activity of Lonca in patients with R/R DLBCL. Efficacy and safety data were presented at ASH 2020 (Caimi *et al*, ASH 2020; abstract 1183).

Aims: Here we present subgroup analyses of duration of response (DoR) to Lonca by demographic and clinical characteristics.

Methods: Adult patients with R/R DLBCL who had received ≥2 prior therapies were enrolled in this Phase 2, multicenter, single-arm, open-label study of single-agent Lonca (150 µg/kg every 3 weeks for 2 doses, followed by 75 µg/kg thereafter for up to 1 year). Informed consent was obtained. The primary analysis has previously been reported, with a primary endpoint of overall response rate (ORR). Patients are being followed-up every 12 weeks for up to 3 years. DoR was a key secondary efficacy endpoint, defined as time from the first documentation of response (central review) to disease progression or death. We analyzed pre-specified demographic and clinical characteristic subgroups for DoR.

Results: As of data cut-off (August 6, 2020), ORR in the total population (N=145) was 48.3% (24.8% had complete response [CR] and 23.4% had partial response [PR]). Median DoR (mDoR) for the 70 responders was 12.58 months. mDoR for patients with CR and PR was 13.37 months and 5.68 months, respectively.

Overall, subgroups with high-risk characteristics for poor prognosis had a DoR comparable to the whole study population. mDoR for patients with double-/triple-hit DLBCL was 13.37 months, with advanced stage disease was 12.58 months, and with transformed disease was 12.58 months. The mDoR for older patients was longer than for younger patients (≥75 years, 13.37 months; 65 to <75 years, 12.58 months; <65 years, 9.26 months). Patients with DLBCL refractory (defined as no response to therapy) to first-line, most recent line, and all prior lines of therapy had mDoRs of 9.63 months, 9.26 months, and 9.63 months, respectively.

Summary/Conclusion: Durable responses were observed with the recommended Phase 2 dose regimen of Lonca in heavily pre-treated patients and those at high risk of poor prognosis, including older patients and those with double-/triple-hit, advanced stage, transformed, and primary refractory DLBCL. Updated DoR data will be presented at the meeting.

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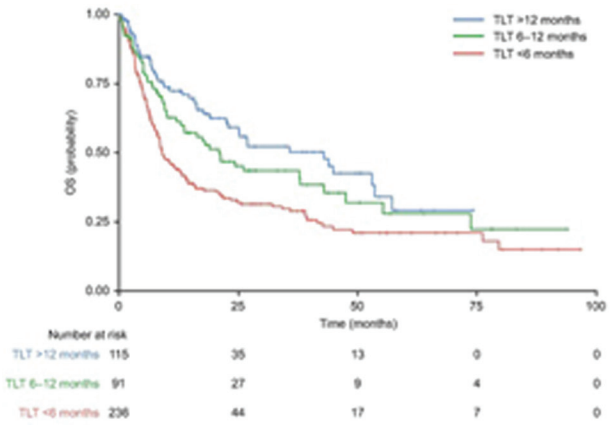
EP519 PROGNOSTIC SIGNIFICANCE OF TIME FROM LAST THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS OF ELECTRONIC HEALTH RECORDS AND CLAIMS DATA IN THE US

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Background: Primary refractory disease is a major challenge in patients (pts) with diffuse large B-cell lymphoma (DLBCL), and is commonly defined as disease progression during first-line (1L) therapy or within 6 months (mo) of completing 1L therapy. Poor outcomes in pts with primary refractory DLBCL were reported in SCHOLAR-1, a study based on data primarily from academic centers (Crump, et al. Blood 2017). A limited number of studies have evaluated real-world outcomes of pts with primary refractory DLBCL in the broader healthcare setting. Here, we report the results of real-world data (RWD) analyses from two US sources.
Aims: To describe outcomes of pts with DLBCL receiving second-line (2L) therapy from RWD according to the time from last treatment (TLT), defined by the time from end of 1L to the start of 2L therapy.
Methods: This study used the nationwide Flatiron Health (FH) electronic health record-derived de-identified database and the Surveillance, Epidemiology, and End Results (SEER)-Medicare (SEER-M)-linked database, which combines the SEER Cancer Registry and Medicare claims database. The majority of pts in the FH database originate from community oncology settings; relative community/academic proportions may vary depending on study cohort. The data of pts with DLBCL who received 2L therapy between Jan 2011–Jan 2020 in FH and Jan 2011–Dec 2015 in SEER-M were reviewed. Pts aged ≥18 years (pts in SEER-M were aged >65 years) with DLBCL, who were treated with cyclophosphamide- and doxorubicin-containing regimens in the 1L setting, were included for analysis. For SEER-M, all pts enrolled in fee-for-service Medicare were required to have complete claims. Data of pts who developed a secondary malignancy were censored at the time of the malignancy, and medical review of treatment regimens was performed for the final cohorts. Pts were grouped into three categories of TLT (<6 mo, 6–12 mo and >12 mo), and the impact of TLT was analyzed for association with overall survival (OS), defined by the time from the start of salvage therapy to death.
Results: Overall, 866 pts were included (FH: n=442; SEER-M: n=424) for analysis. Pt characteristics were similar between the cohorts, except median age at diagnosis (FH: 65 years; SEER-M: 74 years). Pts were mostly white (FH: 72.9%; SEER-M: 91.5%), male (FH: 63.1%; SEER-M: 52.1%), with Stage III–IV disease (FH: 64.9%; SEER-M: 69.5%). The most common 2L regimens were: rituximab (R) + carboplatin + etoposide + ifosfamide (39.8% in FH and 7.5% in SEER-M), R + bendamustine (14.0% in FH and 29.2% in SEER-M), and R + gemcitabine + oxaliplatin (8.4% in FH and 12.5% in SEER-M). Using a TLT cut-off of <6 mo, 236 (53.4%) pts in the FH cohort and 197 (45.3%) pts in the SEER-M cohort were classified as primary refractory. In the FH cohort, median OS for TLT <6 mo, 6–12 mo, and >12 mo were 9.1 mo (95% confidence interval [CI]: 8.1–13.1 mo), 20.9 mo (95% CI: 13.7–47.5), and 42.9 mo (95% CI: 22.8–57.3), respectively (**Figure**). In the SEER-M cohort, median OS for TLT <6 mo, 6–12 mo, and >12 mo were 8.6 mo (95% CI: 6.7–11.4), 11.7 mo (95% CI: 8.8–16 .1), and 18.9 mo (95% CI: 15.7–32.9), respectively.

Figure: OS from start of 2L treatment according to TLT category (<6 mo, 6–12 mo, and >12 mo) in FH



1L, first-line; 2L, second-line; FH, Flatiron Health; mo, months; OS, overall survival; TLT, time from last treatment (defined by the time from end of 1L to start of 2L therapy)

Summary/Conclusion: Our RWD analysis highlights the poor outcomes of pts with shorter TLT, particularly those with primary refractory DLBCL (TLT <6 mo). Novel therapeutic approaches are needed for this high-risk patient population, and future studies of 2L therapy should stratify enrollment by TLT to control for this source of confounding.

EP520 PROGNOSIS AND HEPATIC TOXICITY IN HEPATITIS C VIRUS-POSITIVE PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Increasing evidence suggested that viral infection contributes to lymphomagenesis. Plenty of studies indicated that hepatitis C virus (HCV) infection is associated with diffuse large B-cell lymphoma (DLBCL). However, no clear consensus has been reached about the impact of HCV infection on DLBCL patients' clinical features and outcomes.
Aims: We therefore performed a systematic review and meta-analysis to explore the clinical characteristics and prognosis in DLBCL patients with HCV infection.
Methods: PubMed, Embase and Cochrane Library database were searched for retrospective study up to Dec 31, 2020. The primary outcome was survival outcomes, including overall survival (OS) and progression-free survival (PFS). The secondary outcomes measured rate of complete remission (CR) and partial remission (PR), the incidence of hepatic dysfunction during chemotherapy and clinical characteristics. Newcastle-Ottawa Quality Assessment Scale (NOS) was adopted to assess the methodological quality of included studies. Hazard ratio (HR) or odds ratio (OR) corresponding to 95% confidence interval (CI) were calculated to estimate outcomes. Publication biases were assessed by funnel plots. Statistical analyses were performed by the software RevMan 5.4.
Results: There were in total 11 studies included in the current meta-analysis, comprising of 532 HCV infected DLBCL patients and 7907 HCV non-infected DLBCL patients. All the included studies had reliable quality as indicated by NOS scores ≥ 6 points. Our data demonstrated that DLBCL patients with HCV infection showed significantly shorter OS (HR 2.29; 95% CI 1.85~2.84, P<0.00001) and PFS (HR 1.52; 95% CI 1.27~1.82, P<0.00001), lower rate of CR+PR (OR 0.55; 95% CI 0.42~0.72, P<0.00001) and higher incidence of hepatic dysfunction during chemotherapy (OR 5.89; 95% CI 2.31~15.01, P=0.0002) compared with DLBCL patients without HCV infection. Furthermore, HCV infected DLBCL patients were characterized by higher International Prognostic Index scores (OR 1.36; 95% CI 1.10~1.68, P=0.005), higher level of LDH (OR 1.45; 95% CI 1.16~1.80, P=0.0009) and more frequent involvement of spleen (OR 2.75; 95% CI 1.92~3.95, P<0.00001) and liver (OR 1.87; 95% CI 1.22~2.85, P=0.004) at diagnosis in comparison to HCV non-infected DLBCL patients. However, there was no significant difference in age of disease onset, disease stage, present of B symptoms and incidence of involvement of bone marrow between two groups of patients. Funnel plots indicated no evidence for publication bias.
Summary/Conclusion: The current study provided the compelling evidence about an inferior prognosis and distinct clinical characteristics in HCV infected DLBCL patients. DLBCL patients with HCV infection were prone to undergoing hepatic dysfunction during chemotherapy.

EP521 BASELINE TOTAL METABOLIC TUMOR VOLUME >220CM³ AND DEAUVILLE 5-POINT SCALE OF ≥4 AFTER FOUR CYCLES OF R-CHOP ARE STRONGLY ASSOCIATED WITH INFERIOR PROGRESSION FREE SURVIVAL IN PATIENTS WITH DLBCL

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Background: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) is the standard imaging modality for disease staging and end of treatment assessment of diffuse large B-cell lymphoma (DLBCL). However, its use for response prediction has not been standardized, yet. Baseline total metabolic tumor volume (TMTV) ≥220 cm^3 and change of maximum standardized uptake value (ΔSUV_{max}) after two cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) have been reported to be superior to the visual Deauville 5-point scale (DS).

Aims: Our aim was to assess the prognostic value of TMTV, ΔSUV_{max} and DS in contemporary "real-world" DLBCL patients uniformly treated with R-CHOP given every 21 days (R-CHOP21).

Methods: We conducted a retrospective analysis of 144 patients with DLBCL who were diagnosed and treated with R-CHOP21 at our institution during January 1st 2015 and December 31st 2019. This study was approved by the ethics committee of the Medical University of Graz. All patients underwent PET-CT at diagnosis and after four cycles of R-CHOP21 (i-PET4). SUV_{max} and TMTV were computed using the semiautomatic software Hermes Hybrid 3D Tumorfinder (Hermes Medical Solutions, Stockholm, Sweden). Statistical analyses were performed with Stata (Windows version 15.0, Stata Corp.). Median follow-up was estimated with a reverse Kaplan-Meier estimator. Primary endpoint for all time-to-event analyses was 5-year progression free survival (PFS). PFS was estimated with Kaplan-Meier estimators, and compared between groups using log-rank tests. Uni- and multivariable modeling of PFS functions was performed with Cox proportional hazards models. Harrell's concordance index was calculated to evaluate model fit of different PET parameters.

Results: Results:

Thirty-seven patients were excluded (HIV, n=2; transformed low-grade lymphoma, n=23; primary testicular lymphoma, n=3; primary central nervous system lymphoma, n=4; no interim imaging, n=5). Patients had a median age of 67 years (interquartile range [IQR], 53-74) and a median R-IPI score of 3 points (IQR, 2-4). During a median follow up of 2.4 years (IQR, 1.4-3.6), we observed 19 (18%) primary disease progressions during first line therapy, ten (9%) relapses after initial CR or PR, 16 (15%) deaths related to DLBCL and four deaths from other causes. The estimated 5-year PFS and OS of the whole cohort were 63% (95% CI, 51-73) and 75% (95% CI, 63-84), respectively.

Higher baseline TMTV predicted for higher risk of progression and death. The baseline TMTV threshold of >220cm^3 could be confirmed (Table 1). At i-PET4, TMTV, SUV_{max}, and DS comparably predicted PFS with a good discriminatory performance (c-indices between 0.76 and 0.80). Five-year cumulative incidences of primary disease progression or relapse were 32% and 76% in patients with DS of 1-3 points (n=67) and 4-5 points (n=34), respectively (Gray's test p <0.0001). Complete metabolic response (CMR), a composite of interim TMTV of 0 and SUVmax of 0 (n=60 patients), showed 5-year PFS of 83% and 31% in patients with and without a CMR (log-rank p<0.0001). In a multivariable model of PFS including CMR at i-PET4, double expressor lymphoma biology, cell of origin, and NCCN-IPI, only CMR prevailed as an independent predictor of PFS (HR 9.88, 95% CI 3.94-24.79, Wald test p<0.0001). ΔSUV_{max} was predictive of PFS but not superior to DS.

Variable	N missing (%)	Measured value [IQR], or absolute count (%)	Univariable		Harrell's c-index for PFS
			HR for PFS	95%CI (P)	
Markers at baseline					
TMTV (per doubling)	0	86 [26-188]	1.34	1.11-1.61 (0.002)	0.67
TMTV >220cm³	0	20 (19%)	3.54	1.73-7.22 (0.001)	0.63
NCCN-IPI (points)	0	3 [2-5]	1.34	1.08-1.67 (0.008)	0.60
Interim markers					
SUVmax (per doubling)	6 (5,6%)	0 [0-7]	1.71	1.44-2.03 (<0.001)	0.80
TMTV (per doubling)	6 (5,6%)	0 [0-11]	1.42	1.25-1.60 (0.001)	0.78
DS (per point increase)	6 (5,6%)	1 [1-4]	2.18	1.66-2.87 (<0.001)	0.80
DS	6 (5,6%)	/	/	/	0.76
---1-2 points	/	60 (59%)	ref.	ref.	/
---3 points	/	7 (7%)	1.22	0.15-9.79 (0.849)	/
---4-5 points	/	34 (34%)	8.86	3.86-20.36 (<0.001)	/
Change between baseline and interim					
$\Delta SUVmax_{rel}$ (per doubling)	7	-100 [(-100) – (-57)]	4.33	2.80-6.68 (<0.001)	0.79

Summary/Conclusion: DLBCL patients with baseline TMTV >220cm^3 and DS of ≥4 have an inferior PFS and are therefore prime candidates for new treatment strategies.

EP522 THE IMPACT OF THE GERIATRIC 8 SCORE ON OVERALL SURVIVAL IN OLDER ADULTS WITH DIFFUSE LARGE B-CELL LYMPHOMA.

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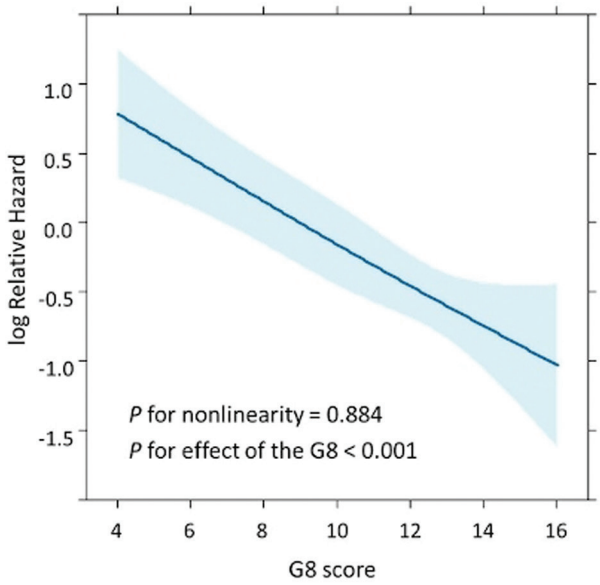
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Background: In aging society, the number of elderly patients with diffuse large B cell lymphoma (DLBCL) is increasing. The elderly patients cannot be managed in the same way as the young patients because of their various comorbidities and levels of frailty. However, the establishment of simple geriatric assessment tool to predict prognosis and management in treatment has rarely been reported in DLBCL.

Aims: The aim of this study was to verify the prognostic impact of the Geriatric 8 (G8) in elderly DLBCL patients, using a Cox hazards model with restricted cubic spline (RCS) model which is more suitable for reflecting the real-word practice.

Methods: To evaluate the usefulness of the G8, we conducted a retrospective, multicenter analysis of elderly DLBCL patients (≥65 years) who received standard therapy between 2007 and 2017 at three tertiary institutions in Japan. Patients treated with the standard regimen as first-line therapy were enrolled in this study. The exclusion criteria were transformed DLBCL, methotrexate-associated lymphoproliferative disorders, central nervous system involvement or undergoing treatment besides standard regimen. The standard regimen was defined as (R-) CHOP regimen (rituximab, cyclophosphamide, adriamycin [ADR], vincristine, and prednisolone) and (R-) THP-COP regimen (the same as CHOP including the doses, except tetrahydropyranyl adriamycin replaced ADR) in this study. The end point was the impact of the G8 on OS, which was defined as the interval from the date of the diagnosis to the date of all-cause death or the last follow-up visit. A multivariate Cox proportional hazards model was used to identify the predictors that were statistically associated with OS. Non-linear regression model with RCS was used to assess the presence of a non-linear relationship between the G8 score and OS. Diagnostic performance was assessed by receiver operating characteristic (ROC) analysis. The optimal G8 cutoff scores for OS were identified by ROC analysis using the Youden index. Survival curves for each group were estimated using the Kaplan-Meier method, and a comparison between risk groups was performed using the log-rank test.

Results: A total of 398 patients were included. With a median follow-up of 22.3 months (0-140.3), the estimated 2-year OS was 47.2%. A total of 196 patients (43.5%) died, including 127 (64.8%) of lymphoma and 10 (5.1%) of therapy-related toxicity. A multivariate Cox proportional hazards model demonstrated that the G8 was an IPI-independent prognostic predictor (HR 0.854, 95% CI 0.808-0.902, p<0.001). According to the multivariate RCS-Cox model, an obvious linear association was observed between G8 scores and mortality even though RCS model can represent in a nonlinear way (p for nonlinearity = 0.884, p for effect of the G8 <0.001). The lower the G8 score, the higher the risk of mortality. Especially, it was found that the mortality risk increases when the G8 score is below 9 to 10. The cutoff level of mortality, 9.5, in ROC analysis was considered robust, as it was consistent with the results of the Cox-RCS model. The Kaplan-Meier analysis showed that the patients with higher G8 had a significantly better prognosis than those with the lower G8 (log rank p<0.001).



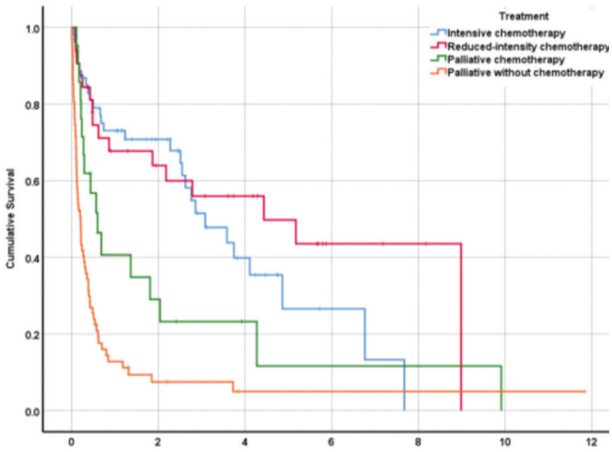
Summary/Conclusion: Our research has revealed the G8 score was found to be an important prognostic predictor in elderly DLBCL patients, in that a lower G8 score proportionally exacerbated the prognosis.

EP523 DOES INTENSIVE CHEMOTHERAPY REALLY HELP OLDER DLBCL PATIENTS LIVE LONGER?

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Background: Diffuse Large B Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin Lymphoma (NHL) and accounts for about 40% of all NHL[1]. There are several treatment options used in the management of DLBCL in older patients (>80 years old) including curative anthracycline-based regimens and palliative regimens; however, this age group appears to be under-represented in clinical trials likely due to concerns regarding patient comorbidities and treatment tolerance. R-MiniCHOP has been shown to be safe and effective in >80 year olds[2]. We present novel data from a multi-centre UK study with a focus on survival outlooks for DLBCL in the >80 age group.
Aims: To assess wether there is any significant difference in overall survival between intensive/reduced intensity/palliative chemotherapy/palliative without chemotherapy, in the frail over 80 age DLBCL group. With an aim to try and inform future treatment decisions.
Methods: Patient demographics and survival data were retrospectively collected (N=173) from Norwich and Sheffield University Hospitals. Four treatment groups were included for analyses: intensive chemotherapy (full dose RCHOP/RGCVP/R-PMitCEBO, N=53); reduced-intensity chemotherapy (R-miniCHOP/RCVP, N=32); palliative chemotherapy (VEDEX/Chlorambucil/Etoposide, N=21) and palliative without chemotherapy (steroids/palliative radiotherapy, N=67). Overall survival (OS) by age (Spearman's correlation) and sex (Mann-Whitney U) was analysed. Median survival by treatment was calculated and a Kaplan-Meier plot was generated. We performed a multivariate analysis (Cox regression) which assessed both age and treatment in relation to OS. Post-hoc Kruskal-Wallis testing detailed specific differences between treatment groups.
Results: Age was significantly negatively correlated with OS (p=.011) whereas there was no significant difference in OS between sexes (p=.653). The overall median OS was 0.57 years. Median OS values by treatment were 1.95 years (intensive), 2.06 years (reduced-intensity), 0.57 years (palliative) and 0.21 years (palliative without chemotherapy). The subsequent multivariate survival analysis showed OS varied significantly between treatment groups (p<.001); in this model, age did not retain its significance (p=0.824). Post-hoc testing revealed treatment differences were primarily driven by palliative (without chemotherapy) conferring a significantly lower OS versus all other treatments. Figure 1 shows how OS varies by treatment group. Of note, reduced-intensity chemotherapy resulted in a higher median OS than intensive chemotherapy (2.06 years vs 1.95 years), however this finding was not significantly different and larger studies may be useful in detecting an effect.



Summary/Conclusion: To conclude, we have shown that age and treatment each significantly predict OS, but when these variables are included together in a multivariate analysis, treatment remains the only significant predictor, possibly due to patients being pre-selected into treatment groups by age. Although not significantly greater than the intensive treatment OS, the reduced-intensity OS was the largest of all treatments included. This may be due to the elderly population having difficulty tolerating intensive chemotherapy leading to treatment 'holidays', an overall decline in health and a lower OS than reduced-intensity chemotherapy - it is therefore highlighted here as a potential point of future research. Better powered analyses should further examine patient factors such as treatment tolerability, complication rates and late effects which may impact on OS in this frail study population.

EP524 PIRTOBRUTINIB (LOXO-305), A NEXT GENERATION, HIGHLY SELECTIVE, NON-COVALENT BTK INHIBITOR IN PREVIOUSLY TREATED RICHTER TRANSFORMATION: RESULTS FROM THE PHASE 1/2 BRUIN STUDY

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Background: Richter transformation (RT) is the development of an aggressive large cell lymphoma in the setting of underlying CLL and is a recurrent reason for treatment failure (5-15%) among patients (pts) receiving CLL directed therapy. Outcomes for pts with relapsed RT are extremely poor, with no standard treatment and overall survival estimated at 5-8 months. Pirtobrutinib is a highly selective and potent non-covalent BTK inhibitor (BTKi) with high oral bioavailability and a long half-life, resulting in robust BTK target coverage even in high-grade malignancies with high BTK protein turnover.
Aims: To evaluate pirtobrutinib safety and efficacy in previously treated pts with RT.
Methods: Pts with previously treated RT were enrolled to either the dose escalation or expansion portion of the multicenter phase 1/2 BRUIN study (NCT03740529). The primary endpoint for this analysis was ORR according to Lugano criteria. A key secondary endpoint was duration of response. Efficacy evaluable pts included all dosed RT pts who underwent their first response evaluation or discontinued therapy as of the data cut.
Results: As of 27 September 2020, 323 pts with B-cell malignancies were treated including 9 pts with previously treated RT (8 of 9 RT pts received the RP2D of 200mg QD, 1 pt received 150mg QD). All 9 pts had received at least one prior RT directed therapy, and the median number of prior RT directed therapies was 2 (range 1-5). Pts had received a median of 4 prior lines of therapy for CLL (range 0-6). Prior RT directed therapies included chemoimmunotherapy (100%, n=9), covalent BTKi (44%, n=4), anti-PD-1 or PD-L1 antibody (33%, n=3), mTOR inhibitor (22%, n=2), PI3K inhibitor (22%, n=2), CAR-T cell therapy (n=1), autologous stem cell transplant (n=1), polatuzumab vedotin (n=1), and pomalidomide (n=1). The ORR for the 8 efficacy evaluable pts was 75% with 6 PR, 1 SD, and 1 NE. These 8 pts have been on treatment for 1.6, 2.3, 2.9+, 2.9+, 3.2+, 3.7, 6.4+, and 7.1+ months (+ indicates ongoing). The remaining pt continues on treatment and is awaiting initial response assessment. No new safety signals were identified in RT pts. Since data cut, 8 additional previously treated pts with RT have been enrolled. Updated data with additional follow-up in all 17 RT pts will be presented.
Summary/Conclusion: Pirtobrutinib showed promising initial efficacy in pts with pretreated RT with extremely poor prognosis, including in pts who had received prior chemoimmunotherapy and covalent BTK inhibitors.

EP525 PRELIMINARY SAFETY DATA FROM PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL MALIGNANCIES TREATED WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL2) INHIBITOR BGB-11417

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Background: BCL2, a key protein regulator of the apoptotic pathway, is aberrantly expressed in many hematologic malignancies, which can lead to pathologic cancer cell survival. Within the cell there is a delicate balance between BH3-only proteins which activate apoptosis and BCL2 which inhibits it. BH3 mimetics have been shown to be safe and effective, resulting in their approval for the treatment of pts with chronic lymphocytic leukemia (CLL) and acute myeloid leukemia. Treatment with currently approved BCL2 inhibitor venetoclax can be limited by common mild gastrointestinal toxicities, neutropenia, and the emergence of specific BCL2 mutations around the BH3-binding groove causing resistance after continued use. BGB-11417 was developed as a potent and highly selective inhibitor of BCL2 and has shown antitumor activity superior to venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) xenograft models (preclinical internal data). BGB-11417 also has a favorable pharmacokinetics profile with low plasma clearance in rodents and dogs. Toxicology studies have shown a broad safety window and an excellent safety profile.
Aims: BGB-11417-101 is an ongoing first-in-human phase 1/1b study (NCT04277637) to determine the safety, tolerability, maximum tolerated dose (MTD) and recommended phase 2 dose of BGB-11417 in pts with R/R B-cell malignancies.
Methods: The study has a dose-escalation component, followed by a safety expansion. For dose escalation, pts with R/R B-cell malignancies were enrolled in 1 of 5 oral BGB-11417 dose cohorts (40, 80, 160, 320, or 640 mg once daily). All pts received a weekly or daily ramp-up to intended target dose; pts with non-Hodgkin lymphomas (NHLs) received a 2-day dose ramp-up (day 1, 25% of intended dose; day 2, 50%) before reaching the intended daily dose (day 3+, 100%). Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0. A Bayesian logistic regression model was used to evaluate dose-limiting toxicities (DLT; assessed during dose ramp-up through day 21 at intended daily dose) rate at different doses and to determine the MTD. The first dose-escalation cohort allowed pts with R/R follicular lymphoma (FL), marginal zone lymphoma (MZL), DLBCL, or transformed NHL.
Results: As of 01-Jan-2021, 7 pts with R/R NHL across 2 dose levels had been treated. The first R/R CLL cohort had just opened with 2 pts treated. Only data from the NHL pts are reported here, including: 5 DLBCL, 1 FL, and 1 MZL with median follow-up of 2.9 mo (range, 1.7-7.7). The 40-mg (n=3) and 80-mg (n=4) dose cohorts have completed with no DLTs. The 160-mg dose cohort is currently being investigated. AEs across all dose levels occurring in >1 pt are listed in **Table 1**. Four pts have discontinued treatment (due to disease progression [n=3; 2 at 40 mg, 1 at 80 mg], or lack of efficacy [n=1 at 40 mg]) and 3 pts remain on treatment. No pt discontinued due to AEs, and no instances of laboratory or clinical tumor lysis syndrome have been observed.

Any AE in >1 Pt (N=7), n (%)	Grade ≥3	All Grade
Nausea	1 (14.3)	4 (57.1)
Constipation	0	3 (42.9)
AST increase	1 (14.3)	3 (42.9)
ALT increase	1 (14.3)	2 (28.6)
Dizziness	0	2 (28.6)
Dyspnea	0	2 (28.6)
Diarrhea	0	2 (28.6)

ALT, alanine aminotransferase; AST, asparatate aminotransferase.

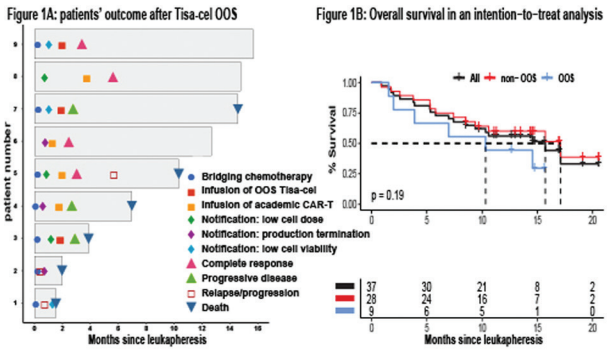
Summary/Conclusion: These early phase 1 results suggest that the BCL2 inhibitor BGB-11417 is tolerable in pts with R/R NHL at dose levels tested. Preliminary activity in this pt population will be assessed with increased enrollment and follow-up. Enrollment of pts with R/R CLL is underway, and decreases in lymphocyte count have already been seen at the initial ramp-up dose of 1 mg. Evaluation of pts with MCL and Waldenstrom macroglobulinemia, and the combination of BGB-11417 and Bruton tyrosine kinase inhibitor zanubrutinib, is planned for future cohorts.

EP526 PATIENTS WITH OUT OF SPECIFICATION TISAGENLECLEUCEL CAN BE SALVAGED WITH POINT-OF-CARE CAR-T CELLS: AN OBSERVATIONAL INTENTION-TO-TREAT SINGLE-CENTER ANALYSIS

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Background: Tisagenlecleucel (Tisa-cel) is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Results from the JULIET trial (Schuster, NEJM 2019) showed best overall response of 52% per-protocol and 34% in an intention-to-treat (ITT) analysis. Outcomes of patients with out-of-commercial specification (OOS) products are not well established. The availability of point-of-care anti-CD19/CD28 costimulatory domain academic CAR T-cells in our center allows us to provide rapid salvage in cases of commercial CAR T-cell production failure.
Aims: To report real-world outcomes of patients treated at a single center with Tisa-cel for DLBCL and describe outcomes in cases of OOS in Tisa-cel production.
Methods: Data of patients who underwent leukapheresis for Tisa-cel were collected and analysed. Patients received lymphodepletion with fludarabine and cyclophosphamide. Survival was calculated from leukapheresis.
Results: Peripheral blood cells were collected from 37 patients with DLBCL between May 2019 and February 2020. The median age at leukapheresis was 63 (range 28-79) years. The median number of previous treatment lines was 2 (range 2-6). Cells from 78% of the patients were collected in progressive disease. Bridging chemotherapy was given in 87% of the patients. Median time from leukapheresis to cell infusion was 1.6 (range 1.3-2.2) months. During this time, disease progression was marked in 45% of the patients. Tisa-cel CAR T-cells were infused in 29 (78%) of the patients. The median follow-up was 14.7 (IQR: 13-17) months.
In 9/37 (24%) patients, manufactured Tisa-cel did not meet specification for commercial release. Causes for OOS were production termination (3/9 [33%]), low CAR T-cells viability (<70%; 3/9 [33%]), and low CAR T-cells dose (<0.6x10^8; 3/9 [33%]). Among patients with OOS products, 3/9 (33%) received Tisa-cel, despite not meeting production standards; 2/9 (22%) did not receive Tisa-cel due to disease progression and death before salvage therapy; and 4/9 (44%) were salvaged with point-of-care academic CD19-directed CAR T-cells, at a median of 35 (range 16-92) days following the notification of production failure. Three of these four patients achieved a complete response (CR) (Figure 1A). In a univariable analysis, risk factors for OOS were ≥ 4 previous lines of treatment (p=0.04) and previous exposure to bendamustine (p=0.04). Previous bone marrow transplantation, age ≥ 65, and time from previous last therapy were not significant risk factors.
Overall response at day-28 post-CAR-T was 46% (CR 24%) and 35% (CR 24%) in per-protocol (i.e., including only patients who received Tisa-cel) and ITT (i.e., including all patients who underwent leukapheresis) analysis, respectively. One year overall survival (OS) was 65% (95% CI 50-85%) in per-protocol and 56% (95% CI 42-75%) in ITT (Figure 1B). In a multivariable ITT Cox regression, factors associated with a shorter OS were ECOG ≥ 2 (HR 6.5; 95% CI 1.9-22.5) and primary refractory disease (HR 3.3; 95% CI 1.2-9.1). Age, disease stage at leukapheresis, and LDH at leukapheresis were not significant risk factors. OOS was not statistically significant as risk factor for a shorter OS (p=0.07).



Summary/Conclusion: Our data show relatively high rates of out-of-specification products following leukapheresis for Tisa-cel. We highlight the ability to rapidly produce point-of-care CAR T-cells, facilitating immune-effector cell salvage of patients who experienced production failure of the commercial product.

EP527 DISCOVERY OF HBW-3-20, THE FIRST REVERSIBLE INHIBITOR OF BRUTON'S TYROSINE KINASE (BTK) WITH HIGH BRAIN EXPOSURE

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Background: It has been an on-demand task to develop a BTK inhibitor of significant brain exposure, a critical property for extending its usages to treat Primary Central Nervous System Lymphoma (PCNSL) and autoimmune disorders. PCNSL is an aggressive extra nodal non-Hodgkin lymphoma that exclusively invades the central nervous system (CNS). Tirabrutinib, an irreversible BTK inhibitor with limited brain exposure, is the first BTK inhibitor approved for the treatment of recurrent or refractory primary central nervous system lymphoma recently. PRN2246 is another irreversible BTK inhibitor claimed to be of brain exposure, and is currently in clinical trials for the treatment of multiple sclerosis.
Aims: Discovery of Reversible Inhibitor of Bruton's Tyrosine Kinase (BTK) with High Brain Exposure
Methods: New reversible BTK inhibitors were designed, synthesized and tested for enzymatic activities against wild-type and C481S-mutated BTK. Highly active compounds were confirmed for growth effects in diffuse large B-cell lymphoma derived TMD8 cells. Their microsomal stability and ADME properties were also assessed. Potent and bioavailable compounds were further measured for brain exposures in rats.
Results: HBW-3-20 has excellent potency against both wild-type and C481S-mutated BTK, with IC_{50} of 2.5 and 3.8 nM, respectively. Its TMD8 cellular potency is 72 nM. In a head-to-head direct comparison of brain exposure experiment, HBW-3-20, tirabrutinib and PRN2246 were all dosed at 10mg/kg orally. The brain and plasma concentration were measured after 1 hour and the data are shown in the table below. The brain to plasma ratio for HBW-3-20, tirabrutinib and PRN2246 are 58%, 11.8% and 4.2% respectively. Our results show that HBW-3-20 has much greater brain permeability than tirabrutinib or PRN2246 in rats.

Compound	tirabrutinib	PRN-2246	HBW-3-20
BTK IC_{50} (nM)	22	2.1	2.5
BTKC481S IC_{50} (nM)	na	na	3.8
TMD8 IC_{50} (nM)	158	29	72
Plasma concentration (ng/mL)	713	387	3457
Brain tissue concentration (ng/mL)	84	16.5	2009
Brain/Plasma Ratio (%)	11.8	4.2	58

Summary/Conclusion: HBW-3-20 is the first potent reversible BTK inhibitor with superior brain permeability. HBW-3-20 provides a very valuable clinical candidate for treating B-cell malignancies in brain and autoimmune disorders!

EP528 CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA WHO RECEIVED ≥3 LINES OF THERAPIES

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Background: Recent years have seen the emergence of novel treatments for Relapse/Refractory diffuse large B-cell lymphoma (DLBCL). There remains a paucity, however, of published analyses examining outcomes of patients(pts) within the evolving treatment landscape.
Aims: To address this data gap, this study examined real-world clinical outcomes among pts with R/R DLBCL who received third or subsequent line (≥3L) of therapy.
Methods: This retrospective analysis included adult pts, diagnosed with DLBCL [01/01/2014 to 31/08/2019], who received ≥3L of therapy. Data were abstracted from COTA, a de-identified database of real-world data, derived from the electronic health records of healthcare providers in the United States. Pts were categorized as receiving 1) chemotherapy or chemoimmunotherapy (CT/CIT), 2) targeted therapy (TT) [brentuximab, vedotin, ibrutinib, venetoclax, lenalidomide, obinutuzumab, nivolumab, polatuzumab, and pembrolizumab], 3) chimeric antigen receptor T cells (CAR-T), or 4) salvage therapy consolidated with hematopoietic stem cell transplantation

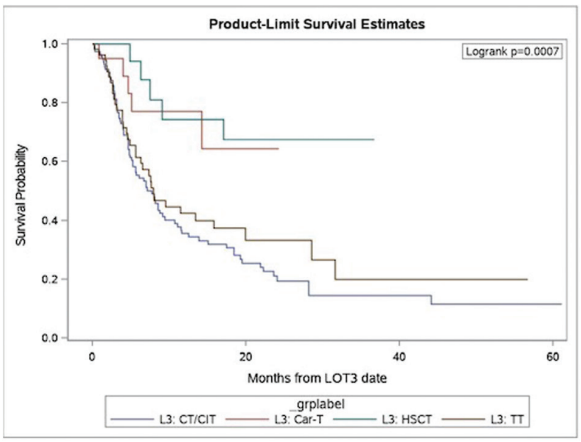
(HSCT). Patient characteristics, response rates, and overall survival (OS) were reported by line of therapy (3L, 4L) for the overall study population and stratified by treatment category. HSCT being a consolidation therapy for pts achieving a complete or partial remission (CR or PR) following salvage treatment, hence; response rates following HSCT were not reported.

Results: Of the 435 pts identified, 212 received 3L and 128 received 4L. At 3L initiation, pts had a mean age of 61yrs (range 18-90) and 59% were male. At 4L initiation, pts had a mean age of 60yrs (range 20-84) and 61% were male. Within a median follow-up of 22.5 months, 14.9% of pts treated with 3L CT/CIT or TT received subsequent CAR-T. Within a median follow-up of 19.3 months, 10.9% of pts treated with 4L CT/CIT or TT received subsequent CAR-T.

CR rates of pts receiving non-cell therapy were substantially lower than pts receiving CAR-T, in both 3L and 4L settings [**Table1**]. OS results for 3L therapy are presented in **Figure 1**. Median OS of non-cell therapy was 7.7 months (CT/CIT: 7.7 months; TT: 7.9 months), and 4.5 months (CT/CIT: 4.5 months; TT: 5.1 months) for 3L and 4L, respectively. Median survival time of pts receiving cell therapy (CAR-T and HSCT) had not reached in either the 3L or 4L setting.

Table 1: Treatment patterns and complete response rates for 3rd Line and 4th Line pts

	3L		4L	
	n (%)	CR rate	n (%)	CR rate
CT/CIT	117 (55)	9.4%	66 (52)	7.6%
TT	57 (27)	8.8%	44 (34)	15.9%
CAR-T	20 (9)	60%	12 (9)	50%
HSCT	18 (8)	N/A	6 (5)	N/A



Summary/Conclusion: Results from this real-world study illustrate that majority of pts treated with 3L CT/CIT or TT, had poor clinical outcomes, which were exacerbated in the 4L setting. Pts who received cell therapy had better clinical outcomes, however, the proportion of pts receiving these treatments is low. Preliminary data suggests that survival outcomes among CAR-T and HSCT pts, are similar in the 3L and 4L settings. Despite various novel treatments, prognosis for pts with R/R DLBCL remains very poor, underscoring the need for more efficacious treatment options.

EP529 REAL WORLD CLINICAL EFFECTIVENESS AND SAFETY OF CT-P10 IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: RESULTS FROM A EUROPEAN NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY

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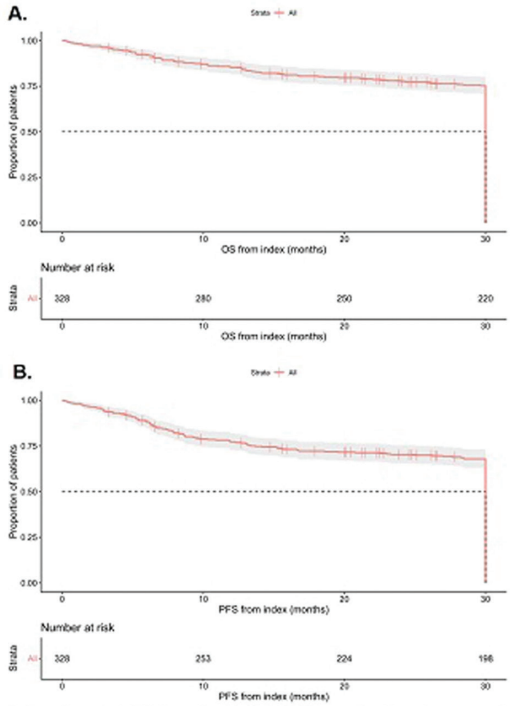
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Background: The rituximab biosimilar CT-P10 was granted European Medicines Agency approval in 2017 for the treatment of rheumatoid arthritis (RA) and specific blood cancers, including non-Hodgkin's lymphoma (NHL). Diffuse large B-cell lymphoma (DLBCL) accounts for 30–50% of NHL cases. Clinical similarity between CT-P10 and rituximab was accepted based on evidence in populations of patients with RA and follicular lymphoma. To-date, DLBCL patients have not been included in clinical trials of CT-P10 and no studies have investigated the effectiveness or safety of CT-P10 treatment in patients with DLBCL in a European real world clinical setting.

Aims: To evaluate the real world clinical effectiveness and safety of CT-P10 in patients with DLBCL in Europe.

Methods: This non-interventional post-authorisation safety study involved collection of patient-level data from hospital medical records for patients with DLBCL who received CT-P10 treatment prescribed in accordance with the marketing authorisation in five European countries (United Kingdom, Spain, France, Germany and Italy). Patients were treated as per routine clinical practice. Effectiveness (overall survival [OS] and progression free survival [PFS], CT-P10 responses), safety (adverse events [AEs] and infusion-related reactions [IRRs]) and CT-P10 treatment pattern data were collected during the 30-month observation period following the index date (date of CT-P10 initiation) or until death, if sooner.

Results: This study included 389 (58% male) patients with a median disease duration at index of 23.0 (Interquartile range [IQR] 12.0–46.0) days. The median age at index was 69.7 (IQR 60.3–76.1) years. Of patients with available data at index, 42% (n=98/191) had Ann Arbor stage IV disease while 21% (n=49/237) had an Eastern Cooperative Oncology Group performance score ≥2; 50% (n=131/263) of patients were classified as intermediate-high or high risk (International Prognostic Index score ≥3). CT-P10 was received as a first-line treatment for DLBCL by 84% (n=328) of patients, second-line for 11% (n=41), and third-line or greater for 5% (n=20). R-CHOP was the most administered chemotherapy regimen at index (68%, n=266/389). The best recorded response to CT-P10 (n=382) was complete response in 82% (n=312) of patients, partial response in 12% (n=46), no response or stable disease in 4% (n=16) and progressive disease in 2% (n=8). At 30-months post-index, for patients taking first-line CT-P10, 74% (95% confidence interval [CI] 69.2–79.1%) of patients were still alive and 67% (95%CI 61.3–72.1%) had not progressed. Kaplan-Meier curves depicting OS and PFS are shown in Figure 1; median OS/PFS was not reached. Overall, 90% (n=351) of patients reported at least one AE (n=2504 total AEs); 46% (n=178) had ≥1 Grade 3 AEs, most commonly neutropenia (9% [n=35/369] of all Grade 3 AEs). 9% (n=180/2100) of AEs were recorded as definitely, probably or possibly related to CT-P10 and 6% (n=24) of patients discontinued CT-P10 due to AEs. IRRs were reported on day 1 or 2 for 8% (n=31) of patients.



A. Overall survival (OS) for patients taking CT-P10 as a first-line of treatment. B. Progression-free survival (PFS) for patients taking CT-P10 as a first-line of treatment. The assessment of disease progression was based on the Revised Response Criteria for Malignant Lymphoma, if these criteria were used and documented locally.

Summary/Conclusion: This study provides new insight into the real world effectiveness and safety of CT-P10 for the treatment of DLBCL. Over three quarters of patients initiated on CT-P10 achieved complete or partial response by 30 months, with CT-P10 appearing to be generally well tolerated by patients. The response and survival rates and overall safety profile for CT-P10 appear consistent with those reported for reference rituximab, supporting CT-P10 use in combination with chemotherapy as a therapeutic option for DLBCL.

EP530 LYMPHOCYTE COUNT EFFECT ON EFFICACY AND SAFETY OF SINGLE AGENT ORAL SELINEXOR IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A POST-HOC ANALYSIS FROM PHASE 2B SADAL STUDY

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Background: Selinexor is a first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound that blocks XPO1, forcing the nuclear retention and functional activation of tumor suppressor proteins including p53, p73, FOXO, IkB and Rb. The phase 2b SADAL study included 134 patients with relapsed or refractory DLBCL with single agent selinexor twice weekly. The overall response rate (ORR) was 29.1%, median duration of response (DOR) 9.3 months and the median overall survival (OS) 9 months. Based on these data, selinexor was approved by the US FDA for the treatment of relapsed or refractory DLBCL, de novo or transformed from follicular lymphoma. Studies have shown that a lower absolute lymphocyte counts (ALC) is a strong prognostic factor for reduced PFS and OS in patients with DLBCL.
Aims: To performed post-hoc analyses of results from the SADAL study to determine the impact of baseline ALC on the efficacy and safety of selinexor.
Methods: The SADAL study was multi-center, open-label Phase 2b study that enrolled patients with DLBCL treated with 2-5 lines of therapy treated with oral selinexor 60mg twice weekly until disease progression. Patients may have recurrence after stem cell therapy (SCT) or were not candidates for SCT. The primary endpoint was ORR, and other endpoints included DOR, OS and safety assessments. For the current analysis, patients were divided into categories based on baseline ALC (≥1000/μL and <1000/μL) in order to compare outcomes.
Results: Of the 134 patients enrolled in the SADAL study, 61 (46%) had baseline ALC of ≥1000/μL and 71 (53%) had levels <1000/μL. The majority of patients in both groups were <65 years old, 79% and 72%, respectively. In this population, *de novo* and transformed DLBCL accounted for 82% and 18% with ALC ≥1000/μL and 72% and 28% in patients with ALC <1000/μL and, respectively. DLBCL subtype was also similarly distributed among patients with GCB and non-GCB in those with ALC ≥1000/μL (51% and 43%) and in those with ALC <1000/μL (44% and 55%), respectively.
The ORR in patients who had baseline ALC ≥1000/μL was 32.8% compared to 25.4% for ALC <1000/μL (p=0.455; complete responses (CR) rates were 13.1% vs 14.1% respectively. The median DOR in patients who had ALC ≥1000/μL was 23.0 months compared to 4.9 months in patients with ALC <1000/μL (p=0.228). The median PFS were 3.6 and 2.1 and median OS were 15.5 and 7.6 months in patients with ALC ≥1000/μL and <1000/μL, respectively (p=0.129; p=0.013).
The most common grade ≥3 treatment-related adverse events (AEs) for patients with ALC ≥1000/μL and <1000/μL were thrombocytopenia (42.6% vs. 38.0%), nausea (6.6% vs. 4.2%) and fatigue (9.8% vs. 11.3%). The incidence of treatment-related serious AEs and AEs leading to discontinuation in patients who had a lymphocyte count of ≥1000/μL vs <1000/μL were 26.2% vs. 16.9% and 11.5% vs. 4.2%, respectively; these differences may have been related to duration of response.
Summary/Conclusion: In this post-hoc analysis in patients enrolled in SADAL with relapsed/refractory DLBCL treated with single agent oral selinexor, those with baseline ALC ≥1000/μL had a ALC a slightly higher ORR (33% vs 25%) but similar CR rates and PFS to those with ALC<1000/μL. Significantly longer overall survival was observed in patients with higher baseline ALC, and responses in these patients trended to longer duration. While consistent with many reports in the literature regarding the poor prognosis of baseline ALC <1000/μL, these results need to be confirmed in larger studies with longer follow up.

EP531 CLINICOPATHOLOGIC DESCRIPTORS OF MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA (MEITL): ANALYSIS OF A POOLED DATABASE OF A NEW ENTITY

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Background: MEITL is a rapidly progressive rare extranodal T-cell lymphoma that arises from the intestinal intraepithelial T lymphocytes. In its 2016 classification, the WHO established MEITL as a separate entity of what was previously known as type 2 enteropathy-associated T-cell lymphoma. While morphologic characteristics are codified in its name, this entity tends to have its own clinicopathologic characteristics.
Aims: We conducted this analysis to explore the clinicopathologic descriptors and prognosticators of this little-known newly established T-cell entity.
Methods: In order to study the demographic characteristics, molecular and immunohistochemical signatures, therapeutic interventions, survival, and prognostic factors, we compiled a pooled database of 116 cases. Descriptive statistics were calculated. Cox proportional-hazards model and Log-rank tests were used to assess the influence of demographic and clinicopathologic factors on overall survival (OS).
Results: A total of 116 patients with confirmed MEITL were identified. The median age was 59.5 years with a peak incidence between ages 56 and 68. There was a male predominance with M:F ratio of 2. As the only involved gastrointestinal (GI) site, Jejunum was the most involved site of the disease (Jejunum (J) 21%, Duodenum (D) 7%, Colorectal (CRC) 10%, Ileum (I) 6%, Gastric (G) 2%). Jejunum was also the most involved site when the disease involved multiple GI sites (J 71%, I 57%, D 46%, C 30%, R 3%). The most frequently involved anatomic combinations were multifocal small intestine 26%, small intestine with colorectal 21%, J&I 7%, D&J 2%. While 25% of patients presented with lymphadenopathy (79% regional, 14% distal, 7% both), only 6% had bone marrow involvement and none had hepatosplenomegaly. Extra-nodal and extra-gastrointestinal involvement comprised lung (5%), CNS (3%), and skin (1%). Stage distribution consisted of Stage I (69%), II (9%), III (6%), IV (16%). Most cases expressed CD2 (77%), CD3 (100%), CD7 (86%), CD8 (80%), CD56 (89%), CD103 (86%), and Granzyme-B (52%). MEITL cases expressed TCR-αβ (39%), γδ (56%), and null (5%). There were no significant differences in age, sex, and CD profiles with respect to TCR-status. The most common clinical presentations were abdominal pain, followed by perforation, diarrhea, and weight loss. The median duration of symptoms prior

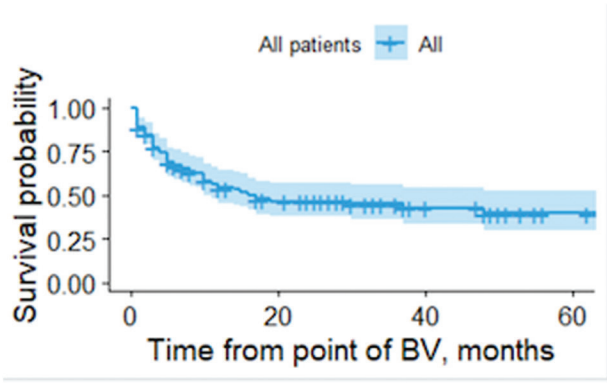
to diagnosis was 4 months. Median OS of the whole group was 11 months. Compared to no treatment, combination chemotherapy and stem cell transplant (SCT) were statistically superior with a median OS of 2, 9, and 34 months respectively (p=0.0005). Furthermore, quality of response and surgical resection imparted a survival advantage. OS was not impacted by sex, presentation with obstruction or perforation, or anatomic site involvement. While older age, weight loss, and TCRγδ seemed to negatively impact OS, they did not reach statistical significance.
Summary/Conclusion: This study presents a comprehensive clinicopathologic data from a pooled cohort of patients with MEITL. It describes the clinicopathologic features of MEITL and identifies major determinants of OS in this rare disease.

EP532 POPULATION-BASED COHORT STUDY OF THE EFFICACY OF BRENTUXIMAB-VEDOTIN IN RELAPSED SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA USING PUBLIC HEALTH ENGLAND DATA

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Background: Systemic anaplastic large cell lymphoma (sALCL) is a T-cell lymphoma, historically associated with low cure rates following relapse. Expression of the ALK protein is more common in younger patients and associated with improved survival outcomes. Following a pivotal phase II study (Pro et al) and European licence, the immuno-conjugate Brentuximab Vedotin (BV) became available in England via the Cancer Drugs Fund (CDF) in 2013. To date, no large-scale population-based studies have described outcomes following BV. Public Health England (PHE) collects information on all cancer diagnoses in England, and since April 2012 all delivered Systemic Anti-Cancer Therapy (SACT).
Aims: We aimed to evaluate whether routinely collected PHE data can reliably assess outcomes of patients with lymphoma. Survival outcomes for BV monotherapy in relapsed ALCL in all England was chosen as a pilot project to explore the value of PHE data due to the well-defined disease and SACT cohort.
Methods: Following NHS REC approval, we requested anonymised Office of Data Release (ODR) information on sALCL patients ≥18 years treated with BV monotherapy between 1st Jan 2014-31st Dec 2019. We excluded primary cutaneous and breast-implant associated ALCL, patients in the ECHELON-2 trial and BV received in combination. We requested baseline demographics, ALK status, dates and number of BV cycles, and SACT data prior to and following BV, prior autologous/allogeneic stem cell transplantation (SCT). Kaplan-Meier survival methods were used to compare the primary outcome of all-cause mortality between groups defined on the basis of age, gender and ALK status (positive vs. negative) in univariate analyses.
Results: 173 patients were identified, of whom 46 were excluded. The final cohort comprised 127 patients with r/r ALCL with a median age of 60 years at initiation of BV and median follow up time of 10 months. 49 (38.6%) patients were ALK+ve and 78 (61.4%) ALK-ve. The median time from diagnosis to BV was nine months (range 1-143). 106 (83.5%) received BV second line, and 13 (10.2%) third or fourth line. 95 (74.8%) received CHOP first line. Based on SACT data 18 (14.2%) received SCT in first remission (16 auto, 2 allo). The median number of BV cycles received was five. Median 2-year overall survival (OS) was 46.6%. The majority (59) of deaths occurred within the first 18 months, followed by a survival plateau with only four subsequent deaths. There were 20 (15.7%) deaths prior to cycle 5, the timepoint where the CDF mandates response assessment. There was no difference in OS between ALK+ve and ALK-ve (p=0.78), age <40 vs ≥40 years(p=0.89), age <60 vs ≥60(p=0.96), between genders(p=0.25), or receiving prior SCT (p=0.55). Two patients received SCT after BV, with both alive 20+ months post-transplant. Receiving BV second line therapy was associated with improved survival, with 2-year OS of 50.3% versus 29.7% for those third or fourth line(p = 0.03).



Summary/Conclusion: We confirm BV is a highly effective treatment for r/r sALCL with real world survival outcomes across sub-groups highly comparable with clinical trial data. Weaknesses of this study include lack of information on toxicity and data from double blind studies, although this data is now being collected. Analysis of routinely collected PHE data offers the opportunity to undertake high quality, nationwide population-based studies, to inform the efficacy of high-cost drugs such as BV in routine clinical practice.

EP533 COMBINED TREATMENT OF AUTOLOGOUS HEMATOPOIETIC STEM CELLS TRANSPLANTATION WITH CAR T-CELL THERAPY IMPROVES OUTCOMES IN MANAGEMENT OF ADVANCED RELAPSED/REFRACTORY CENTRAL NERVOUS SYSTEM B-CELL LYMPHOMA

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Background: The Chimeric antigen receptor (CAR) T-cell therapy has shown very promising future in relapsed/refractory B-cell lymphoma while the central nervous system lymphoma(CNSL) remained one of exclusion criterion in CAR T-cell therapy due to its fatal neurotoxicity.Recently several studies reported CAR T-cell therapy was safe and effective in treatment of advanced CNS disease, however, its resultant remission seemed short-lasting.
Aims: 1.Investigate the effect and safety of CAR T-cell therapy in advanced refractory/relapsed central nervous system B-cell lymphoma(R/RCNSBL).2.Compare effects of combination of autolougs hematopoietic stem cell transplantation(ASCT)with CAR T-cell therapy, and sequential multiple targets of CAR T-cell therapy towards survival of the subjects.
Methods: 17 patients (aged 19-66 years) with advanced R/RCNSBL were enrolled from 01/10/2018 to 01/10/2020,and are reviewed. Prior to administration of CAR T-cell therapy, all of the patients received chemotherapy and targeted drugs treatment to reduce tumor loads. Only patients who had responded to chemotherapy would be treated with stem cell mobilization and collection. The ASCT combined with CD19, CD20 or CD22 CAR T-cell therapy would be then administered to patients whose stem cells were successfully collected or had been already prepared. While other patients would be given with sequential therapy with targeting CD19, CD20 or CD19-22 CAR T-cell therapy. After CAR T-cells were infused, mannitol was also given for prophylaxis. The T-cells with specific CAR expression in peripheral blood and cerebrospinal fluid were dynamically detected by flow cytometry. After CAR T-cells infusion, PET-CT, PET-MRI or contrast-enhanced MRI were performed every 3 months. Patients were followed up till 1/31/2021
Results: 1.8 cases of 17 patients, who completed treatment of ASCT and CAR T-cell therapy, and the other 9 cases with completed multi-target sequential therapy. 2.The incidence of cytokine release syndrome (CRS) was 94.11%, of which 41.17% was severe CRS(≥grade 3), as the incidence of immune effector cells associated neurologic toxicity(ICANS) was 35.29%, of which 29.41% was severe ICANS. In comparison, in ASCT group and non-ASCT group, the incidence of severe CRS(≥grade 3)were 50% and 33.33%(P=0.486),respectively;and that of severe ICANS (≥grade 3) were 25% and 33.33% (p=0.14), respectively. There were no death related to the treatment.3. In 3 months, complete remission rate was 64.70% (11/17), partial remission rate was 5.88% (1/17) and the objective response rate was 70.59% (12/17). The remission rate of the ASCT group was higher than that of the non-ASCT group (100% vs 44.4%, P < 0.01). the median of progression-free survival length(PFS)

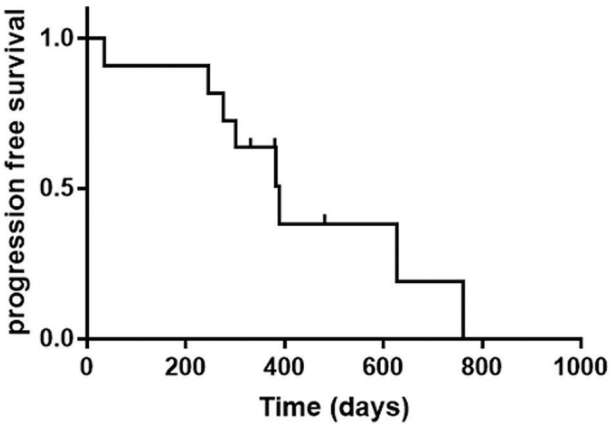
was 8 months (ranging 2-17 months). The overall survival length (OS) was 6 to 21 months. In comparison, in the group of ASCT combined with CAR T-cells therapy, patients in remission had longer PFS (11 months vs 4 months, P=0.02), with no significant difference in the overall survival length between the two groups (11 months vs 9 months, P =0.52).
Summary/Conclusion: 1.The CAR T-cell therapy could augment its efficacy in treatment of advanced R/RCNSBL.2.The neurotoxicity of CAR T- cells therapy could be mitigated, and there was no death related to treatment.3.The combined treatment of ASCT and CAR T-cell therapy could increase sustained response and longer survival length.

EP534 LENALIDOMIDE AND RITUXIMAB REGIMEN COMBINED WITH INTRAVITREAL METHOTREXATE FOLLOWED BY LENALIDOMIDE MAINTENANCE FOR PRIMARY VITREORETINAL LYMPHOMA: A PROSPECTIVE PHASE II STUDY

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Background: Primary vitreoretinal lymphoma (PVRL) is a rare variant of primary central nervous system (CNS) lymphoma, for which currently there are no optimal treatment options.
Aims: To balance the adverse events (AEs) of chemotherapy and achieve sustained control of lymphoma, we conducted a single-arm, phase II trial for newly diagnosed B-cell PVRL to evaluate the efficacy and safety of the R2 regimen with intravitreal MTX
Methods: This prospective single-center study enrolled immunocompetent patients with newly diagnosed PVRL between August 2018 and January 2020. Patients received local and systemic therapies: intravitreal methotrexate (MTX, 400 μg, 0.1 mL) injections for 1 year (total 16 injections) and six cycles of the rituximab (375 mg/m^2 on day 1) and lenalidomide (25 mg on day 1–21; R2) regimen. Lenalidomide was maintained for 2 years in patients who had achieved a response. This trial is registered with ClinicalTrials.gov (number NCT 03746223).
Results: We enrolled 11 patients with a mean age of 58 (range, 48–70) years, of which 10 achieved complete remission at the first evaluation. The median follow-up period was 18.3 (range, 10.6–27.8) months, and the median progression-free survival was 12.7 months. Moreover, a total of eight patients relapsed. The most common adverse event (AE) was neutropenia, which occurred in seven patients (63.6%), followed by grade 3 ocular toxicities, including cataract formation, in six patients (54%).



Summary/Conclusion: These findings suggest that the R2 regimen combined with intravitreal MTX, followed by lenalidomide maintenance, is a safe option for PVRL with moderate efficacy.

EP535 BASELINE TUMOR BURDEN CORRELATES WITH RESPONSE BUT NOT TOXICITIES IN PATIENTS TREATED WITH BISPECIFIC ANTI-CD20, ANTI-CD19 CAR-T CELLS

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Background: Bispecific anti-CD20, anti-CD19 (LV20.19) CAR T-cells may improve outcomes in relapsed, refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) by limiting relapse due to single antigen downregulation. We reported outcomes of a phase I trial of LV20.19 CAR T-cells in R/R NHL & CLL (Shah et al. Nature Med. 2020). There is evidence that higher LDH and baseline tumor burden (as measured by total lesion glycolysis [TLG] and metabolic tumor volume [MTV]) predict inferior response and increased toxicities for single antigen targeted anti-CD19 CAR-T cells. In the context of bispecific CAR T-cells, the impact of tumor burden on outcomes is not known.
Aims: We analyzed whether baseline LDH and tumor burden assessed by whole-body TLG correlated with response and/or toxicities for bispecific CAR T-cells.
Methods: To evaluate the relationship of baseline LDH and tumor burden on day 28 response and toxicities (cytokine release syndrome [CRS] and neurotoxicity), we included patients from the previously mentioned Phase 1 clinical trial treated with LV20.19 CAR T-cells (NCT03019055) who had a pre-CAR-T PET/CT within 45 days of lymphodepleting chemotherapy (LDC). Patients with CLL were excluded. Baseline tumor burden was assessed by measurement of whole body TLG on most recent pre-CAR-T PET/CT within 45 days of LDC. LDH was assessed on day 0 of LDC. Threshold values for high and low tumor volume groups were selected based on the median TLG as previously reported. Continuous and categorical variables were analyzed using t-test, Pearson's chi-squared test and Fischer's exact test where appropriate. All tests were two sided. A p value <0.05 was considered significant.
Results: 15 patients were included in the analysis (9 DLBCL, 6 MCL). Patient characteristics are summarized in table 1. Median age was 56, median lines of prior therapy was 7 (range 3-11) and 67% received bridging therapy after apheresis. Median baseline LDH was 228.5 U/L. Median TLG was 592 (range 3-9775) and served as the threshold value for low and high tumor burden groups (≤592 and >592 respectively). On day 28, 53% (n=8) had a complete response (CR), 20% (n=3) a partial response (PR), and 27% (n=4) had progressive disease (PD). CRS occurred in 60% and neurotoxicity in 27% of patients. Mean baseline LDH was significantly lower in patients who had a response (CR or PR) (243 vs 600, p=0.03) and in those with CR (196 vs 504.2, p=0.046). Low tumor burden on PET/CT was associated with overall response (CR or PR) vs PD (p=0.026) but not with a CR (p=0.13). High tumor burden was not associated with the development of any grade CRS (p=0.83) or neurotoxicity (p=0.18).

Table 1

Demographics and outcomes	n=15
Age, median (range)	56 (47 – 69)
Sex	80% male (n=12) 20% female (n=3)
Disease	DLBCL 60% (n=9) MCL 40% (n=6)
Lines of prior therapy, median (range)	7 (3-11)
Prior autologous HCT	53% (n=8)
Prior allogeneic HCT	20% (n=3)
Prior CAR T-cell therapy	7% (n=1)
Pre-CAR-T tumor lesion glycolysis (TLG), median (range)	592 (3 – 9775)
Received bridging therapy	67% (n=10)
Days between pre-CAR-T PET/CT and LDC, median (range)	19 (11 – 43)
LDH (U/L) at day 0 of LDC, median (range)	228.5 (142 - 863)
Day 28 response	CR 53% (n=8) PR 20% (n=3) PD 27% (n=4)
CRS	60% (n=9)
Grade ≥3 CRS	7% (n=1)
Neurotoxicity	27% (n=4)
Grade ≥3 Neurotoxicity	7% (n=1)

Summary/Conclusion: This is the first study demonstrating that baseline tumor burden (by TLG on PET/CT) correlates with clinical outcomes in the context of bispecific CAR T-cells for NHL. Moreover, both patients with CR and CR+PR had a significantly lower baseline LDH than patients who had PD +/- PR on day 28 scans. Interestingly, baseline tumor burden did not correlate with development of CRS or neurotoxicity with bispecific LV20.19 CAR T-cells. In single targeted CD19 CAR T-cells, high baseline tumor burden has previously been correlated with toxicity as well as lower response rates. In our LV20.19 experience, overall CRS and neurotoxicity rates were low and the low overall incidence

may limit statistical power to detect an association with tumor burden. With accumulating evidence that higher pre–CAR-T tumor burden is associated with inferior response rates, developing novel approaches to debulk patients safely prior to CAR-T is indicated.

EP536 IMPACT OF TP53 AND RECURRENT SOMATIC MUTATIONS ON THE OUTCOMES OF DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR-T)

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Background: Diffuse large B-cell lymphoma (DLBCL) exhibits clinical and molecular heterogeneity, and prior studies identified genetic subtypes of DLBCL associated with different trends in response rates and survival. Chimeric antigen receptor T-cell therapy (CAR-T) is approved for the treatment of relapsed/refractory (R/R) DLBCL, but relapses post-CAR-T still occur. Clinical and biological predictors of response to CAR-T remain unclear.
Aims: We investigate the impact of pre-CAR-T next generation sequencing (NGS) results in outcomes of R/R DLBCL post-CAR-T.
Methods: This is a single center experience of R/R DLBCL patients treated with CAR-T between 1/1/2017 and 12/31/2019 who had NGS results via Foundation Medicine (FoM) platform available from prior to CAR-T infusion. The primary objective was to identify predictive mutation profiles with endpoints of overall response rate (ORR), complete response (CR), day 90 CR, and 3-month progression rate. Progression free survival (PFS) probability was calculated with log-rank testing and Kaplan Meier method. Outcomes compared based on NGS results included *TP53* mutation (*TP53mut*) versus wild-type (*TP53wt*), presence of *CDKN2A/B* loss, *BCL2* rearrangements, and tumor mutation burden (TMB).
Results: We identified 15 patients with DLBCL who had available NGS results prior to receiving CAR T-cell infusion. Fourteen out of 15 (93%) received axicabtagene ciloleucel, and 1/15 (7%) received tisagenlecleucel. Median age at time of CAR-T was 65 years (range 33-81 years), and 5/15 (33%) were female. FoM specimens were from tumor in 14/15 (93%) and peripheral blood in 1/15 (7%). The most common mutations identified were *TP53mut* in 7/15 (47%), *BCL2* rearrangements in 7/15 (47%), and *CDKN2A/B* loss in 5/15 (33%). TMB was low (0-5) in 4/15 (27%), intermediate (6-10) in 4/15 (27%), and high (> 10) in 6/15 (40%). One TMB could not be determined.
Outcomes are depicted in Table 1. Best ORR and CR rates were 13/15 (87%) and 8/15 (53%) respectively. ORR (CR) rates were 100% (71%) for *TP53mut* and 75% (38%) for *TP53* wild-type (*TP53wt*). Day 90 CR rates were 71% for *TP53mut* and 13% for *TP53wt*. At last follow-up, 8/8 (100%) *TP53wt* progressed, but only 2/7 (29%) *TP53mut* progressed with 5/7 (71%) remaining in CR. The 3-month progression rate was 2/7 (29%) for *TP53mut* and 6/8 (75%) for *TP53wt* with significantly higher PFS probability in *TP53mut* patients (p = 0.002). The 3-month progression rates for *CDKN2A/B* loss and wild-type were 5/5 (100%) and 3/10 (30%) respectively with lower PFS probability in patients with *CDKN2A/B* loss (p<0.001). There was no significant difference in PFS based on *BCL2* rearrangement or TMB.
There was no significant difference in patients' age, gender, lactate dehydrogenase, international prognostic index score, extranodal disease, stage, number of prior lines of therapy, history of autologous stem cell transplant, or frequency of bridging therapy between *TP53*, *CDKN2A/B*, and TMB groups.

Table 1: Responses by Mutation for DLBCL Post-CAR-T

Mutation	# Patients n (%)	ORR n (%)	CR Day 90 n (%)	Progressed Post-CART n (%)
All Patients	15 (100%)	13 (87%)	6 (40%)	10 (67%)
TP53mut	7 (47%)	7 (100%)	5 (71%)	2 (29%)
TP53wt	8 (53%)	6 (75%)	1 (13%)	8 (100%)
CDKN2A/B loss	5 (33%)	3 (60%)	0 (0%)	5 (100%)
CDKN2A/Bwt	10 (67%)	10 (100%)	6 (60%)	5 (50%)
TMB 0-5	4 (27%)	4 (100%)	3 (75%)	2 (50%)
TMB 6-10	4 (27%)	3 (75%)	2 (50%)	2 (50%)
TMB > 10	6 (40%)	5 (83%)	1 (17%)	5 (83%)

Summary/Conclusion: In this small dataset, our findings show a potential prognostic role of NGS in R/R DLBCL treated with CAR-T. Significant differences were seen with better outcomes post-CAR-T associated with the presence of *TP53* mutations and worse outcomes with *CDKN2A/B* loss. Improved responses with *TP53mut* may be related to higher T-cell infiltration, tumor inflammation signature, expression of immune checkpoints, and tumor microenvironment changes that have been reported in *TP53mut* acute myeloid leukemia (Vadakekolathu J et al. *Blood Adv* 2020). Larger studies are needed to further characterize the impact of NGS and molecular changes on outcomes in DLBCL post-CAR-T.

EP537 CHIDAMIDE PLUS CHOP VERSUS CHOP AS FRONTLINE TREATMENT IN PERIPHERAL T CELL LYMPHOMA: A RETROSPECTIVE CASE-CONTROL STUDY

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Background: Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive non-Hodgkin lymphoma. The most common frontline regimen for PTCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens. Several histone deacetylase inhibitors(HDACi) have been approved for relapsed and refractory PTCL patients(pts). Chidamide is a novel and orally active benzamide class of HDACi, which has been approved for treatment of PTCL after failure of at least one prior systemic therapy in China. However, whether the frontline treatment with combination of HDACi andCHOP could benefit PTCL is still controversial.
Aims: To retrospectively evaluate the efficacy and safety of chidamide plus CHOP versus CHOP as the frontline treatment for PTCL.
Methods: Medical records of 408 PTCL pts in Sun Yat-sen University Cancer Center between January 2014 and July 2020 were reviewed. We included newly diagnosed PTCL pts treated with chidamide plus CHOP(C-CHOP) or CHOP alone as frontline treatment. Pts with insufficient clinical data or treated with other regimens were excluded. A total of 22 C-CHOP pts and 22 CHOP-based controls were included after a 1:1 ratio case-control matching procedure was conducted, according to International Prognostic Index (IPI). Chidamide was administered at 20 mg, P.O., twice per week. Pts achieving complete response (CR) or partial response (PR) were arranged to chidamide maintenance treatment. Overall response rate(ORR), progression free survival (PFS), overall survival (OS) and adverse events (AEs) were analysed. Baseline clinical characteristics were compared using non-parametric test, $\chi 2$ test or Fisher's exact test. Survival outcomes were assessed with Kaplan-Meier method. All statistical analyses were performed using SPSS v.24.0 software (IBM SPSS Statistics). A P value < 0.05 was considered significant.
Results: Median age of C-CHOP and CHOP group were 54.5 years (range 27-78) and 56.0 years (range 32-86) respectively. After matching, 10 female pts(45.5%) and 11 female pts (50%) were included in C-CHOP and CHOP alone group respectively. 31.8% (7/22) pts and 68.2%(15/22) pts were IPI 0-1 and IPI≥2 respectively in both groups. Baseline clinical characteristics were well balanced between two groups (P>0.05, Table 1). ORR of patients in C-CHOP group versus CHOP group was 86.4% versus 76.3%, with CR rate of 68.2% versus 59.1%(P>0.05). With a median follow-up of 22.3 months (range, 5.3–23.1 months), PFS of patients in C-CHOP group showed a statistically significant improvement versus CHOP group. Median PFS of patients in C-CHOP group versus CHOP group was not reached versus 14.2 ± 5.7 months(P=0.035, Figure 1A). However, no benefit in OS was found when CHOP was combined with chidamide in frontline treatment (not reached versus 53.1, P=0.783, Figure 1B). Most grade 3–4 AEs in C-CHOP or CHOP group were hematological toxicity, including neutropenia (36.4% versus 22.7%), thrombocytopenia (22.7% versus 9.0%) and anemia (22.7% versus 4.5%) (P>0.05).

Table 1 Baseline clinical characteristics

Charactersitics	Chidamide + CHOP (n=22)	CHOP (n=22)	P value
Age (years)			
Median	54.5	56.0	0.217
Range	27-78	32-86	
Age at diagnosed			0.517
<60	16(72.7%)	14(63.6%)	
≥60	6(27.3%)	8(36.4%)	
Gender			0.763
Female	10(45.5%)	11(50.0%)	
Male	12(54.5%)	11(50.0%)	
ECOG proformance status			1.000
0-1	21(95.8)	22(100.0%)	
2-4	1(4.2)	0	
Number of extranodal sites			1.000
<1	21(95.8%)	22(100.0%)	
≥2	1(4.2%)	0	
Serum LDH (IU/ml)			0.220
Elevated	11(50.0%)	15(68.2%)	
Normal	11(50.0%)	7(31.8%)	
B symptoms			0.079
Absent	21(95.8%)	17(77.3%)	
Present	1(4.2%)	5(22.7%)	
Bone marrow involvement			0.607
Absent	19(86.4%)	21(95.5%)	
Present	3(13.6%)	1(4.5%)	
Ann Arbor stage			1.000
I-II	4(18.1%)	4(18.1%)	
III-IV	18(81.9%)	18(81.9%)	
Subtype			0.476
PTCL-NOS	7(31.8%)	12(54.5%)	
AITL	6(27.3%)	4(18.1%)	
ALCL	5(22.7%)	4(18.1%)	
Others	4(18.1%)	2(9.1%)	
EBV			1.000
Negative	15(68.2%)	15(68.2%)	
Positive	7(31.8%)	7(31.8%)	
CD30			0.353
Negative	10(45.5%)	7(31.8%)	
Positive	12(54.5%)	15(68.2%)	
KI-67			0.757
< 70%	14(63.6%)	13(59.1%)	
≥70%	8(36.4%)	9(40.9%)	

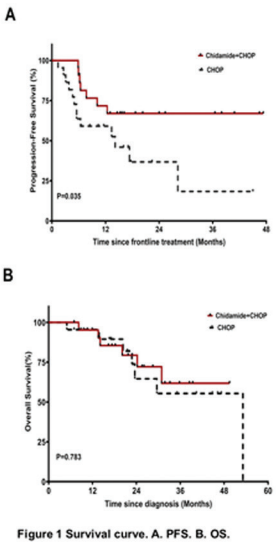


Figure 1 Survival curve. A. PFS. B. OS.

Summary/Conclusion: Our preliminary data suggests that the addition of chidamide 20mg twice per week to frontline CHOP regimen is effective and well-tolerated in PTCL. Although chidamide plus CHOP may prolong PFS in PTCL, no benefit in OS and ORR were observed. The hematological toxicity of chidamide plus CHOP should be cautioned. The combination of chidamide and CHOP as frontline treatment for PTCL deserves further extended clinical trial.

EP538 HIGH PREVALENCE OF CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY IN A PEDIATRIC T-CELL LYMPHOBLASTIC LYMPHOMA COHORT

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Background: Pediatric T-cell lymphoblastic lymphoma (T-LBL) arises from the malignant transformation of immature T-cells. T-LBL is characterized by massive infiltration of blasts in the mediastinum and lymph nodes mostly without or occasionally with low percentages of blasts in the bone marrow (<25%). Patients are assigned to different treatment regimens based on Murphy staging, which is determined by disease localization and dissemination. These treatment protocols have not been essentially changed over the last decades, showing the need to improve our knowledge on T-LBL.

Aims: This study investigated the clinical characteristics and the occurrence of secondary malignancies and comorbidities in an unselected cohort of pediatric T-LBL patients.

Methods: We present a retrospective pediatric T-LBL cohort (n=88) for patients who were diagnosed between January 2007 and September 2020 and who were treated according to the EURO-LB02 protocol in one of the former pediatric oncology centers in the Netherlands.

Results: Median age at diagnosis for this T-LBL cohort was 9 years (range 0-18), with a male to female ratio of 1.7:1. Disease localizations mainly involved the mediastinum which was enlarged in 94% of the patients and enlarged lymph nodes in 68% of the patients. Nine percent of the patients had evidence of blast infiltration in the bone marrow (BM) (range 5-16% blasts). Two patients presented with CNS3 and had more than 5 white blood cells/µl (WBC) in the cerebral spinal fluid (CSF), whereas nine patients presented with CNS2 and having less than 5 WBC/µl CSF fluid. In total 10.2% (9/88) of the patients were diagnosed with a cancer predisposition syndrome, almost exclusively constitutional mismatch repair deficiency (CMMRD) (8/88), based on their presentation with multiple café-au-lait maculae in all patients and a history of previous or secondary cancers in various patients. All CMMRD patients in our cohort had biallelic germline mutations in either *PMS2* or *MSH6*. Clinical and patient characteristics of CMMRD patients at time of T-LBL diagnosis were compared to sporadic T-LBL patients and summarized in **Table 1**. Whereas their clinical presentation was comparable, the percentage of CMMRD patients who had one or multiple enlarged lymph nodes seemed lower than for sporadic patients albeit not significant (p=0.1179). None of the CMMRD patients presented with BM involvement at T-LBL diagnosis in comparison to 25% of sporadic T-LBL patients who had >1% blasts in their BM at time of diagnosis (and 8% having >5% blasts). Two sporadic patients presented with CNS3 while nine patients had CNS2 (9/80) in contrast to none of the CMMRD patients, indicating that the T-LBL manifestation for CMMRD patients is more localized compared to sporadic T-LBL patients. Currently, the presence of preceding or secondary (childhood) malignancies is the main indicator for the presence of an underlying cancer predisposition syndrome. Therefore, diagnosis of a cancer predisposition syndrome is often missed at time of diagnosis of the first (childhood) malignancy, highlighting the alertness of the treating physician as crucial factor for diagnosis.

	T-LBL sporadic n=80	T-LBL CMMRD n=8
Age year (median, range)	9 (0-18)	10 (0-16)
Sex (n)		
Male	50	5
Female	30	3
Localizations (n, %)		
Mediastinal enlargement	75 (94)	8 (100)
LN involvement	55 (68)	3 (38)
Bone marrow involvement (n, (%))		
1-4%	15 (19)	0 (0)
≥5%	7 (9)	0 (0)
CNS status (n, (%))		
CNS1	58 (84)	8 (100)
CNS2	9 (13)	0 (0)
CNS3	2 (3)	0 (0)

Summary/Conclusion: This study describes the high prevalence of CMMRD patients in a complete T-LBL cohort. As the frequency of an underlying predisposition syndrome among T-LBL patients may be underestimated at present, we advocate for screening all pediatric T-LBL patients with café-au-lait maculae for the presence of germline mutations in mismatch repair genes.

EP539 CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA RECEIVING CONVENTIONAL THIRD-LINE THERAPY: A MULTICENTER, RETROSPECTIVE, REAL-WORLD STUDY IN THE UNITED KINGDOM

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Background: Large B-cell lymphomas (LBCLs), including diffuse LBCL (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (tFL), are treated with combination chemoimmunotherapy at diagnosis. First-line treatment can result in a cure in approximately 60% of cases; however, 10%–15% of patients do not respond and a further 20%–25% relapse. For those patients with

chemotherapy-sensitive disease who relapse, autologous hematopoietic stem cell transplantation (auto-HSCT) is an option. For patients who are ineligible for or relapse post–auto-HSCT, the prognosis is poor. Less than 50% of patients respond to subsequent third-line (3L) treatment and few are cured. Median overall survival (OS) with 3L conventional chemotherapy treatment is 4–10 months. Few publications report outcomes of patients treated with 3L conventional chemotherapy in the UK.
Aims: To describe real-world clinical outcomes of patients with relapsed or refractory (R/R) LBCL initiating conventional 3L treatment in the UK.
Methods: This multicenter retrospective analysis was conducted across 6 centers in the UK. Eligible patients were ≥18 years of age with a documented diagnosis of LBCL in 2003 or later. Diagnoses included DLBCL not otherwise specified (NOS; de novo or tFL), high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, follicular lymphoma grade 3B, or PMBCL. Patients had to have received 2 prior lines of systemic treatment, which included an anthracycline and anti-CD20–targeting monoclonal antibody (mAb). Patients with primary central nervous system lymphoma or who had received chimeric antigen receptor (CAR) T cell therapy were excluded. Progression-free survival (PFS) was calculated based on available information for response assessments, receipt of subsequent treatment, and death. PFS and OS were summarized from the start of 3L therapy to progression or death using the Kaplan-Meier method.
Results: A total of 129 patients met the stringent eligibility criteria. The median age of patients was 58 years (range, 22–87 years), 64% were male (n=82), 76% had a disease histology of DLBCL NOS (n=98), 76% had an Eastern Cooperative Group performance status of 0–2 (n=98), and 44 of the 66 patients (67%) who had an International Prognostic Index score had a score of 0–2. The median time from diagnosis to start of 3L treatment was 14.6 months (range, 4–161 months). All patients had received rituximab, 11% received prior auto-HSCT (n=14), and 57% were chemotherapy refractory (n=73). The most common 3L treatment regimens were salvage chemotherapy without an anti-CD20 mAb (44%, n=57), salvage chemotherapy with an anti-CD20 mAb (22%, n=28), salvage chemotherapy followed by auto-HSCT (10%, n=13) or allogeneic HSCT (8%, n=10), pixantrone (4%, n=5), and lenalidomide (4%, n=5), respectively. Clinical and/or imaging assessment data related to 3L treatment was available for 104 patients. The overall response rate was 38% (n=40). Median PFS from the start of 3L treatment was 1.97 months (95% CI, 1.68–2.56 months). Median OS from the start of 3L treatment was 7.00 months (95% CI, 4.73–9.23 months). Additional analyses for patient subgroups will be presented.
Summary/Conclusion: This UK real-world analysis provides insights into clinical practice and highlights the poor outcomes achieved with conventional (non–CAR T cell) 3L treatment options in the UK, demonstrating the need for more effective treatments in patients with R/R LBCLs.

EP540 EARLY GCSF AFTER ANTI-CD19 CAR T-CELLS DECREASES INCIDENCE OF FEBRILE NEUTROPENIA WITHOUT WORSENING TOXICITIES AND EXPANSION OF CAR T-CELLS IN REFRACTORY/RELAPSED B-CELL LYMPHOMA.

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Background: Anti-CD19 chimeric antigen receptor cells (CAR T) integrated treatment algorithm for relapsed/refractory large B-cell lymphoma (R/R LBCL). GCSF use is controversial regarding safety and efficacy of CAR T-cells and protection towards infection is not established.
Aims: To evaluate safety, cytopenia, infectious risk and expansion with GCSF in patients (pts) with R/R LBCL treated with Tisagenleuclecel (Tisa-cel) or Axicabtagene-ciloleucel (Axi-cel).
Methods: We included 122 pts treated with CAR T-cells (Axi-cel=63, Tisa-cel=59) between 06/2018 and 11/2020. After 03/2019, GCSF administration from Day (D)5 until ANC >1 G/L showed no impact on CAR T-cells safety and efficacy (1). Hence, after 03/2020 systematic GCSF prophylaxis at D2 was proposed. We identified 3 Groups (G) based on GCSF use: 35 pts in G1 did not receive GCSF during first 10 days, G2 included 33 pts who received systematic D2 GCSF and 54 pts in G3 received GCSF between D5-D10 after CAR T. We analyzed neutropenia duration, infection rate during the first 30 days, cytopenia at month (M)1 and M3, CRS and ICANS incidence and CAR T expansion in the whole population and between groups.
Results: Except for older age (median 52 in G1 vs 65 and 62 in G2 and G3, p=.022) and prior median lines of treatment (G1=3, G2=2, G3=2.5, p<.0001), demographics did not differ in groups. A difference was found for ANC (1570 [0;6540] in G1, 990 [0;4820] in G2 and 920 [0;3630] in G3, p=.007) and lymphocyte count (40 [0;410] in G1, 20 [0;790] in G2 and 30 [0;250] in G3, p=.004) at day 0. Hemoglobin and platelet counts were similar (p=.63 and p=.24 respectively). More pts in G2 had abnormal LDH levels at D0 without significance (p=.059). Median follow-up was 9.6 months after CAR T-cells infusion. Median duration of grade 4 neutropenia was 3 days [0;16] in G1, 4 [0;31] in G2 and 5 [0,63] in G3 (p=.11). 75% of pts experienced febrile neutropenia, with a difference between G1 (74%), G2 (58%) and G3 (85%) (p=.018). 34% of pts in G1, 33% pts in G2 and 26% pts in G3 developed infections in the first month, mostly bacterial (23% in total, 20% in G1, 30% in G2, 20% in G3). Viral infection incidence was 15% in G1, 12% in G2 and 13% in G3 (p=.75). Fungal infections occurred in 3% pts in G1, 3% in G2 and 2% in G3 (p=1). 37% of pts had persistent Grade 3 cytopenia at M1 evaluation, neutropenia being the most frequent (29% vs 8% anemia, vs 28% thrombocytopenia). The same pattern was observed at M3 (21% overall, neutropenia 18% vs 1% anemia, vs 9% thrombocytopenia). CRS occurred in 73% pts overall, mostly of grade 1 (46%) and 2 (27%) without difference on prevalence between the 3 groups (p=.93) nor when considering severe CRS (grade 0-1 vs grade ≥ 2) (p=.28). ICANS, mainly of grade 1 (13%), occurred in 25% patients without difference on prevalence (p=.62) nor on severity (p=.88) when comparing the 3 groups. CAR T-cell expansion did not significantly differ among groups (Fig1A). Tisa-cel and Axi-cel pts were analyzed separately. For Tisa-cel, median relative Cmax CAR T/CD3+ T-cells was 4.3% (median absolute 28 CART/µL) without differences in Gs (median 8.6% and 50/µL in G2 and 3.6% and 13/µL in G3, vs 4.3% and 13/µL in G1) (Fig1B). For Axi-cel, median relative Cmax CAR T/CD3+ T-cells was 21.9% (median absolute 32 CART/µL) without differences according to GCSF use (median 16.5% and 26/µL in G2 and median 24% and 53/µL G3, versus median 3.3% and 12/µL in G1)(Fig1B).

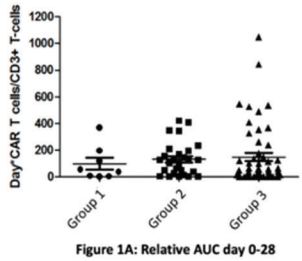


Figure 1A: Relative AUC day 0-28

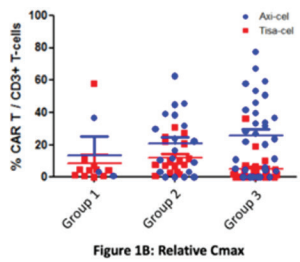


Figure 1B: Relative Cmax

Summary/Conclusion: In our experience, early GCSF administration decreases the incidence of febrile neutropenia, with no impact on severity of CRS, ICANS, and CAR T-cells expansion.

EP541 OUTREACH: PRELIMINARY SAFETY & EFFICACY RESULTS FROM A PHASE 2 STUDY OF LISOCABTAGENE MARALEUCEL (LISO-CEL) IN THE NONUNIVERSITY SETTING

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Background: Concerns about adverse event management related to CAR T cell therapy have resulted in administration of this therapy largely in an inpatient setting. Infusion and monitoring of patients (pts) who

receive CAR T cell therapy at nonuniversity medical centers (NMCs) and in outpatient settings have not been studied specifically.
Aims: To evaluate safety and efficacy of liso-cel in pts with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) across inpatient and outpatient settings at NMCs in OUTREACH (NCT03744676).
Methods: This open-label, multicenter, phase 2 study enrolled adult pts with R/R LBCL at NMCs, including centers naïve to CAR T cell therapy. Eligible pts had R/R PET-positive disease after ≥2 lines of prior systemic therapy, ECOG PS ≤1, and adequate organ function. Prior autologous HSCT was permitted. After leukapheresis and lymphodepleting chemotherapy, pts received sequential infusions of equal target doses of $CD8^+$ and $CD4^+$ cells at a total target dose of 100×10^6 CAR^+ T cells. The primary endpoint was incidence of grade ≥3 cytokine release syndrome (CRS) graded per 2014 Lee criteria, neurological events (NEs), prolonged cytopenias (Day 29 grade ≥3 lab values), and infections. Secondary endpoints were safety and overall response rate (ORR). All study sites had a multidisciplinary CAR T cell therapy team and standard operating procedures (SOPs) for toxicity monitoring/management of pts treated and/or monitored as outpatients.
Results: At data cutoff, 46 pts (inpatients, n = 16, outpatients, n = 30) were treated with liso-cel. Median age was 63 (range, 34–83) y, 63% had diffuse LBCL not otherwise specified, and 91% were refractory to last therapy. Inpatients and outpatients had similar demographics and baseline disease characteristics. CRS was reported in 6 (38%) inpatients and 13 (43%) outpatients, with no grade ≥3 events. NEs were reported in 5 (31%) inpatients and 9 (30%) outpatients, with 1 grade 3 event in the inpatient group and 2 grade 3 events in the outpatient group. Median (range) time to onset of CRS and NEs, respectively, was 2.5 (1–3) and 10 (3–16) days for inpatients and 5 (2–9) and 9 (6–14) days for outpatients. Tocilizumab and/or corticosteroid use for CRS and/or NE management was generally low (inpatients, n = 3 [19%]; outpatients, n = 6 [20%]). Overall, the most common treatment-emergent adverse events (TEAEs) were neutropenia (32, 70%), leukopenia (22, 48%), and anemia (18, 39%). Any grade infections occurred in 3 (19%) inpatients and 8 (27%) outpatients, with 1 grade 3 bacterial infection in inpatients and 5 grade 3–4 pathogen unspecified infections in outpatients. Prolonged cytopenias (grade ≥3 lab values at Day 29) were reported for 2 (13%) inpatients and 9 (30%) outpatients. No grade 5 TEAEs were reported. Early (study Day ≤4) and overall hospitalization in outpatients was reported in 27% and 63%, respectively; median time to hospitalization was 5 (2–61) days and median length of stay was 6 (1–28) days. For efficacy-evaluable pts (n = 44), ORR was 75% for inpatients and 79% for outpatients; CR rates were 50% and 61%, respectively.
Summary/Conclusion: Liso-cel was successfully administered to pts with R/R LBCL in the outpatient setting and pts were monitored for CAR T cell therapy–related toxicities by multidisciplinary teams using SOPs. Incidences of severe CRS and NEs and tocilizumab and/or corticosteroid use were similar in inpatients and outpatients. Data were consistent with pivotal study observations (Abramson, *The Lancet* 2020). Updated data with longer follow-up will be presented.

EP542 CONCURRENT GAIN/AMPLIFICATION OF MYC, BCL2 AND/OR BCL6 GENES BY FLUORESCENCE IN SITU HYBRIDIZATION: ANOTHER SUBGROUP OF HIGH-GRADE B-CELL LYMPHOMA WITH POOR PROGNOSIS?

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Background: Double/triple hit lymphoma (DHL/THL) is classified as high-grade B-cell lymphoma (HGBL) and is known to have a poor prognosis. These lymphomas present with concurrent rearrangements (R) of MYC and BCL2 and/or BCL6, detected by fluorescence in situ hybridization (FISH) (Swerdlow, 2017; Li, 2015; Riedell, 2018). However, little is known about other genetic alterations (e.g. gain (G) or amplification (A)) in these genes and their impact on protein over-expression detected by immunohistochemistry (IHC) and overall survival (OS).
Over-expression of MYC, BCL2 and BCL6 is currently analyzed by IHC and entities with concurrent MYC and BCL2/BCL6 over-expression are called 'double/triple expressor lymphomas' (DEL/TEL) and are classified as DLBCL according to WHO (Swerdlow, 2017). Nevertheless, IHC is subjective and definition of positivity is not universally standardized.
Aims: The aim of this study was is to analyze whether genetic alterations of MYC/BCL2/BCL6 genes other than rearrangements (e.g. gain/amplification) detected by FISH, contribute to the identification of a new subtype of DHL/THL and if these gains/amplifications are correlated with IHC over-expression.
Methods: FISH results from 166 samples between 2011 and 2021 were retrospectively collected and categorized into several groups: 'DHL/THL' (n=29), 'Alternative DHL/THL' (concurrent MYC R and BCL2 and/or BCL6 G/A or concurrent MYC G/A and BCL2 and/or BCL6 R; n=22), 'Lymphomas with concurrent MYC G/A and BCL2 and/or BCL6 G/A' (n=25), 'single BCL2 and/or BCL6 alterations' (R or G/A; n=35) and 'No alterations' (n=55). Available IHC results from these samples (DHL/THL samples excluded; n=82) were divided into 'DEL/TEL' (n=39) and 'No DEL/TEL' (n=43). FISH and IHC results were compared and correlated with OS. All statistical analyses were performed using MedCalc windows (MedCalc Software, Ostend, Belgium). OS was estimated according to Kaplan-Meier and compared by the log-rank test. FISH and IHC results were compared using the Chi-squared test. P values < 0.05 were considered significant.
Results: According to FISH results, patients with 'DHL/THL' and 'Alternative DHL/THL' had significantly worse overall survival while this was not the case for the other groups (Fig. 1A). On the contrary, 'DEL/TEL' determined by IHC had no significant difference in outcome in comparison with samples without double expression (Fig 1B).
There was a significant correlation between BCL2 G/A detected by FISH and protein over-expression detected by IHC (p=0.0212). On the other hand, no statistically significant correlation was seen between MYC/BLC6 FISH G/A detected by FISH and protein over-expression detected by IHC (p=0.5518 resp. p=0.6627).

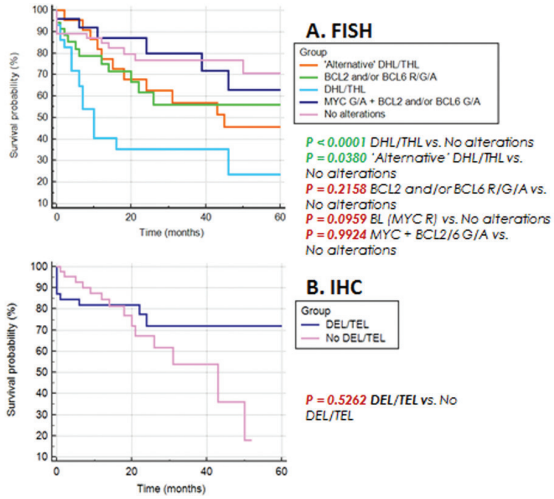


Figure 1. Kaplan-Meier survival curve for overall survival by FISH (A) and IHC (B).

Abbreviations: FISH = fluorescence in situ hybridization – IHC = immunohistochemistry – DHL/THL = double/triple hit lymphoma – R = rearrangement – G/A = gain/amplification – DEL/TEL = double/triple expressor lymphoma

Summary/Conclusion: In the present study, the previously reported adverse prognosis of DEL/TEL (Li, 2015; Riedell, 2019; Huang, 2019; Amrallah, 2019; Ting 2019) could not be confirmed. FISH results, on the other hand, showed that only 'DHL/THL' and 'Alternative DHL/THL', which both carry MYC and BCL2/BCL6 alterations with at least one R, showed worse prognosis. Taken together, samples with only G/A in MYC and BCL/BCL6 are not correlated with adverse outcome. In addition, IHC does not effectively predict the MYC, BCL2 and BCL6 G/A detected by FISH.
In conclusion, FISH remains the golden standard and should always be performed when a HGBL is suspected in order to identify entities with poor outcome, such as 'DHL/THL' and 'Alternative DHL/THL'.

EP543 VENETOCLAX AS SINGLE AGENT IN BCL2-POSITIVE RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMAS. A PHASE 2 STUDY OF THE FONDAZIONE ITALIANA LINFOMI.

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Background: Relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL) patients have a poor prognosis with an expected survival of less than one year. Recent acknowledgement in the biology of PTCLs (*Zaja F, et al. Am J Hematol 2016*) lead to identification of BCL2 protein as a potential therapeutic target. Indeed, BCL2 is over-expressed in about 30% to 88% of PTCL patients. Venetoclax is an orally, selective BCL2 inhibitor with proved activity in B-cell malignancies.
Aims: FIL (Fondazione Italiana Linfomi) sponsored an open-label, multicenter, prospective, Simon two-stage, phase II study to determine the efficacy and safety of Venetoclax in R/R BCL2-positive PTCL.
Methods: Patients aged ≥18 years with biopsy-confirmed R/R PTCLs (PTCL not otherwise specified [PTCL-NOS], angioimmunoblastic T-cell lymphoma [AITL] and other nodal T-cell lymphomas of T-follicular helper origin [TFH]) with a percentage of BCL2 positive tumor cells ≥ 25% were included into the study. Venetoclax was administrated after 1 week ramp-up at 800mg once daily on 28-day cycles until progression or unacceptable toxicity. The primary endpoint was to evaluate the overall response rate (ORR) after the first 3 cycles according to the Lugano 2014 criteria. Treatment would have been considered active with an ORR 30% or more (according to the Simon two-stage design: 3 out of 18 patients of stage 1 phase and 7 out of overall 35 patients). Secondary objectives were to further assess the efficacy and to determine the safety of Venetoclax.
Results: Between May 2018 and November 2019, 17 patients were enrolled. Median age was 70 years (range 55-76) with 58.8% of males. Histologies were PTCL-NOS (76.5%) and AITL (23.5%). The majority (64.7%) had stage IV lymphoma and patients had received a median of 2 prior systemic therapies (range 1-15; in 8 patients > 2). ECOG performance status was > 1 in 29% of patients. We observed 1 complete response (6%) (CR) and 2 stable disease (12%) (SD) with an overall therapeutic activity in 3/17 patients (18%); at a median follow up of 8.2 months [0.85-17.5 months] two patients are currently still on treatment (1 CR and 1 SD). Because of the ORR rate < 30%, the enrollment was stopped. The majority of patients (76.4%) interrupted the treatment due to disease progression, all but one within cycle 5 of therapy. Median overall and progression free survival were 8.8 months (7.1-not reached) and 3.6 months (2-3.8), respectively. A total of 12 patients experienced grade 3-4 hematological toxicities: neutropenia (42%), thrombocytopenia (25%) and anemia (25%). Nine patients experienced grade 3 extra-hematological toxicities while no cases of tumor lysis syndrome were registered.
Summary/Conclusion: In this preliminary experience Venetoclax monotherapy showed therapeutic activity in a small proportion of patients with BCL2-positive R/R PTCL, with manageable toxicity. Better understanding of the mechanism of response might allow in the future to select patients to be treated with this agent.
This research was supported by a grant from AbbVie Srl.

EP544 POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA: INTERIM ANALYSIS.

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Background: The outcomes of relapsed or refractory B-cell non-Hodgkin lymphoma (r/r B-NHL) are very dismal with no standard of therapy. Relapsed or refractory B-NHL are heterogeneous group of lymphoproliferative malignancies with histological, cytogenetic and molecular differences, but all of them have a B-cell receptor. CD79b is a B-cell receptor component and the antibody-drug conjugate polatuzumab vedotin is an anti-CD79b antibody linked to antimitotic agent – monomethyl auristatin E. Polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR) demonstrated efficacy in patients with r/r B-NHL.
Aims: To evaluate the safety and effectiveness of Pola-BR in patients with r/r B-NHL in real clinical practice.
Methods: This is interim analysisof single-center prospective study evaluates efficacy and safety of Pola-BR for treatment patients with aggressive r/r B-NHL. All patients received bendamustine 90 mg/m2 on days 1 and 2, rituximab 375 mg/m2 on day 1 and polatuzumab vedotin 1,8 mg/kg on day 1 of each 21-day cycle. The PET-CT scan was performed before treatment initiation and after 2, 4, 6 cycles of Pola-BR. The responses were evaluated using Lugano 2014 criteria. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.
Results: Total of 26 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (n=18), primary mediastinal B-cell lymphoma (PMBCL) (n=7) and gray zone lymphoma (GZL) (n=1) were included. All diagnoses were histologically confirmed. Median age was 43 years (range 20-68). Most of the patients 73% (n=19) had primary chemoresistant disease. The median number of prior therapy lines was 3 (range 2-10). Five patients underwent autologous stem cell transplantation and four patients received anti-CD19 CAR-T cell therapy. At the start of Pola-BR treatment stage III-IV disease had 73% (n=19) patients and 27% (n=7) of patients had bulky disease. Median number of Pola-BR cycles was 4 (range 2-6). Nine patients (35%) completed 6 cycles of Pola-BR. Eight patients (31%) interruptedPola-BR treatment due to disease progression. The overall response rate (ORR) in the group was 61% (n=16) with 46% (n=12) of complete responses (CR) and 15% (n=4) of partial responses (PR). Two patients (8%) had stabilization of the disease as best response. The ORR in patients with DLBCL was 57% (CR 44%), in patients with PMBCL ORR was 57% (CR 43%) and one patient with GZL achieved CR. The ORR in patients with bulky disease was 14% (CR 14%) and ORR 79% (CR 58%) in patients without bulky disease. In patients with relapsed disease ORR was 86% (CR 57%) and in patients with primary chemoresistant disease ORR was 53% (CR 42%). Two patients (50%) with primary CAR-T cell therapy achieved CR. With a median follow up time 6,8 (range 2-12) month overall survival and progression free survival were 71% and 57%, respectively. During Pola-BR treatment grade 3-4 anemia, neutropenia, and thrombocytopenia developed in 19% (n=5), 42% (n=11) and 12% (n=3) patients, respectively. Other adverse events included febrile neutropenia 8% (n=2) and maculopapular rash 8% (n=2). None of the patients had peripheral neuropathy. Two patients with PR died due to Covid-19 infection.
Summary/Conclusion: Our real-life data confirms that Pola-BR has an acceptable toxicity profile and it is
promising method of immunochemotherapy for patients with r/r B-NHL.

EP545 RATIONALE FOR TREATMENT SELECTION, AND COMORBIDITIES IN OLDER PATIENTS (PTS) WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): INSIGHTS FROM REAL WORLD DATA (RWD)

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Background: Not all elderly pts with DLBCL will receive first-line (1L) rituximab (R)-CHOP or R-miniCHOP regimens; those who do not may have suboptimal outcomes (Williams et al. Cancer 2015). There is a lack of data regarding comorbidities or other factors (e.g. pt preference) that influence 1L treatment choice.
Aims: To use RWD to describe factors influencing 1L treatment decisions in elderly pts with DLBCL.
Methods: This study used the nationwide Flatiron Health (FH) electronic health record-derived de-identified database. The FH database is longitudinal, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. To analyze treatment rationale and pt comorbidities at diagnosis, trained clinical abstractors performed a detailed review of clinic notes. Pts aged ≥71 years at diagnosis, with a DLBCL diagnosis on or after January 1, 2011 and with follow-up until May 31, 2020, were included. Selected pts were untreated, or treated with: R-CHOP (standard dose), reduced-dose R-CHOP (<80% standard dose cyclophosphamide and doxorubicin), R-monotherapy (R-mono), R-Benda, R-CVP or R-Len. We analyzed pt demographics, comorbidities, treatment details and treatment rationale (categorized as: age, comorbidity, disease burden, International Prognostic Index [IPI], pt request, performance status [PS], or other).
Results: Pts (N=404) were aged ≥71 years, 94% were treated in a community setting, 90% had DLBCL-not otherwise specified, and 45% had Stage III/IV disease at diagnosis. A proportion of pts had comorbidities at

diagnosis (anemia: 24.8%; arrhythmia: 19.6%; congestive heart failure: 6.7%; diabetes: 18.3%; hyperlipidemia: 36.6%; hypothyroidism: 14.6%; previous myocardial infarction: 9.7%; chronic kidney disease: 13.4%; previous stroke: 6.9%). Treatments over the study period (n [%]) were: R-Benda (56 [14]); R-CHOP (59 [15]); R-CVP (58 [14]); R-mono (57 [14]); reduced-dose R-CHOP (115 [28]); no treatment (57 [14]). R-Len-treated pts (n=2) were not included due to small sample size available. Median time from diagnosis to 1L treatment was 24 days (interquartile range: 12–39). Overall, 315 treatment rationales were given, with 122 pts having one rationale and 90 pts having ≥2 rationales. Rationale by 1L treatment is shown in the **Table.** Comorbidity was the principal rationale for several pts receiving: reduced-dose R-CHOP (19.1%), R-Benda (26.8%), and R-CVP (34.5%). Age was a reason for attenuated regimen selection in pts receiving: reduced-dose R-CHOP (35.7%); R-mono (36.8%); R-CVP (37.9%). No evidence of a rationale could be found for 86.4% of pts who received the standard-of-care, R-CHOP, potentially indicating that factors related to age or frailty were not significant in the choice of their treatment. In pts not receiving any treatment (systemic therapy or radiotherapy) for whom a rationale was given, this was pt request for 30.4%, and was age, comorbidities, PS, or disease burden for most other pts (>60%).

Table 1. Clinical rationale for treatment assignment by 1L regimen in elderly patients with previously untreated DLBCL

Treatment group	Treatment rationale							
	Age	Comorbidity	Pt request	Disease burden	IPI	PS	Other	No rationale stated
Total (N=404)	24.5%	17.3%	5.0%	4.5%	0.5%	12.1%	2.5%	36.6%
R-CHOP (n=59)	3.4%	1.7%	5.1%	0.0%	0.0%	5.1%	1.7%	86.4%
Reduced-dose R-CHOP (n=115)	35.7%	19.1%	3.5%	6.1%	1.7%	11.3%	3.5%	40.0%
R-CVP (n=58)	37.9%	34.5%	3.5%	5.2%	0.0%	20.7%	0.0%	29.3%
R-Benda (n=56)	21.4%	26.8%	3.6%	3.6%	0.0%	12.5%	5.4%	41.1%
R-mono (n=57)	36.8%	19.3%	15.8%	10.5%	0.0%	24.6%	1.8%	19.3%
No treatment (n=57)	15.8%	12.3%	12.3%	0.0%	0.0%	5.3%	3.5%	50.6%

Benda, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide vincristine prednisone; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; mono, monotherapy; PS, performance status; Pt, patient; R, rituximab; 1L, first-line.

Summary/Conclusion: Age, comorbidities and PS are decisive factors in 1L treatment selection for older pts with DLBCL; disease burden or IPI are rarely stated as the rationale. The main reasons for not treating pts appear physician-driven rather than pt-requested, suggesting more pts may receive treatment if physicians have better options. If more tolerable chemotherapy-free options were available, fewer pts may refuse therapy, as illustrated by more R-mono-treated pts requesting their therapy compared with chemotherapy-treated pts. Further analysis of the impact of pt-related factors on treatment decision-making is warranted.

EP546 VALIDATION OF THE BURKITT LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (BL-IPI) IN PATIENTS FROM TWO CHEMOIMMUNOTHERAPY TRIALS (BURKIMAB-08 AND BURKIMAB-14) BY THE PETHEMA AND GELTAMO GROUPS

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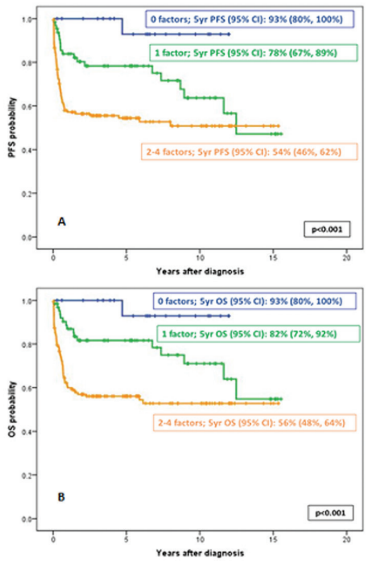
Background: The Burkitt Lymphoma International Prognostic Index Consortium has developed an International Prognostic Index for Burkitt Lymphoma (BL-IPI)(J Clin Oncol 2021: DOI https://doi.org/10.1200/JCO.20). From analysis of a cohort of 633 patients (pts) with BL, four independent variables were identified: age >40 yrs, performance status >2, serum lactate dehydrogenase (LDH) >3 x upper limit normal (ULN), and CNS involvement. This score was externally validated in an independent cohort of 457 patients.

Aims: Our objective was to validate this score in two sequential chemoimmunotherapy trials for patients with BL or leukemia (BLL).

Methods: From 2008 to 2020 two consecutive prospective trials of chemoimmunotherapy for patients with BLL (BURKIMAB-08 and BURKIMAB-14, (Ribera et al Cancer. 2013;119:1660-8, Ribera et al Blood 2019;134 (Suppl 1): 2584) were developed by the Spanish PETHEMA and GELTAMO groups. As the complete response (CR) and overall survival (OS) were similar (CR 85% vs. 80%, 5-yr OS 72% vs. 68%), both trials were merged for validation of the BL-IPI.

Results: 277 pts were included (BURKIMAB-08: 185, BURKIMAB-14: 92), median age (range): 47 (15-83) yrs, Burkitt lymphoma: 193 (70%), Burkitt leukemia: 84 (30%), HIV positive: 74 (27%). Age >40 yrs: 181 (65%), performance status ≥2: 105/272 (39%), LDH ≥3 xULN: 129/220 (59%), CNS involvement: 39/276 (14%). The distribution of patients according to the number of risk factors was: 0: 22 (10%), 1: 65 (28%), 2: 85 (37%), 3: 44 (19%), and 4: 14 (6%). With a median (range) follow-up of 5.4 (0.1-15.5) yrs, the 5-yr progression-free survival (PFS) (±95% CI) for the whole series was 69±6%, and the 5-yr OS (±95% CI) was 71±5%. The 5-yr PFS according to risk groups was: low-risk (0 risk factors; 10% of patients; 93 ±13%), intermediate risk (1 risk factor; 28% of patients; 78±11%), and high-risk (≥2 factors; 62% of patients; 54±8%)(p<0.001, Figure 1A). In turn, the 5-yr OS (±95% CI) according to risk groups was: low-risk (0 risk factors; 10% of patients; 93 ±13%), intermediate risk (1 risk factor; 28% of patients; 82±10%), and high-risk (≥2 factors; 62% of patients; 56±8%)(p<0.001, Figure 1B).

Figure 1. Progression free survival (A) and Overall survival (B) by BL-IPI score in the present series



Summary/Conclusion: The outcome of our series of pts with BLL was similar to that of BL-IPI series, making feasible the validation. The distribution of patients according to the number of risk factors, as well as the 5-yr PFS and OS according the BL-IPI risk groups were superimposable to that of the BL-IPI. Consequently the BL-IPI was fully validated in our series of pts with BLL.

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EP547 EXTRANODAL DISEASE IS AN INDEPENDENT NEGATIVE PREDICTIVE MARKER FOR PROGRESSION-FREE SURVIVAL AFTER CD19-CAR T-CELL THERAPY FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: CD19 CAR T cells induce complete remissions in ≥40% of heavily pretreated patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). However, a significant proportion of patients shows refractory disease or relapses early after therapy. Thus, the identification of predictors of durable responses is of interest not only to guide patient selection, but also to investigate resistance mechanisms and improve efficacy.
Aims: We assessed the predictive value of clinical and laboratory parameters for progression-free survival (PFS) of r/r DLBCL patients treated with CD19 CAR T cells.
Methods: Patient and disease characteristics, toxicities, PET/CT response and survival of r/r DLBCL patients treated with Axicabtagene Ciloleucel or Tisagenlecleucel at our institution were retrospectively assessed. We assessed pre-defined patient and lymphoma characteristics known to confer adverse outcomes in DLBCL for their association with PFS by univariable log-rank tests, as well as multivariable forward stepwise Cox regression analyses. Analysed Characteristics encompassed age, refractoriness to first-line therapy and no. of prior therapy lines. Additionally, tumor volume, presence of bulky disease (>10cm), presence of extranodal disease (END), Ann Arbor stage, IPI, LDH and ECOG, all assessed at time of lymphodepletion, were included in the analysis.
Results: As of November 2020, 41 DLBCL patients have been leukapheresed, and 35 patients have been transfused. Median age was 60 years (range 19-82). ECOG was 0-1 in 23, and 2-3 in twelve patients at time of CAR T-cell transfusion. Only 3 of the 35 transfused patients (9%) would have met the inclusion criteria of the pivotal clinical trials at all timepoints (enrolment, apheresis, and time of lymphodepletion).
CRS occurred in 32/35 patients (80% CRS °1-2, 11% °3). 16 patients (45%) experienced ICANS (29% °1-2, 14% °3-4, and 3% °5). Median follow-up was 4.4 months. Response assessment after three months was available for 34/35 patients. Objective response rate was 53%, with complete remission in 15 (44%) and partial remission in three patients (9%).
In univariable analyses, apart from primary refractory disease (p=0.79), all pre-selected markers were suggestive to be associated with PFS (p=0.002-0.061). We therefore included all variables that were indicative of shorter PFS (p<0.1) in univariable analyses in multivariable AIC-based forward stepwise Cox regression analyses. In the resulting model, presence of END was associated with inferior PFS (Hazard ratio [HR] 11.3, p=0.02), adjusted for prior therapy lines (HR 1.3, p=0.06) and ECOG>1 (HR 2.3, p=0.12). Other variables did not improve the prognostic validity of the model. The relevance of END for PFS was confirmed in additional two-variable Cox regression analyses, each adjusted for one marker from the multivariable model.
Summary/Conclusion: We provide real-world evidence that CD19 CAR T cells induce remissions in a substantial proportion of r/r DLBCL patients, although only 9% of our patients would have met the inclusion criteria of the pivotal trials. In the patient cohort, extranodal disease at transfusion was associated with significantly shorter PFS both in uni- and multivariable analyses. To understand and overcome this potential resistance mechanism, we have set up a comprehensive immunomonitoring program with specific focus on the lymphoma microenvironment in nodal and extranodal sites.

EP548 ZANUBRUTINIB, LENALIDOMIDE PLUS R-CHOP (ZR2-CHOP) AS THE TREATMENT FOR DIFFUSED LARGE B-CELL LYMPHOMA (DLBCL)

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Background: R-CHOP is the standard first-line therapy of DLBCL. Although over half of patients have been cured under R-CHOP, the remaining patients shared poor prognosis with median OS less than 1 year when progression after front-line treatment. Zanubrutinib, a second-in-class inhibitor of BTK, disrupts BCR signaling and decreases NF-κB activity. Lenalidomide is an oral immunomodulatory agent which downregulates IRF4 and MYD88 signaling. Both two drugs have demonstrated activity in DLBCL.
Aims: To evaluate the safety and efficacy of zanubrutinib, lenalidomide plus R-CHOP (ZR^2-CHOP) as the treatment for DLBCL patients, we conducted this single-arm retrospective observational study.
Methods: We enrolled patients aged 18 to 75 years old with high-risk DLBCL (including but not limited to double-hit, double-expression DLBCL). Oral zanubrutinib was given continuously (160mg twice daily) from Day 0, lenalidomide 25mg daily Day 1-7. Patients were administered intravenously rituximab (375mg/m^2 on Day 0), cyclophosphamide (750mg/m^{2}on Day 1), doxorubicin (50mg/m^2 on Day 1), vincristine (1.4mg/m^2 on Day 1), and oral prednisone (50mg/day Day 1-5). All patients were recommended to receive 6 cycles of ZR^2-CHOP (R-CHOP or R^2-CHOP were allowed in cycle 1-2 due to poor physical condition at treatment) and patients older than 70 years old were administered ZR^2-miniCHOP (**Figure 1**). CT or PET-CT scans were conducted to assess mid-term efficacy and assessment after 6 cycles was made by PET-CT scan. ctDNA was dynamically detected before treatment, after 3 cycles and 6 cycles to evaluate tumor mutational burden. The primary endpoint was complete response ratio (CRR) after mid-term and 6 cycles. The secondary endpoint was overall response rate (ORR), ctDNA and the number of adverse events (AE). AEs were graded based on CTCAE (version 5.0).
Results: 10 DLBCL patients diagnosed in Pukou CLL Center were enrolled in this cohort between July 2020 and February 2021, with 9 treatment-naïve DLBCL and 1 Relapsed/Refractory DLBCL (PD after 4 cycles of bendamustine plus rituximab). The median age of patients was 55 years old and all patients had ECOG-PS ≤2. 1 patient (1/10) was diagnosed as double-hit DLBCL and 7 patients (7/10) as double-expression. 8 patients were non-GCB and 2 were GCB. 7 patients (7/10) were classified as high-intermediate and high-risk group according to NCCN-IPI (**Table 1**). At data cutoff (1st March, 2021), the median follow-up was five months (3-8 months) with all patients have completed at least 3 cycles and mid-term assessment could be conducted. The ORR was 100.0%, with 9 patients achieved CR (9/10) and 1 patients achieved PR (1/10). ctDNA was dynamically detected in five patients. The median number of baseline somatic mutation was 5 and all 5 patients showed undetectable ctDNA after 3 cycles. 4 patients have received 6 cycles, all of them achieved CR (4/4) and undetectable ctDNA (4/4) (**Figure 1**). The most common hematological toxicity events were lymphocytes count decreased, neutrophil count decreased, thrombocytopenia and anemia, with 3-4 level occurrence rate was 70.0%, 30.0%, 20.0% and 20.0%. The most common non-hematological toxicity events were nausea and fatigue. One patients discontinued oral zanubrutinib and lenalidomide more than seven days due to drug rash.

Table 1. Baseline Clinical Characteristics of DLBCL patients.

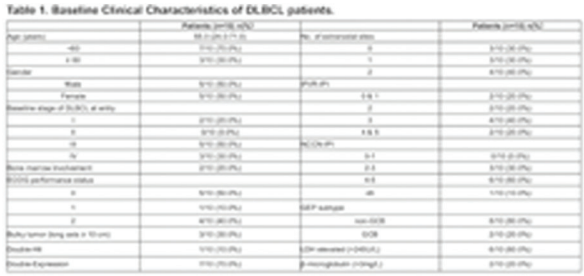
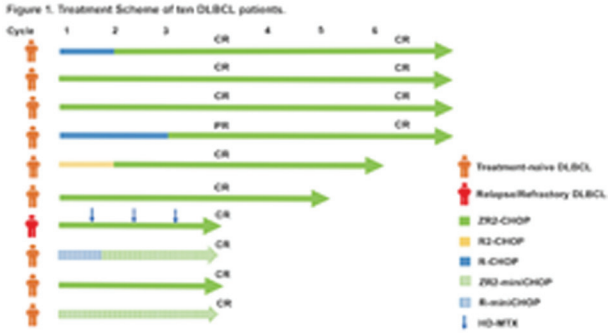


Figure 1. Treatment Scheme of ten DLBCL patients.



Summary/Conclusion: ZR²-CHOP for high-risk DLBCL patients with fair physical condition could achieve high CRR and high proportion of early-stage undetectable ctDNA. The overall tolerability was under control. ZR²-CHOP could be one of the promising choice for the treatment of high-risk DLBCL.

EP549 COMPARISON OF CHIDAMIDE-CONTAINED TREATMENT MODALITIES VERSUS CHEMOTHERAPY IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA

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Background: Peripheral T-cell lymphoma(PTCL) are characterized by an aggressive clinical behavior. Outcome and treatment options for relapsed or refractory (RR) PTCL patients are poor. Chidamide, an oral novel histone deacetylase inhibitor, has been approved for the treatment of RR PTCL in China.
Aims: We compared the efficacy of chidamide-contained regimens with chemotherapy in RR PTCL patients, in order to identify potentially effective regimens for this cohort.
Methods: We collected the clinical data of ninety-six RR PTCL patients managed in Sun Yat-sen University Cancer Center from January, 2014 to July, 2020. retrospectively. Eligibility criteria included those with R/R disease who had received one prior systemic therapy. Based on the first retreatment regimen, patients were divided into three groups, including chemotherapy(ChT), chemotherapy combined with chidamide(chidamide+ChT) and chidamide combined with or without other targeted agents (targeted therapy) group. Progression-free survival(PFS), overall survival(OS), overall response rate(ORR) and complete response(CR) among three groups were compared. Statistical analysis was performed using IBM SPSS Statistics software (version 24.0). Clinicopathological variables of three treatment groups were assessed by $\chi 2$ test or Fisher' s exact test. Survival curves were plotted using the Kaplan-Meier method and were compared using the log-rank test, with P <0.05 considered to be statistically significant.
Results: The median follow up time was 20.1 months (range, 4.5-162.4 months). Baseline characteristics of these patients, including the median age, gender, second-line International Prognostic Index (IPI), subtypes of PTCL, CD30 expression and EBV infection, were listed in Table 1. ChT group included more patients with PTCL-NOS, targeted therapy group included more paitents with AITL, other characteristics were well balanced across treatment groups. Chidamide+ ChT group had a significantly better PFS (p=0.046, Figure 1). Median PFS for Chidamide+ChT group was 4.5 months (range 0.4-35.4 months), compared with 3.5 months (range 0.5-65.8 months) for the ChT group and 1.8 months (range 0.4-13.6 months) for the targeted therapy group. No difference in OS was observed(p=0.912, Figure 2). Among patients with high second-line IPI(3-5), there was a significant difference in PFS among three groups(p=0.045, Figure 3). Among patients younger than 60 years, chidamide+ChT group demonstrated a PFS benefit (p =0.027, Figure 4) over other groups. In the subgroup of CD30(-) patients, PFS was superior in the Chidamide+ChT group as compared with other groups (p =0.002, Figure 5). In contrast, there was no statistical difference between the three groups in patients with low second-line IPI (0-2) (p=0.075), or patients older than 60 years (p=0.446) or CD30(+) patients (p =0.575). We found a trend for improved OS for patients with high second-line IPI who received chidamide+ChT as compared with ChT(p=0.188, Figure 6).The ORR for patients in ChT group, chidamide+ChT group and targeted therapy group were 54.8% 64.9% and 64.7%(p=0.607), respectively, with CR rate of 16.7% 18.9% and 35.3%(p=0.262).

Table1.Baseline characteristics of 96 R/R PTCL pts

Characteristics	Overall n=96 (%)	ChT n=42(%)	Chidamide+ChT n=37(%)	Targeted therapy n=17(%)	P
Median age (range)	57(25-90)	55(30-77)	56(29-76)	65.5(25-90)	0.225
Gender					0.680
Male	62(64.6%)	28(66.7%)	22(59.5%)	12(70.6%)	
Female	34(35.4%)	14(33.3%)	15(40.5%)	5(29.4%)	
IPI2					0.841
0	7(7.3%)	4(9.5%)	3(8.1%)	0	
1	23(24.0%)	11(26.2%)	8(21.6%)	4(23.5%)	
2	33(34.4%)	15(35.7%)	10(27.0%)	8(47.1%)	
3	26(27.1%)	9(21.4%)	13(35.1%)	4(23.5%)	
4	6(6.3%)	2(4.8%)	3(8.1%)	1(5.9%)	
5	1(1.0%)	1(2.4%)	0	0	
Subtype					0.030
PTCL-NOS	43(44.8%)	26(61.9%)	12(32.4%)	5(29.4%)	
AITL	22(22.9%)	4(9.5%)	11(29.7%)	7(41.2%)	
ALCL,ALK-	7(7.3%)	2(4.8%)	4(10.8%)	1(5.9%)	
ALCL,ALK+	4(4.2%)	0	3(8.1%)	0	
EATL	6(6.3%)	4(9.5%)	1(2.7%)	1(5.9%)	
SPTCL	6(6.3%)	3(7.1%)	3(8.1%)	0	
Others	8(8.3%)	3(7.1%)	3(8.1%)	3(17.6%)	
CD30					0.535
Positive	45(46.9%)	21(50.0%)	19(51.4%)	5(29.4%)	
Negative	34(35.4%)	15(35.7%)	12(32.4%)	7(41.2%)	
Unknown	17(17.7%)	6(14.3%)	6(16.2%)	5(29.4%)	
EBV					0.125
Positive	35(36.5%)	12(28.6%)	14(37.8%)	9(52.9%)	
Negative	53(55.2%)	28(66.7%)	19(51.4%)	6(35.3%)	
Unknown	8(8.3%)	2(4.8%)	4(10.8%)	2(11.8%)	

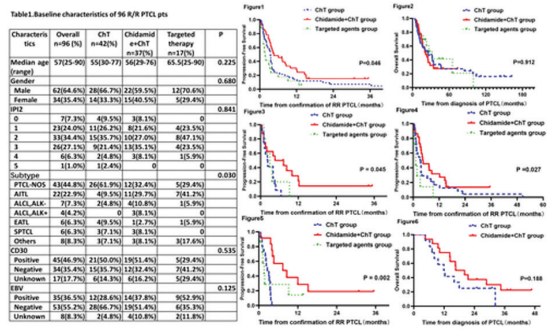


Figure1. PFS curve based on types of therapies; Figure2. OS curves based on types of therapies; Figure3. PFS curves of patients with high second-line IPI(3–5) based on types of therapies; Figure4. PFS curves of patients younger than 60 years based on types of therapies; Figure5. PFS curves of CD30(-)patients based on types of therapies; Figure6. OS curves of patients with high second-line IPI(3–5) based on types of therapies.

Summary/Conclusion: Despite this retrospective study with a small sample size, first retreatment with chidamide+ChT regimen showed more PFS benefit than ChT and targeted therapy for RR PTCL patients, especially those with high second-line IPI, younger than 60 years and CD30(-). The combination of chidamide with ChT may be an effective treatment strategy for RR PTCL patients but requires further investigation.

EP550 CELL OF ORIGIN IMPACTS DELTASUVMAX CUTOFF FOR PREDICTION OF RELAPSE IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: The role of interim positron emission tomography (PET) as a predictor for progression free survival (PFS) in patients with DLBCL remains controversial. The incorporation of volumetric and quantitative parameters aims to improve the identification of patients with high risk for treatment failure. Recently, the role of delta SUVmax, defined as a reduction between the maximum uptake at initial PET and interim PET(iPET) has been tested as a predictor of PFS. In most studies, a cutoff of 66% reduction successfully identified patients at high risk for treatment failure.
Aims: We aimed to analyze the role of DeltaSUVmax in predicting relapse in a cohort of Brazilian patients with DLBCL, and the impact of cell of origin (COO) in this analysis.
Methods: We retrospectively analyzed a cohort of patients with DLBCL from Sao Paulo, Brazil. All diagnoses were made by the same hemepathologists, and COO was defined using Hans algorithm. PET scans were obtained at baseline and after 2-3 cycles of therapy (iPET). All PET-CTs were read by the same physician, blinded for the COO and other clinical features. Delta SUVmax was calculated by the difference in % between initial PET SUVmax and iPET. Event free Survival was defined as the time from diagnosis to the time to progression or death.Initially a cut off 66% reduction was used for analysis, but due to low number of patients not achieving a 66% reduction in the activated B cell (ABC) subgroup, the optimal cutoff was selected based on the ROC curve.
Results: A total of 54 patients were available for analysis. Median age of all patients was 61 years old, and 61% of patients had a germinal center B-Cell (GCB) phenotype. The median maximum uptake at baseline was 31 for the germinal B-cell (GCB) and 34.1 for the activated B-Cell (ABC) phenotype. For all patients, ΔSUVmax <66 was strongly related to relapse (HR=0.065, p=0.0005). In the GCB cohort (n=33), ΔSUVmax <66 was also strongly related to relapse (H=0.02, p=0.0004). In the ABC cohort (n=21), only one patient failed to achieve ΔSUVmax>66. A ROC curve identified a ΔSUVmax>90 as a better cutoff for relapse, and patients not achieving 90% reduction had a higher risk for relapse (p=0.03). MYC/Bcl-2 expression was also compared, and ΔSUVmax <66 was related to events in both double-expressors (DE, p=0.0003) and in non-DE (p=0.036).
Summary/Conclusion: A reduction <66% in SUVmax from baseline PET to iPET was strongly related to the risk of relapse in a cohort of 54 patients with DLBCL. However, the cutoff of 66% was only significant in patients with GCB DLBCL, mostly due to the low number of ABC patients who did not reach a 66% in SUVmax. For ABC patients, a ΔSUVmax>90 improved the identification of patients at high risk for relapse. Larger cohorts of patients are needed to validate our exploratory findings.

EP551 COMPARISON OF IMMUNOCHEMOTHERAPY WITH RITUXIMAB-DOSE-ADJUSTED EPOCH (R-DA-EPOCH) OR RITUXIMAB-CHOP (R-CHOP) IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

T. Vassilakopoulos [1,*], Z. Mellios [2], E. Verigou [3], S. Papageorgiou [4], C. Chatzidimitriou [1], C. Kalpadaki [5], E. Katodritou [6], H. Giatra [2], V. Xanthopoulos [7], G. Gainaru [7], E. Vrakidou [7], T. Leonidopoulou [8], M. Palassopoulou [9], S. Karakatsanis [10], M. Tsirogianni [11], E. Hatzimichael [12], E. Terpos [13], P. Zikos [14], M. Arapaki [1], P. Katsaouni [3], J. Asimakopoulos [1], J. Drandakis [1], D. Galopoulos [1], E. Konstantinou [1], G. Kourti [10], T. Assimakopoulou [8], M. Michail [15], M. Dimopoulos [13], M. Siakantaris [1], G. Karianakis [7], A. Symeonidis [3], D. Grentzelias [7], K. Sakellariou [2], P. Tsirigotis [4], E. Papadaki [16], E. Plata [1], M. Bakiri [2], M. Angelopoulou [1], K. Konstantopoulos [1], T. Karmiris [2]

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Background: Further to the impressive results with R-da-EPOCH in a phase 2 NCI trial, retrospective comparisons have shown a modest, non-significant benefit in disease control but also a reduced need for consolidative radiotherapy (RT) administration with R-da-EPOCH vs R-CHOP in PMLBCL. However, the choice of treatment was at the discretion of the treating physician, inevitably introducing systematic bias.
Aims: To compare the efficacy of R-da-EPOCH vs R-CHOP with an as much as possible unbiased selection of controls and to investigate the physicians' compliance with the dose escalation protocol in routine practice.
Methods: R-da-EPOCH was adopted as the treatment of choice in all consecutive patients with PMLBCL <60 years (n = 86) in 16 participating Centers in Greece, all of which administered R-CHOP as standard of care until then. The first control group (CG) of R-CHOP-treated patients (CG-1) was devised without any bias from the same Centers' patient database, selecting in reverse chronological order an equal number of patients to those treated with R-da-EPOCH at the same Center if possible, thus minimizing selection bias. Due to lack of an equal number of controls (13 patients less in the R-CHOP arm) and the administration of R-CHOP-14 to 18 patients in 5/16 Centers, the core group of 55 patients was maintained (86-13-18=55) and 2 more R-CHOP-21 CGs were devised. In CG-2, the 31 missing patients were replaced by 27 patients all treated at Nicosia General Hospital, Cyprus. In CG-3, 29 consecutive patients from 4 already participating Centers of similar care services capacity to the 4/5 aforementioned Centers were included, and 2 from another similarly suitable Center. Hence, all 86 CG-3 patients had received R-CHOP-21 and were consecutively selected from a previously created patient list.
Results: The groups of R-da-EPOCH-treated patients and R-CHOP CG-1 (n = 73), CG-2 (n = 82) and CG-3 (n = 86) were comparable at baseline except for worse PS in the former. Two patients developed acute myeloid leukemia (AML) 10.4 and 22 months after starting R-da-EPOCH and having reached dose escalation levels 6 and 4, respectively. The 5-year freedom from progression (FFP), event-free survival (EFS) and overall survival (OS) rates did not differ significantly and are shown in table 1 [there was a marginal difference regarding FFP only in comparison to CG-3 (p = 0.06)], while RT was administered to far fewer potentially eligible for RT patients in the R-da-EPOCH group. In the multivariate analysis of FFP, the difference between R-da-EPOCH and R-CHOP remained non-significant when comparing to CG-1 and CG-2 but became statistically significant when compared to CG-3 [p = 0.035, HR = 0.40 (0.16 - 0.94)]. Only 40 (61%) out of the 65 patients who had completed R-da-EPOCH and had available data received the regimen completely according to the protocol, reflecting real-world data on R-da-EPOCH administration. These patients had a 5-year FFP ratio of 92% and 55% of them had reached ≥4 dose escalation level (Table 1), similarly to the original NCI study.

Table 1. Comparison of efficacy and long-term complications between R-da-EPOCH-treated patients and 3 patient control groups (CGs) receiving R-CHOP.

	R-da-EPOCH	R-CHOP (CG-1)	p (CG-1)	R-CHOP (CG-2)	p (CG-2)	R-CHOP (CG-3)	p (CG-3)
Patients (#)	86	73		82		86	
5-year FFP	88%	80%	0.33	78%	0.22	75%	0.06
5-year EFS	85%	78%	0.31	76%	0.21	73%	0.13
5-year OS	96%	90%	0.32	91%	0.39	88%	0.14
Radiotherapy (%)	14%	73%		76%		58%	
Secondary neoplasias	2 AML	Thymoma		Thymoma		Thymoma, Hodgkin lymphoma	
R-da-EPOCH parameters	**5-year FFP**	**p**	**AML (#)**	**AML (%)**	**5-year OS**	**p**	**% of patients receiving dose level 4-6**
Strict protocol adherence	92%	0.30	1/40	2.5%	95%	0.56	55%
Protocol deviations	84%		1/25	4.0%	100%		25%
Received dosage level ≥4	87%	0.89	2/29	6.9%	95%	0.98	
Received dosage level <4	86%		0/40	0%	96%		
Received dosage level ≥3	90%	0.18	2/52	3.8%	94%	0.45	
Received dosage level <3	78%		0/17	0%	100%		

Summary/Conclusion: This comparative study between R-da-EPOCH and R-CHOP carried the least possible systematic error in the retrospective setting. Five-year FFP and EFS rates appeared less impressive than initially reported and 2 AML cases have been reported so far. However, R-da-EPOCH minimized the need for RT and demonstrated a numerically better disease control. Finally, in real-world situations, R-da-EPOCH is seemingly not given *lege artis* in a considerable proportion of patients.

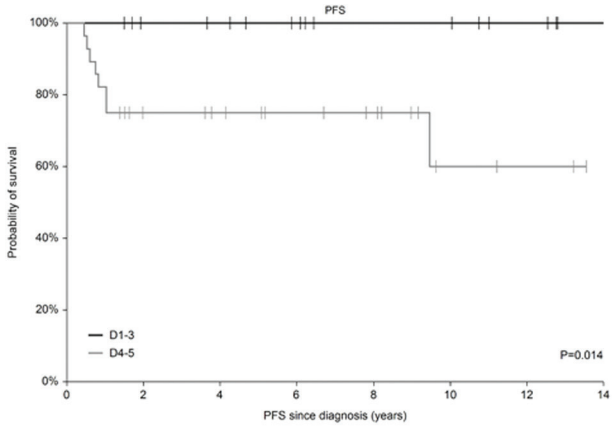
EP552 PREDICTIVE VALUE OF INTERIM FDG-PET/CT SCAN IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a specific clinicopathological and molecular subtype of non-Hodgkin lymphoma characterized by rapid progression of anterior mediastinal mass, commonly affecting younger patients. Standard therapeutic approach to PMBCL is immunochemotherapy with antracyclines followed by mediastinal radiation. PMBCL is nowadays considered to have better outcome than DLBCL, with PFS approximately 80% and OS 90%, respectively. Considering new therapy options (immune checkpoint inhibitors) seems to be important to identify chemorefractory patients with early relapse regarding early indication of novel drugs. As a powerful tool for response assessment is positron emission tomography with fluorodeoxyglucose (FDG). Even though this method is commonly used, the prognostic value of interim PET/CT is considered to be unclear and controversial.
Aims: To assess a predictive value of interim PET/CT as potentially useful tool for early recognition and further management of chemorefractory PMBCL.
Methods: We conducted a retrospective study of patients diagnosed with PMBCL. Between 2005-2019 we identified 53 patients, interim FDG PET/CT has been performed in 45 of them. Imaging studies were conducted using the Siemens Biograph 16 HI-REZ (2008-2015) and Siemens mCT 40 (2015-2017) systems with the same image acquisition protocols at the same centre. Both PET/CT scanners were accredited by EARL, a European Association of Nuclear Medicine research initiative. Images were read by two independent experts blinded for patient outcome.
Results: This cohort consisted of 27 females and 18 males with median age of 33 years. All of the patients have been treated with immunochemotherapy regimen containing rituximab and antracyclines, 30 of them have undergone autologous stem cell transplant and 4 of them had radiotherapy. All but two patients had final PET/CT, according to this 33 (73.3%) of them achieved CR, six (13.3%) PR, four (8.8%) had progressive disease. Interim FDG PET/CT was considered positive in 27 (60%) from 45 patients using visual evaluation. Interim PET/CT was assessed as negative (Deauville 1-3) in 17 (37.8%) patients and positive (Deauville 4-5) in 28 (62.2%) patients, respectively. In the negative interim FDG-PET/CT group no patient has relapsed, in positive interim PET/CT group 8 patients relapsed with median time to progression 9

months. Five-year PFS reached 75% and 100% (p=0,014) and 5-y OS 78.2% and 100% in groups D4-5 vs D1-3. Positive and negative predictive values were 28.6% and 100% for PFS-event.



Summary/Conclusion: Interim FDG-PET/CT negativity is associated with high negative predictive value for lymphoma progression. We can consider negative interim FDG-PET/CT as single valued method in detection of early response in chemosensitive patients. Regarding positive predictive value, for better identification of chemorefractory disease and patients suspect of early progression further analyses are needed. Extensive studies to estabilish the role of the interim PET/CT should contain assessment of specific metric values available in PET/CT scan as SUV max (maximum standardized uptake volume), MTV (metabolic tumor volume), TLG (total lesion glycolysis) or metabolic heterogeneity.
Acknowledgement: supported by AZV NU21-03-00411 and IGA_LF_2021_001 grants

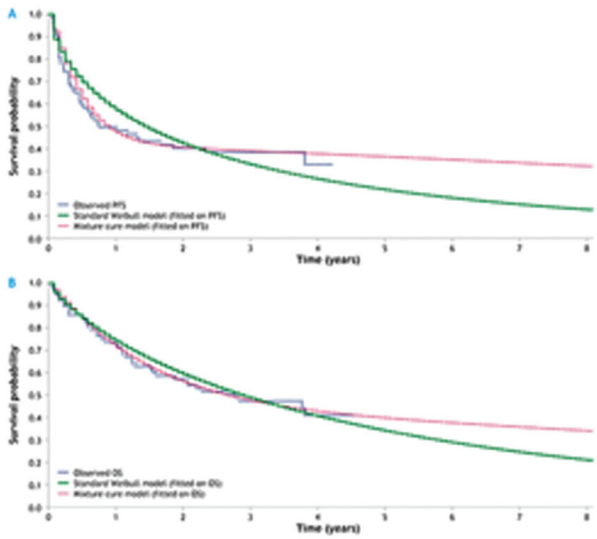
EP553 ESTIMATION OF LONG-TERM SURVIVAL WITH TAFASITAMAB + LENALIDOMIDE (LEN) IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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Background: L-MIND (NCT02399085) is an ongoing, open-label, single-arm, Phase II study of tafasitamab + LEN in patients (pts) with R/R DLBCL who are ineligible for ASCT. Progression-free survival (PFS) strongly correlates with overall survival (OS); however, while PFS estimates study drug treatment effect, OS also includes effects of subsequent cancer treatments or palliative care. Given that not all OS and PFS events may occur even during a long follow-up, traditional survival analyses may underestimate survival benefit for tafasitamab + LEN by assuming the same mortality rate for the whole study population.
Aims: To estimate the proportion of long-term survivors (LTS) and survival benefit associated with tafasitamab + LEN treatment using mixture cure models.
Methods: In the L-MIND study (data cut-off: Oct 30, 2020), 80/81 enrolled pts with R/R DLBCL received tafasitamab + LEN, with a median and maximum follow-up duration of 42.7 months (95% confidence interval (CI): 38.0–47.2) and 54.6 months, respectively. Kaplan–Meier (KM) plots of PFS and OS were observed to plateau after 30 months, with the majority of events (PFS: 45/46 [97.8%]; OS: 36/41 [87.8%]) reported up to that time-point. LTS exhibit a high survival benefit from tafasitamab + LEN treatment and were defined as pts without a PFS event and who did not decease after the observed plateau. Thus, the pt population can be considered to consist of two sub-populations: LTS and non-LTS. A 'mixture cure model' was fitted on L-MIND observed PFS and OS data to estimate the proportion of LTS and associated mean survival for the two sub-populations. To incorporate background mortality, age- and sex-specific US mortality rates were factored in for the entire study population (enrolled in Europe and US). The weighted average of the mean survival for the two sub-populations provided an estimate of the mean survival for the whole population. For comparative purposes, standard parametric models without considering an LTS proportion were also fitted on PFS and OS data. Sensitivity analyses were performed considering different survival distributions (exponential distribution, Weibull distribution and log-logistic distribution).
Results: Using a mixture cure model fitted to PFS and OS data, the estimated proportion of LTS for the tafasitamab + LEN combination was 41.7% (95% CI: 30.0–54.5) and 44.6% (95% CI: 28.1–62.4), respectively. The predicted mean survival when the mixture cure model was fitted on PFS data was 16.7 years for LTS pts vs 0.5 years for non-LTS pts, yielding 7.4 years for the overall population. Further, survival rates for pts with tafasitamab + LEN treatment were predicted as 40.7% and 36.5% at 2 and 5 years, respectively. Similar results were obtained when the mixture cure model was fitted on OS data. By comparison, using a standard parametric model (Weibull distribution), the predicted mean survival in the overall population was 3.6 years fitting PFS data (Figure 1A) and 5.2 years fitting OS data (Figure 1B).

Figure 1: Kaplan-Meier plot of (A) investigator-assessed PFS and (B) OS as observed in L-MIND and predicted outcomes by mixture cure model and Weibull survival model



Summary/Conclusion: PFS and OS KM curves for the L-MIND study reaching a long plateau and not following a standard Weibull distribution suggest the presence of an LTS subgroup. Standard parametric models may fail to capture the survival plateau of LTS, leading to a poor estimate of OS benefit in such pts. The mixture cure model suggests that the treatment of R/R DLBCL pts with tafasitamab + LEN is associated with a high LTS proportion of 41.7%.

EP554 SAFETY OF AMBULATORY HIGH-DOSE METHOTREXATE (HDMTX) ADMINISTRATION AMONG HEMATOLOGICAL MALIGNANCIES PATIENTS IN TERTIARY CARE CENTER

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Background: Methotrexate (MTX) is an antimetabolite, that mainly acts through the inhibition of the enzyme dihydrofolate reductase and the subsequent depletion of intracellular folate stores. High-dose MTX (HDMTX)is defined by the dose of more than 1 g/m^2. The utilization of HDMTX is commonly used in solid malignancies such as osteosarcoma and hematological malignancies such as acute lymphoblastic leukemia and non-Hodgkin's Lymphoma. Urine Alkalinization using intravenous sodium bicarbonate and calcium folinate to facilitate clearance of MTX are crucial two steps in MTX clearance and to avoid or minimize side effects such as nephrotoxicity and hepatotoxicity. For that reason, most institutions are requiring patients to be admitted with a minimum length of stay of 72 hours until methotrexate clearance is achieved with a serum level of < 0.1 micromol/L.
Aims: Here, we are assessing the safety of ambulatory HDMTX among adult patients. Regular laboratory monitoring, adequate oral hydration and oral medications were utilized to enhance methotrexate clearance

without the necessity to use devices at home for infusion or admitting the patient

Methods: This trial is open-labeled, single arm study that aims to evaluate the safety of high dose methotrexate administration in an outpatient setting among adult patients with hematological malignancies in a tertiary care center. The study aims to cover a cohort of patients with hematological malignancies from 14 to 60-years-old treated at KFMC scheduled to receive HDMTX from (February-2020) to (February-2021). treatment protocol is showing in figure 1.

Results: Twenty-seven (n=27) cycles were done until now. Around 70.37% of the patients were diagnosed with diffuse large B cell lymphoma (DLBCL).

Thirteen patients (48.1) % of the patients achieved MTX level less than 0.1 micromol/L by 48 hours and 24 patients (88.8%) achieved the same level by 72 hours.

Only three (11.1%) patients did not clear their methotrexate by the end of 72 hours; one patient was admitted due to acute kidney injury, the second was managed as outpatient as that occurred at the mid of COVID-19 bed crises, and the third one refused admission and was following his labs at the hospital at his hometown. By 72 hours, 29.63% had reversible asymptomatic elevation of creatinine, and all of them were grade one.

By 72 hours, around 44.44% had reversible asymptomatic hepatotoxicity, and all of them were grade 1. Among the 27 patients, only one suffered from acute kidney injury that necessitated admission for supportive care, which was totally reversible. The patient was not compliant to the treatment protocol and was excluded for subsequent cycles.

Figure 1

Pre-Chemo	Start the following medications 24 hours prior to methotrexate administration and continue until methotrexate level is less than 0.1 micromol/L				
	Sodium bicarbonate 1950 mg PO q4 h				
	Acetazolamide 250 mg PO q6h.				
	Oral water intake 3 L/day				
Chemotherapy	If urine pH is ≤ 7, start sodium bicarbonate 100 mEq + 20 mEq Kcl in 1 Liter D5W IV @ 150 mL/hr. Start 4 hours prior to methotrexate infusion and continue until the end of the methotrexate infusion. Keep urine out put (UOP) >100 mL/hr				
	Methotrexate 3000 mg/m² = mg IV in 1 L normal saline over 3 hours on day 1 (% dose reduction)				
	Avoid/Discontinue: Bactrim, Flouroquinolones, NSAIDs, Penicillins, and PPIs) at least 48 hours prior HDMTX and Resume when the level of methotrexate is less than 0.1 micromol/L				
Anti-emetics	Granisetron 1 mg IV 30 minutes prior to chemotherapy If granisetron not available, give ondansetron 8 mg PO BID (give 1st dose prior to methotrexate)				
	Dexamethasone 8 mg IV/PO 30 minutes prior to chemotherapy on day 1				
	Ondansetron 8 mg PO BID on days 2-3				
	Metoclopramide 10 mg PO/IV q6h PRN nausea/vomiting				
Post-HDMTX	Leucovorin 30 mg PO q6h. Start exactly 24hr after the start of methotrexate infusion and continue until methotrexate level is less than 0.1 micromol/L.				
Time from the start of methotrexate	Methotrexate Level (micromol/L)				
	< 0.1	0.1 – 2	2-20	20-100	>100
At 24 hours	None	Continue as ordered	30 mg PO q4h	10mg/m2 IV q6h	100 mg/m² IV q6h
At 48 hours	None	30 mg PO q4h	15mg/m² IV q6h	10mg/m² IV q3h	100 mg/m² IV q3h
At 72 hours	None	15mg/m² IV q6h	10mg/m² IV q3h	100mg/m² IV q3h	1000mg/m² IV q3h

Summary/Conclusion: Our preliminary results suggest that ambulatory HDMTX is safe, cost effective, more comfortable for patients.

These results encourage the use of this approach more frequently as it decreases hospitalization and thus reduces cost, increases patient satisfaction and helps to solve the issue of bed crisis.

EP555 OUTCOME OF RITUXIMAB-POLATUZUMAB-BENDAMUSTINE IN THE TREATMENT OF RELAPSED/ REFRACTORY HIGH GRADE LYMPHOMA AND TRANSFORMED HIGH GRADE LYMPHOMA – A MULTI-CENTRE ANALYSIS.

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Background: The combination chemotherapy incorporating polatuzumab along with rituximab and Bendamustine has shown a significant response in relapsed /refractory high grade lymphoma. .

Aims: To review the response of all patients who received rituximab, polatuzamab and bendamustine (RPB) for relapsed /refractory diffuse large B cell lymphoma (DLBCL) and transformed high grade lymphoma in 4 district general hospitals in the East Anglia Cancer Network.

Methods: Retrospective analysis of data from 4 district general hospitals which serves a population of 1.26 million. All patients who had combination chemotherapy of rituximab, polatuzumab and bendamustine as stand-alone treatment or for bridging to Chimeric Antigen Receptor T cell (CAR T) therapy were identified from from June 2019. Patients were given 1.8mg/kg of polatuzumab, 375mg/m2 of rituximab on day 1 and 90mg/m2 of Bendamustine on day 1 and day 2 in a three weekly cycle. Objective clinical and radiological responses were assessed using modified Lugano Classification on interim staging CT scan after 3 cycles of treatment and positron emission tomography (PET) scan at the end of treatment.

Results: A total of 24 patients were identified from four district general hospitals in the East of Anglia Cancer Network. The mean age is 70.6 years (range 27-87) with M:F ratio of 2:1. The median ECOG was 2. De novo cases constituted 66% (16/24) of the patients. 29.1% (7/24) of the patients had transformed low grade lymphoma – 5 from follicular lymphoma and 1 each from marginal zone lymphoma and chronic lymphocytic lymphoma). There was 1 patient with primary mediastinal B cell lymphoma. 62.5% (15/24) of the patients had stage IV disease and 20% (5/24) of the patients had stage III disease. 16% (4/24) of patients had bulky disease prior to RBP cytotoxic chemotherapy. 75% (18/24) of the patients had extranodal involvement ranging from 1-5 extranodal sites. Mean IPI of the study group was 2.83. 29% (7/24) had double expresser phenotype on immunohistochemistry with 1 case of double hit lymphoma. Mean number of lines of therapy before RBP was 1.73. Only one patient was exposed to Bendamustine prior to RBP. All patients has had rituximab combination as a line of prior therapy and 37% (9/24) of patients were refractory to RCHOP chemotherapy. 54% (13/24) of patients were refractory to one line of prior therapy. 62.5% (15/24) of patients had less than 12 months of remission before RBP therapy. None of the patients had CAR T, autologous or allogeneic bone marrow transplant prior to the therapy. 75% (18/24) patients had the treatment as a standalone treatment, while 25% (6/24) had RBP as a bridge to CAR T cell therapy. In the standalone group, the median number of cycles of RBP was 4.33 with infection and peripheral neuropathy manifested in 3 and 1 patients respectively. Of the patients who had an interim and end of treatment scan, 31% (6/19) had complete remission, 36% (7/19) had partial remission (PR), with an overall response rate of 66% (13/19). 66.6% (4/6)of patients who had treatmet to bridge to CAR T cells had 25% (1/4) had complete remission, 50% (2/4) had partial remission and 25% (1/4) had progressive disease following CAR T cell therapy

Summary/Conclusion: Rituximab, polatuzumab along with Bendamustine is an effective treatment strategy in patients with relapsed / refractory high grade lymphoma. More data are required to consider RBP as a salvage treatment, with or without consolidation autologous bone marrow transplant for ralpased DLBCL.

EP556 TREATMENT EFFICACY AND OUTCOMES OF RARE HIV-RELATED PLASMABLASTIC LYMPHOMA: THE RESULTS OF MULTICENTER RETROSPECTIVE STUDY IN RUSSIA

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Background: Plasmablastic lymphoma (PbL) is a rare and aggressive B-cell malignancy highly associated with HIV. Despite improved understanding of this disease, its prognosis remains poor with short overall survival. There is no standard of care for this entity. Recent advances in the therapy of HIV-associated and aggressive lymphomas do not seem to have had a positive impact on the outcome of patients with PbL.

Aims: To estimate epidemiological characteristics and the results of the treatment of the HIV-related PbL

Methods: We investigate epidemiological characteristics and the results of the treatment of the HIV-related PbL in large cohort of HIV-related lymphoma patients for a 7-year period (2014-2020). During the observation period, 22 cases of HIV-related PbL were registered in three centers and selected for the analysis from the national multicenter retrospective study database. The median follow-up was 17,8 (4-57,4) months.
Results: The PbL accounted for 8,9% of lymphomas in HIV-infected patients (22/247). The median age was 42 years (32-61), males – 9 (41%). Most of the patients (n=19, 86%) had III-IV stages and B-symptoms were present in 8 patients (36%). CNS involvement was diagnosed in 8 patients (36%). The median of ECOG score was I (I-III). Half of patients had viral hepatitis as a co-infection including HCV (n=9), HCV and HBV (n=1), HCV, HBV and HDV (n=1). In 7 patients (32%) HIV and lymphoma were diagnosed simultaneously. Median time from HIV infection to the lymphoma onset was 4 years (1,5 month – 17,5 years). The only one patient did not receive cART for an unknown reason. The median number of CD4+ cells at the moment of chemotherapy (CT) started was 151 cell/mcl (13 – 374). Frontline CT were following: CHOP±E – 9 (41%), EPOCH – 11 (50%), hyper-CVAD – 1 (4,5%), dexamethasone – 1 (4,5%), bortezomib was added to frontline treatment in 3 (13,6%) patients, HDC with auto-HSCT had been done as a first line therapy in 2 (9%) patients. A total of 16 patients responded to the first line therapy with the overall response rate (ORR) of 72,7% including CR and PR in 4 (18,2%) and 12 (54,5%) patients respectively. Remaining patients had progression disease (n=5, 22,8%) and stable disease (n=1, 4,5%). The median course to achieve the ORR was 4 (2-6) cycles. Overall (OS) and progression-free survival (PFS) at 2 years after first line treatment was 59,1% and 40,9%, respectively. The median time to progression (TTP) was 7,95 (0,33-23,93) months. The addition of bortezomib and auto-HSCT in first-line chemo improved OS (100% vs 47,1%, p=0,027, Fig.1), but non PFS (p=0,1) and TTP (p=0,4). Nine patients received second-line CT: DHAP – 4 (44,4%), ICE – 4 (44,4%), EPOCH – 1 (11,2%). Response was evaluated in 8 patients. CR, PR and progression disease was registered in 1 (12,5%), 2 (25%) and 5 (62,5%) patients respectively. PBSC harvesting was only successful in 1 of 3 cases (33%) and this patient received HDC with auto-HSCT. OS and PFS at 2 years after second line treatment was 44,4% and 22,2%, respectively.
Two years after second line CT, 4 patients were still alive, including those after ICE, EPOCH (n=2), HDC with auto-HSCT (n=1) and nivolumab (27 cycles) as a third line therapy (n=1).
Summary/Conclusion: In a large cohort of patients PbL accounted for 8.9%.of all HIV-related lymphomas. The bortezomib addition and auto-HSCT in first-line chemo significantly improved OS. Prospective studies are needed for optimization of HIV-related plasmablastic lymphoma therapy.

EP557 ANALYSIS OF PROGNOSTIC FACTORS IN PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA TREATED BY DA-EPOCH-R AND R-CHOP

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is distinct clinical, pathological and molecular entity of diffuse large B-cell lymphoma (DLBCL) which accounts less than 3% of all non-Hodgkin's lymphomas (NHL). The standard 1st line treatment of PMBCL does not currently exist. A lack of prospective data comparing the efficiency of R-CHOP and DA-EPOCH-R regimen, does not allow to establish the best front line treatment options. Due to the age specificity and mediastinum localisation the implementation of the International Prognostic Index (IPI) in PMBCL is limited. Thus, this clinical entity needs better definition of prognostic factors and a standard of treatment approach.
Aims: The purpose of the study was to assess the treatment outcomes (5-year OS and PFS), and the potential prognostic factors for patients with PMBCL.
Methods: The study included 84 patients with PMBCL from 6 Ukrainian centers (Aug 2011 to Dec 2015). Patients were randomized into two groups: DA-EPOCH-R (44 pts) and R-CHOP (40 pts). Median age in DA-EPOCH-R group was 29 years (range 24.5-34) and in R-CHOP group - 32.5 (27-44) (p=0.036). Initial data included age, sex, stage, presence of B symptoms, bulky disease, ECOG, IPI score, pleuritis and pericarditis (Table 1). To analyse prognostic factors which may have impact on OS and PFS (treatment regimen, age > 40 years old, stage III-IV, ECOG≥2, ≥ 2 exstranodal sites, elevated LDH, male sex, presence of B-symptoms, pleuritis, pericarditis, bulky disease, and number of risk factors) we provided a multivariate Cox analysis.
Results: ORR and CR rates were significantly higher in the DA-EPOCH-R group: 97.7% vs 85% (p = 0.049) and 81.8% vs 50% (p = 0.003), respectively. The 5-year PFS in the DA-EPOCH-R group reached 90.9% vs 64.1% in the R-CHOP-regimen group (p = 0.002). The 5-year OS rate was also higher in the DA-EPOCH-R arm compared to R-CHOP – 97.7% vs 73.8%, respectively (p = 0.002). The median OS was not reached in either group. Using the Cox proportional-hazards model to assess the effect of a treatment regimen on OS, a significant reduction in the risk of death was seen for the patients in the DA-EPOCH-R group [p=0.016 (HR = 0.08, 95%CI 0.01 - 0.63)]. When adjusted for age and IPI, the risk of death from PMBCL in the DA-EPOCH-R group was also lower [p=0.010 (HR=0.046, 95%CI 0.005 - 0.478)]. Moreover, the higher risk of deaths due to PMBCL occurred with an increase in number of risk factors [p=0.01 (HR = 1.8, 95%CI 1,2 – 3,0). Additionally was defined that the risk of disease progression in the first 14 months after end of treatment was associated with 3 prognostic factors: treatment regimen, ≥ 2 extranodal sites and number of risk factors [Se 100% (95CI 80.5% - 100%); Sp 76.7% (95CI 64.0% - 86.6%)].

Characteristic	*DA-EPOCH-R*	*R-CHOP*	*p value*
No of patients	44	40	
IPI	n=40	n=43	
Low	17 (42.5)	26 (60)	
Intermediate	22 (55)	15 (34.9)	0.179
High	1 (2.5)	2 (4.6)	
Median age	29 (24.5-34)	32.5 (27-44)	0.036
LDH > upper limit of normal (n=43/40)	25 (58.1)	29 (72.5)	0.170
Age > 60 years old	0	2 (5)	0.224
ECOG>2	18 (40.9)	21 (52.5)	0.381
Extranodal lesions ≥2	5 (11.4)	9 (22.5)	0.243
Pericarditis	18 (40.9)	16 (40)	>0.999
B symptoms	17 (38.6)	11 (25)	0.356
Pleurisy	18 (40.9)	15 (37.5)	0.825
Stage III-IV, *N* (%)	11 (25)	10 (25)	>0.999
Bulky>10cm, *N* (%)	28 (63.6)	24 (60)	0.823

Summary/Conclusion: The DA-EPOCH-R regimen might overcome the effect of adverse prognostic factors. Our model could stratify patients with PMLBC and help guide selection of treatment. Thus, more prognostic studies that take into account novel biomarkers and novel prognostic features are warranted.

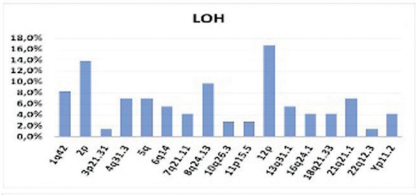
EP558 VALUE OF MICROSATELLITE INSTABILITY MARKERS IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA DIAGNOSTICS

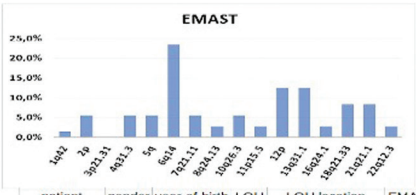
N. Risinskaya [1,*], Y. Mangasarova [1], E. Nikulina [1], Y. Kozhevnikova [2], A. Yushkova [1], V. Zheleznova [1], S. Kravchenko [1], A. Sudarikov [1]

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Background: Loss of heterozygosity (LOH) in STR loci, elevated microsatellite alteration at selected tetranucleotides (EMAST) and instability of mononucleotide tandem repeats (MSI - microsatellite instability) are intrinsic features of diverse tumor cells and appropriate analysis might be used as indication for the therapy with immune checkpoint inhibitors. For primary mediastinal B-cell lymphoma (PMBCL) these molecular factors to determine the prognosis of the disease have not been described yet. A set of five mononucleotide microsatellite repeat markers BAT-25, BAT-26, NR-21, NR-24, and NR-27 might not be informative in aggressive lymphoma cases since low occurrence (up to 5%). Furthermore, in about half of the cases, the altered allele may also present in the control material, possibly characterizing not the tumor, but the genetic features of the patient. According to the literature data, EMAST-H (high degree) is associated with MSI-H in solid tumors. Overlapping combinations of enzymes of the DNA repair complex are responsible for the repair of unpaired bases and the removal of oligonucleotide insertion loops. Therefore certain defects in the DNA repair complex (MMR) may lead to both MSI and EMAST.
Aims: To analyze the frequency of LOH and EMAST in tumor cells of PMBCL patients at diagnosis and to check possible association with PD-L1 mRNA overexpression.
Methods: STR profiles of the DNA of tumor cells were analyzed on a cohort of 72 de novo diagnosed PMBCL patients undergoing treatment

at the National Research Center for Hematology (Moscow, Russia). DNA was isolated from tumor biopsy samples taken at diagnosis. Control DNA samples were taken from the blood of patients in complete remission or from the buccal epithelium. STR-profiles for LOH and EMAST analysis were assessed by PCR with COrDIS Plus multiplex kit for amplification of 19 STR-markers and amelogenin loci (Gordiz Ltd, Russia). The fragment analysis was performed on ABI3130 Genetic Analyzer. For 15 patients LOH and EMAST status was evaluated relatively PD-L1 mRNA expression level checked at diagnosis.
Results: LOH was revealed in 37 out of 72 patients (51.4%). EMAST was found in 40 patients (55.5%); in 24 of them, EMAST was accompanied by LOH. For all EMAST-positive patients, the number of involved loci was no more than 4 from 19 (EMAST low, less than a third of the microsatellite markers panel). Among 15 patients with a known level of PD-L1 mRNA expression, six patients have no EMAST and no PD-L1 overexpression. Three patients have EMAST with 2-3 involved loci and PD-L1 overexpression. For 4 patients combination of EMAST and normal PD-L1 expression and for 2 patients no EMAST and PD-L1 overexpression were found. Standard therapy failure should be noted for patients with EMAST and PD-L1 overexpression.





STR-marker	Locus
D1S1656	1q42
D2S441	2p14
D3S1358	3p21.31
D5S818	5q23.2
D7S820	7q21.11
D8S1179	8q24.13
D10S1248	10q26.3
D12S391	12p13.2
D13S317	13q31.1
D16S539	16q24.1
D18S51	18q21.33
D21S11	21q21.1
D22S1045	22q12.3
CSF1PO	5q33.1
FGA	4q31.3
SE33	6q14
TH01	11p15.5
TPOX	2p25.3
VWA	12p13.31
Amelogenin X	Xp22.1–22.3
Amelogenin Y	Yp11.2

patient	gender	year of birth	LOH	LOH location	EMAST	EMAST low	PD-L1
GOR	m	1981	+	1 (1q, 2p)	-	-	+
ZHAM	f	1983	+	1 (13q)	+	1 (2p)	-
LOK	f	1968	+	1(10q, 22q,2p,8q)	-	-	+
MANS	f	1985	+	1 (2p, 5q, 12p)	+	1 (18q, 12p)	-
POLEZ	m	1995	+	1 (2p)	-	-	-
RAU	f	1987	-	-	-	-	-
YAR	f	1963	+	1(2p)	+	1 (12p, 21q)	-
OSTR	m	1987	-	-	-	-	-
ARE	f	1989	-	-	-	-	-
KRAS	f	1989	+	1 (12p)	+	1(11p, 13q,16q)	-
BUN	f	1988	+	1 (13q)	-	-	-
SASH	f	1988	-	-	+	1 (6q, 13q)	+
POT	f	1968	+	1 (12p)	+	1 (6q, 7q, 8q)	+
DANCH	f	1968	-	-	+	1 (4q, 13q)	+
IVAN	f	1969	-	-	-	-	+

Summary/Conclusion: The high incidence of LOH and EMAST in PMBCL can cause standard therapy failure in a significant number of patients. EMAST as a variant of microsatellite instability might be useful for further consideration as a predictor of response to checkpoint inhibitor therapy. The patients with EMAST and a high level of PD-L1 expression should be considered as the first candidates for immunotherapy. *This study was supported by Rakfond grant 2/2020*

EP559 DIAGNOSTIC YIELD AND SAFETY OF IMAGE-GUIDED PERCUTANEOUS SPLENIC BIOPSY – A TWO-CENTRE EXPERIENCE FROM THE EAST OF ENGLAND

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Background: Incidental or symptomatic abnormalities in the spleen can be found in a large spectrum of diseases. In most cases a diagnosis can be reached without splenic histology. Image-guided core biopsy of the spleen would be helpful in selected cases but is performed less often due to the perceived bleeding risk and low diagnostic utility.
Aims: To assess the diagnostic yield and safety of the image-guided splenic biopsy performed between January 2011 and October 2020 at 2 centres.
Methods: Retrospective data of all image-guided splenic biopsies performed at Colchester Hospital and Ipswich Hospital over 10 years were reviewed
Results: A total of 41 splenic biopsies were performed in 38 patients- 20 male and 18 female patients. The mean age was 66.5 years. The mean platelet count was 198 x 10^9/L (range 27 x 10^9/L – 558 x10^9/L). Only one patient received a prophylactic platelet transfusion. All biopsies were performed under ultrasonographic guidance. For the forty-one procedures 18-gauge needles were used in 90.2%, 16-gauge in 7.4% and 20-gauge in 2.4%. The mean number of core biopsy samples obtained were 3 (range 1-5 cores). 4 patients subsequently had elective splenectomy.
Adequate tissue for histological analysis including immunohistochemistry was obtained in 38 procedures (92.6%). Lymphoproliferative disorder was confirmed in 17 patients and was suspected in further 2 cases. These 2 patients later underwent splenectomy which confirmed the initial suspicion of DLBCL and low grade lymphoma. Of the 17 confirmed cases, DLBCL (10 cases) was the most frequent diagnosis and the remaining included 2 cases each of low grade B cell lymphoma, Hodgkin lymphoma, T-LGL and one case of T-cell rich B cell lymphoma. Non-haematological neoplasm was diagnosed in 4 patients. These included 2 cases of metastatic adenocarcinoma, 1 case of metastatic testicular germ cell tumour and 1 case of Littoral cell angioma.
Other histological diagnoses included 6 cases with reactive changes, 3 cases of sarcoidosis and one case each of Leishmaniasis, necrotising granulomata and extra-medullary haematopoiesis. A patient with reactive changes on splenic biopsy had features of extramedullary haematopoiesis identified on a subsequent splenectomy. Of the 5 remaining patients with reactive changes, 3 were discharged, 1 patient was later diagnosed to have chronic liver disease and 1 case remains under annual follow up.
Sufficient splenic tissue was not gained in 3 procedures (7.4%). 2 of these patients were later diagnosed to have low grade lymphoma – one following splenectomy and the other subsequent to molecular anaylsis of blood. The remaining patient with insufficient tissue declined further investigations. Three patients underwent a second splenic biopsy. The initial sample in these cases were deemed adequate but proved non diagnostic. The second biopsy secured a diagnoses of DLBCL, Hodgkin lymphoma and sarcoidosis in these patients.
1 patient developed peri-splenic haematoma which required an overnight admission for blood transfusion. This patient with thrombocytopenia (27 x 10^9/L) and a normal coagulation screen underwent a splenic biopsy using a 16-gauge needle following a single prophylactic platelet transfusion.
Summary/Conclusion: This case series demonstrates that ultrasound guided splenic biopsy by an experienced operator using a 18-gauge needle is a straight forward and minimally invasive procedure with a low complication rates and a high diagnostic yield.

EP560 IDENTIFYING THE INTRAVASCULAR LARGE B-CELL LYMPHOMA BY FDG PET/CT IMAGING: A SINGLE-CENTER, MATCHED CASE-CONTROL STUDY

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Background: Intravascular large B cell lymphoma (IVLBCL) is a rare and aggressive lymphoma. Early diagnosis of IVLBCL is difficult. Random skin biopsies and repetitive bone marrow biopsies are recommended to improve discrimination. Few studies focus on feasibility of PET/CT directed diagnosing in IVLBCL.
Aims: We conducted a single-center retrospective case-control study to explore the significance of PET/CT scans in patients with IVLBCL.
Methods: Data of consecutive 6 patients with IVLBCL from October 2018 to May 2020 were analyzed. 24 cases were extracted from patients with DLBCL NOS stage IV admitted and received treatment during the same period at a ratio of 4:1. The age of the patient in both IVLBCL and DLBCL cohorts was well matched. 5 patients in IVLBCL cohort received R-CHOP for 8 cycles and high-dose MTX (HD-MTX) for 2 cycles. 1 had the central nervous system (CNS) involvement besides systemic disorder at the diagnosis received autologous transplantation after 6 cycles of R-CHOP and 2 cycles of HD-MTX. 24 patients in DLBCL cohort received 8 cycles of R-CHOP. Patients who were at a high risk

of secondary CNS lymphoma stratified with CNS-IPI or had involvement of sinus, bone marrow, adrenal glands or kidney received 2 cycles of HD-MTX. Patients were evaluated with PET/CT scan at diagnosis, interim and at the end of treatment. A comparison of clinical characteristics, PET/CT findings and outcome of patients in both cohorts was conducted.

Results: The characteristic PET/CT imaging of IVLBCL was summarized by comparing with DLBCL NOS. (Figure 1) IVLBCL involves multiple extranodal organs rather than lymph nodes, with a non concordance of PET and CT findings: 1). Patches without clear contour along the vessels traced by 18FDG; 2). Variable mild increase of SUVmax; 3). Normal CT imaging of solid organs; 4). Thickening subcutaneous/submucosal tissue or interstitial of the lung. All IVLBCL patients were diagnosed with the PET/CT directed biopsy, which led to a similar duration from the first symptom to diagnosis with those patients with DLBCL NOS (2.5 (1-10) vs. 2.5(1-12) months, P=0.798). No patients had concomitant hemophagocytic lymphohistiocytosis in both cohorts. Patients with IVLBCL achieved a complete metabolic response at both interim and at the end of treatment. With comparable IPI, COO and the time from diagnosis to treatment, there was a trend that patients with IVLBCL had superior progression-free survival than those with DLBCL stage IV (2-year PFS 100% vs. 50%, P= 0.057). (Figure 2)

Figure 1. Multiple organs involvement and a nonconcordance of PET and CT findings in IVLBCL.

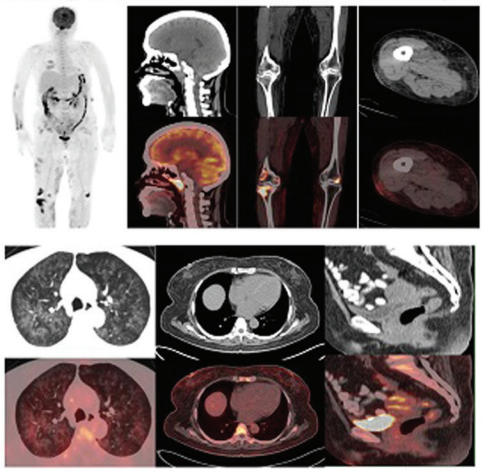
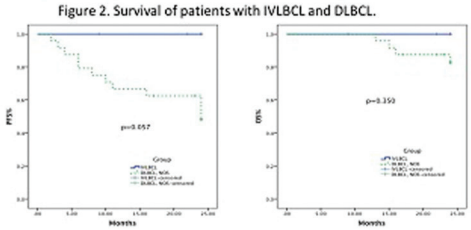


Figure 2. Survival of patients with IVLBCL and DLBCL.



Summary/Conclusion: A PET/CT-directed biopsy may be helpful for an early diagnosis of IVLBCL. Earlier chemoimmunotherapy may improve the prognosis of IVLBCL.

EP561 GLOMERULAR FILTRATION RATE (GFR) IS AN INDEPENDENT PROGNOSTIC FACTOR AFFECTING SURVIVAL OF PATIENTS WITH B-LARGE CELL LYMPHOMAS (B-LCL)

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Background: GFR is an independent prognostic factor for survival in some types of cancer, but its effect on outcome of patients with B-LCL has not been systematically analyzed.

Aims: To analyze the effect of GFR on outcome of patients with B-LCL, independently and in relation to IPI factors, bulk and treatment.

Methods: We analyzed overall survival (OS) and progression-free survival (PFS) of newly diagnosed patients with B-LCL treated at our institution between 2012 and 2019 and correlated these outcomes to the international prognostic index (IPI), bulky disease at diagnosis, treatment and GFR, calculated according to the CKD-EPI equation. Patients were excluded from the study if they had previous chronic kidney disease or obstructive nephropathy at diagnosis.

Results: We identified 288 patients fulfilling entry criteria, 151 (52%) male and 137 (48%) female. Median age was 58 and range 18-87. 136 patients were treated with R-CHOP21, 82 with R-CHOEP14 (patients younger than 60 with aaIPI 2-3), 38 with DA-R-EPOCH (fit patients older than 60 with aaIPI 2-3 since 2016) and 32 with R-miniCHOP or R-CEOP (unfit or patients with significant cardiac comorbidities). Responding patients with bulky or extranodal disease or in partial remission were irradiated after end of systemic treatment.

Age (p<0.001), IPI (p<0.001), treatment (p=0.02) and GFR (p=0.01) were statistically significantly associated with overall survival in univariate analysis. Only age (p=0.013) and GFR (p=0.004) remained significant in multivariate analysis. The effect of GFR was similar in all subgroups irrespective of treatment or IPI. Adding GFR to IPI resulted in 3 groups of patients with significantly different prognosis.

Summary/Conclusion: GFR is a significant prognostic factor in patients with B-LCL independent of IPI, bulk or treatment. The combination of GFR with IPI might result in better prognostic stratification of patients than IPI alone.

EP562 A NOVEL LIPID-COVERED PROGNOSTIC SCORING MODEL FOR NEWLY DIAGNOSED MATURE T AND NK CELL LYMPHOMAS

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Background: The current prognostic scoring systems for mature T and NK cell lymphomas have been found limitations in predicting survival outcomes. Novel predictors and precise risk stratification systems are lacking. Abnormal lipid metabolism was reported to influence the initiation and progression of malignancies. Nevertheless, the significance of dyslipidemia in mature T and natural killer (NK) cell lymphomas remains unexplored.

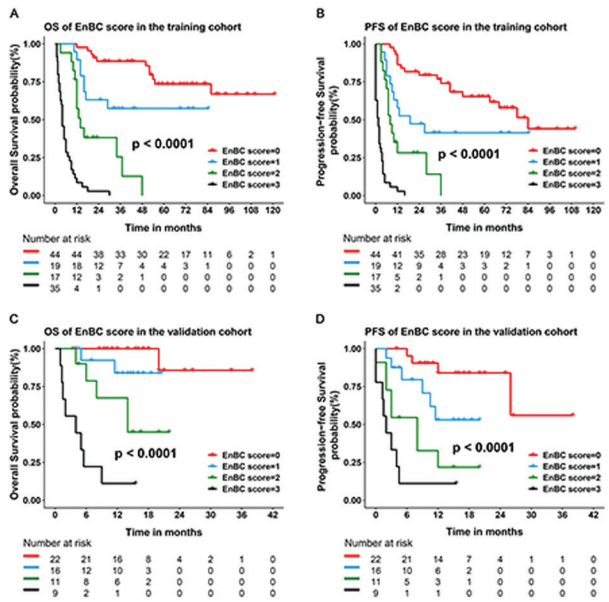
Aims: To investigate the association between serum lipid metabolism level and clinical outcomes, and further develop a lipid-covered prognostic model for newly-diagnosed mature T and NK cell lymphoma patients.

Methods: A total of 173 patients (1/2006-6/2020) were enrolled in this study, of which 115 constituted the training cohort while 58 composed the prospective validation cohort. The basic data comparison of the two cohorts was performed by Student *t* test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical data. Univariate analysis and multivariate Cox regression analysis were performed to detect independent predictors and generate a novel prognostic model, whose performance was further assessed in the training and validation cohort from multiple aspects, including Harrell's C-index, calibration curves, Kaplan-Meier survival analysis, time-dependent receiver operating characteristic curves, Brier score and decision curve analysis.

Results: Univariate analysis verified declined cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and increased triglycerides (TG) were associated with inferior survival outcomes in mature T and NK lymphomas. Multivariate analysis revealed extranodal involved sites≥2 (HR: 2.505; P=0.031), β2-MG≥3mg/L (HR: 3.964; P=0.005) and TC<3.58mmol/L (HR: 3.320; P=0.000) were three independent predictors. Thus, a novel prognostic model, EnBC score, was constituted with these three variables. EnBC score possessed satisfactory discrimination and calibration since the Harrell's C-index for OS prediction was 0.840 (95% CI, 0.810-0.870) and the calibration curves showed an optimal agreement between the prediction and actual observation. The prognostic significance of the novel model was verified in Kaplan-Meier survival analysis by dividing patients into four risk groups with different long-term survival (median OS, NA vs. NA vs. 14.0 vs. 4.0 months, P <

0.0001; median PFS, 84.0 vs. 19.0 vs. 8.0 vs. 1.5 months, P < 0.0001) (**Figure 1**). Compared with the present International Prognostic Index (IPI), EnBC score presented better discrimination (time-dependent AUCs of OS, EnBC 0.883-0.963 vs. IPI 0.785-0.873, P<0.001) and better calibration (Brier score of OS, EnBC 0.146-0.271 vs. IPI 0.154-0.296, P=0.023). Moreover, the decision curve analysis showed that EnBC score provided larger net benefits than IPI in the entire patient population.

Figure 1



Summary/Conclusion: Serum lipid metabolism level was firstly demonstrated significantly prognosis-related in mature T and NK cell lymphomas. Furthermore, a novel lipid-covered prognostic scoring system was established and performed well in predicting the prognoses of treat-naïve mature T and NK cell lymphoma patients.

EP563 UTILITY OF PROGNOSTIC INDICES IN DIFFUSE LARGE B-CELL LYMPHOMA FOR THE DETECTION OF HIGH RISK PATIENTS.

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Background: In recent years, different prognostic indices have been developed for diffuse large cell B-cell lymphoma (DLBCL) like the IPI, the R-IPI, the NCCN-IPI and, in our environment, the GELTAMO-IPI which is the only that includes the beta-2 microglobulin. Since the introduction of rituximab, an improvement in response rates and survival has been observed. Nevertheless, patients with an adverse clinical course continue to be observed and their identification is essential to assess alternative therapies

Aims: To analyze the reproducibility of prognostic indices for LBDCG in our serie of patients treated outside of clinical trials; and assess the capacity of the prognostic indices to detect in high-risk patients.

Methods: 137 patients diagnosed with DLBCL between June 2004 and June 2020 were included. The treatment was R-CHOP or similar (39 with liposomal doxorrubicin and 5 with etoposide associated to treatment). Furthermore, 29 patients received a 2nd-line treatment, 7 of them with auto-HSCT. We analyzed the prognostic characteristics at diagnosis and the overall survival. We applied 4 prognostic indices: IPI, R-IPI, NCCN-IPI and GELTAMO-IPI.

Survival was studied using the Kaplan-Meyer method and the survival curves were compared with the Log-Rank test. The Cox method was used to calculate the Hazard ratio

Results: Table 1 shows the main prognostic characteristics at diagnosis in our group of patients. With a median follow-up of 25 months, the median overall survival was 120 months (95% CI 42-198). Table 2 shows the different prognostic indices depending on the risk group. In the table 3 we observe the 5-year overall survival, with significant differences in the Log-Rank test with all indexes. All prognostic indices have been significant for the correct distribution of patients according to the risk group, being the GELTAMO-IPI index the best to identify high-risk group patients.

TABLE 1: DATA AT DIAGNOSIS

Age: middle	Sex (M/F)	ECOG>2	High LDH	Stage III/IV	High Beta-2 microglobulin
66 (16-88)	58/79	34(28%)	90 (66%)	88 (64%)	63(45%)

TABLE 2: PROGNOSTIC INDICES DISTRIBUTION BY RISK GROUP PATIENTS

	IPI	R-IPI	NCCN-IPI	GELTAMO-IPI
LOW	39 (28%)	8 (6%)	10 (7%)	15 (11%)
INTER-LOW	31 (23%)	62 (45%)	48 (35%)	81 (59%)
INTER-HIGH	29 (21%)		52 (38%)	32 (23%)
HIGH	38 (28%)	67 (49%)	27 (20%)	9 (7%)

TABLE 3: 5-YEARS OVERALL SURVIVAL BY RISK GROUPS.

	IPI	R-IPI	NCCN-IPI	GELTAMO-IPI
LOW	0,82 (0.57-0,93)	1	1	1
INTER-LOW	0,73 (0,47-0,87)	0,74 (0.56-0,86)	0,77(0,55-0,89)	0,65 (0,50-0,76)
INTER-HIGH	0,57 (0.34-0,75)		0,54 (0,37-0,69)	0,51 (0,27-0,71)
HIGH	0,40 (0,22-0,58)	0,47(0,33-0,61)	0,42 (0,20-0,63)	0,18 (0,01-0,53)
Long-Rank; p	0,002	0,002	0,002	<0,001
R, Cox: HR and p value	4,3 (1,8-10,5) 0,001	7,64 (1,0-57,8) 0,049	10,9 (1,4-86,6) 0,024	22,9 (4,3-121,3) <0,001

Summary/Conclusion: - The application of the prognostic indices to our serie of patients, shows the reproducibility of prognostic indices in real life patients.

- The GELTAMO IPI is the best index to differenciate high-risk patients group, despite the small number of cases.

EP564 MODIFIED R-BFM IMMUNOCHEMOTHERPY RESULTS HIGHER FREQUENCY OF COMPLETE REMISSION THAN R-DA-EPOCH/R-CHOP IN PATIENTS WITH HIGH-GRADE B-CELL LYMPHOMA DOUBLE-HIT TRANSFORMED FROM FOLLICULAR LYMPHOMA.

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Background: High-grade B-cell lymphoma double-hit (HGBL DH) can arise from follicular lymphoma (FL). In the case of transformation of FL it accumulates a large number of additional mutations and secondary *c-MYC* gene rearrangement, which can make it resistant to standard immunochemotherapy.

Aims: To evaluate an efficacy of induction regimen R-CHOP/R-DA-EPOCH and modified BFM chemotherapy with rituximab in treatment of HGBL DH raised from FL.

Methods: We studied 13 FL pts with double- (9 - with *c-MYC/8q24* and *BCL2/18q21;* 4 - with *c-MYC/8q24* and *BCL6/3q27*) and one pt with triple translocations involving *c-MYC/8q24*, *BCL2/18q21* and *BCL6/3q27*

genes and deletion of 17p13. 10 pts had morphological signs of transformation into aggressive lymphoma; 4 pts had FL 3A. There was 8 women and 6 men aged from 30 to 60 y. o. (median 47 y.o.). Lymph node with the highest FDG-accumulation according to PET-CT was chosen for biopsy and consequent immunohistochemistry and cytogenetics.
The majority of pts had high 12/14 and 2/14 - high-intermediate FLIPI score. All pts had advanced (III-IV) stage according to Ann-Arbor classification. 3 out of 14 pt had a history of low-grade FL (16-96 months) without *c-MYC* rearrangement in primary biopsy samples, in other 11 cases - anamnesis varied from 0,5 to 4,0 months. Lymphoma manifested by rapidly spread aggressive tumor with bulky disease: 2 pts had leukemic presentation of FL; 1 pt had FL cells in cerebrospinal fluid; 12/14 out of pts had several extranodal sites of involvement such as ovaries (2/8), kidneys or adrenals (6/14), paranasal sinuses (1/14); bones (3/14); soft tissues (4/14); lungs (3/14); stomach or intestine (4/14); spleen (4/14); liver (1/14). Ki-67 varied from 40 to 90%. An expression of c-MYC protein higher than 40% in 11/13 of FL pts. We didn't revealed *TP53* mutation within 7 out of 7 analyzed pts.
Results: None of pts had previous therapy. 4 pts were treated with R-CHOP-21. 3/4 (75%) out of pts died due to progressive disease (PD), 1/4 (25%) had partial remission (PR) after consequent therapy including obinutuzumab. 7 pts underwent modified BFM-protocol with Rituximab. 6/7 (86%) out of pts achieved complete remission (CR) after first-line treatment, 1 pt died due COVID-19 in PD status (14%). Autologous stem cell transplantation (auto-SCT) was performed in 4 out of 7 pts. 3 pts underwent R-DA-EPOCH. 1 pt achieved a CR after 6 courses, 1 pt - after second-line 2 R-DHAP; auto-SCT was performed for consolidation. 1 pt (33%) had PD after R-DA-EPOCH and another therapy. Rituximab supportive treatment was administrated only in 4 cases due to epidemiological situation. Median of observation was 9 months (1,0-59,5). We couldn't study *TP53* mutation status in pts with PD, but we observed PD in one case with deletion of 17p13.
Summary/Conclusion: For better diagnostics of FL transformation into HGBL DH we should perform biopsy of lymph node with the most active FDG accumulation according to PET-CT. We observed a higher rate of CR in this pts cohort when treated with intensive induction immunochemotherapy (modified BFM chemotherapy with rituximab) in comparison with R-CHOP/R-DA-EPOCH (86% vs 25% and 33%, respectively), and lower rate of primary resistance/PD (14% vs 75% and 33%). Our data needs consequent confirmation or consideration within metanalysis due to rare diagnostics of FL with double translocations of *c-MYC* and *BCL2/BCL6*. We should initiate a randomized study to estimate if auto-SCT had any benefits in comparison with a new immunotherapy modalities in FL transformed into HGBL DH.

EP565 DEVELOPMENT AND VALIDATION OF A PROGNOSTIC NOMOGRAM FOR PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is rare, and most patients present with large anterior mediastinal tumors that progress rapidly. In PMBCL, the predictive effectiveness of the International Prognostic Index (IPI) is limited by the age composition of the disease and the fact that lesions are usually confined to the mediastinum. This is reflected clinically by the fact that more than half of the patients exhibit lower IPI score. Therefore, a new risk stratification profile is needed to guide the prognostic stratification of PMBCL patients. In addition, the certainty of existing models needs further validation in the era of modern treatments. The nomogram, as a graphical representation of a mathematical model, can be used in clinical practice to combine different information from various features to predict specific outcomes. By combining various important factors, a nomogram can estimate the feasibility of each patient event, such as the likelihood of death or recurrence. Thus, the nomogram has developed into an important tool for predicting clinical outcomes in various types of cancer and can provide physicians with optimal treatment options.
Aims: Our goal was to develop a reliable nomogram to predict overall survival (OS) and progression free survival (PFS) in patients with PMBCL.
Methods: Based on data from Sun Yat-Sen University Cancer Center and the First Hospital of Guangzhou Medical University,116 patients diagnosed with PMBCL were enrolled in this study. Independent prognostic factors were screened by Cox regression analysis. R-coding was used to construct nomograms predicting OS and PFS. Discriminations and corrections of the new model were evaluated using the consistency index (C-index), subject operating characteristic curves (ROC) and calibration curves, and compared with the conventional International Prognostic Index (IPI) using decision curve analysis (DCA) to assess its accuracy and benefit.
Results: Multivariate models showed that post-treatment Deauville score, Ann Arbor staging and hemoglobin level were significantly associated with PFS, while post-treatment Deauville score, MUM1 expression and Ki67 index were significantly associated with OS, and the corresponding nomograms were plotted. In the training cohort, the C-index of the nomogram for PFS and OS was 0.833 and 0.931, respectively. The C-index of the validation cohort was 0.649 and 0.661, respectively. The calibration curves of the nomogram also showed high predictive accuracy. Compared to the IPI scores,the C-index and ROC curves of the Nomogram had better results and also showed better results in the decision curve analysis, yielding better net benefits.

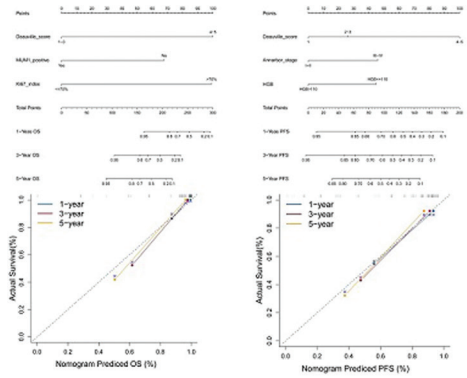


Figure Nomogram for predicting the 1-, 3-, and 5-year OS and PFS of PMBCL.

Summary/Conclusion: In summary, we have successfully established a valid nomogram for predicting OS and PFS in PMBCL patients, which can help clinicians to select appropriate individualized treatment for their patients.

Bleeding disorders (congenital and acquired)

EP566 EFFICACY AND SAFETY OF EFGARTIGIMOD PH20 SUBCUTANEOUS IN ADULT PATIENTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA: ADVANCE SC, A GLOBAL PHASE 3 CLINICAL TRIAL IN PROGRESS

V. McDonald [1,*], C. Broome [2], S. Jain [3], S. Babu [4], E. Oliva [5], W. Parys [6], A. Hultberg [6], K. De Beuf [6], D. Gandini [6], Y. Miyakawa [7], W. Ghanima [8]

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Background: Primary immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by a low platelet count, increased risk of bleeding and fatigue. Immunoglobulin G (IgG) autoantibodies directed against platelet surface antigens can be detected in most patients with ITP. These autoantibodies accelerate platelet clearance, can inhibit platelet production, and may impair platelet function. IgG homeostasis is regulated by the neonatal Fc receptor (FcRn). Efgartigimod, a human IgG1 antibody Fc-fragment, is a natural ligand of the FcRn engineered to competitively bind to FcRn and prevent the recycling of endogenous IgG. In a Phase 2 trial in 38 patients with primary ITP, efgartigimod 5 mg/kg or 10 mg/kg administered in 4 weekly IV infusions was well tolerated compared to placebo (Newland AC. *Am J Hematol*. 2020;95:178-187. NCT03102593). Efgartigimod induced a rapid reduction of total IgG levels (up to 63.7% mean change from baseline), which was associated with clinically relevant increases in platelet counts (38% vs 0% achieved ≥50×10^9/L for at least 10 cumulative days), and a reduced proportion of patients with bleeding. These data warrant further evaluation of FcRn antagonism as a novel therapeutic approach in ITP. A subcutaneous (SC) formulation (efgartigimod PH20) has been developed to offer additional flexibility and convenience for patients.

Aims: ADVANCE SC, a Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial (NCT04687072), will evaluate the efficacy and safety of efgartigimod PH20 in adults with persistent or chronic ITP.
Methods: Eligible patients must have a mean platelet count <30×10^9/L over a minimum of 3 qualifying platelet evaluations and have received at least 2 prior ITP treatments or 1 prior and 1 concurrent treatment, with response to at least one. Patients will enter a 24-week treatment period and receive SC treatment with either efgartigimod (fixed dose of 1,000 mg) co-formulated with PH20 (recombinant human hyaluronidase PH20, an enzyme used to increase the dispersion and absorption of co-administered substances when administered SC) or matching placebo (randomization 2:1). Permitted concurrent ITP treatments include corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib and/or oral TPO-RAs. Efgartigimod PH20 or placebo PH20 will be given weekly from visits 1 to 4 and then either weekly or every other week from visits 5 to 16, as determined by platelet counts. Dosing schedule will be fixed from visits 17 to 24. The primary endpoint is the proportion of patients with a sustained platelet count response defined as platelet counts of ≥50×10^9/L for at least 4 of the 6 visits between study weeks 19 and 24 (study visits 20 to 25). Secondary endpoints include overall platelet count response, safety and tolerability, bleeding severity, use of rescue therapy, quality of life and patient-reported outcome measures, and the immunogenicity and pharmacokinetic/pharmacodynamic effects of efgartigimod PH20. Efficacy analyses will be performed on the full analysis set, consisting of all randomized patients. Safety will be assessed in all patients who receive ≥1 dose of study treatment.
Results: ADVANCE SC recruitment is ongoing with a target of approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP across approximately 170 sites in Asia-Pacific, Europe, Japan, Latin America, Middle East, Africa and USA.
Summary/Conclusion: Trial participants will be eligible for continuation into ADVANCE SC+, a long-term open-label extension trial.

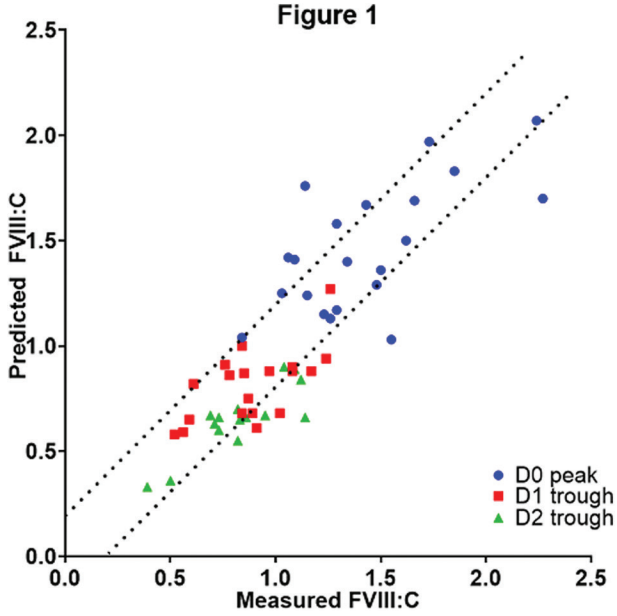
EP567 PERI-OPERATIVE PK-GUIDED DOSING OF DESMOPRESSIN COMBINED WITH FVIII CONCENTRATES IN HEMOPHILIA A: FINAL RESULTS OF THE DAVID STUDY

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Background: Patients with non-severe hemophilia A can perioperatively be treated with desmopressin or factor VIII (FVIII) concentrate. Desmopressin produces an increase of FVIII plasma levels. However, interpatient variability in the FVIII response is high. If the response is sufficient, minor procedures can be performed with desmopressin only. In case the response is insufficient, FVIII concentrate needs to be administered. The 2020 WFH guideline states that this combination therapy can overcome downsides associated with use of only DDAVP or FVIII concentrate. However, treatment of desmopressin combined with FVIII concentrate is not common practice and difficult to implement. Furthermore, as desmopressin is less expensive than FVIII concentrate, combination therapy may lead to considerable FVIII savings and would be useful in case of limited FVIII concentrate resources.
Aims: To assess accuracy, safety and FVIII concentrate savings of peri-operative pharmacokinetic (PK)-guided dosing of desmopressin combined with FVIII concentrate in non-severe hemophilia patients.
Methods: Hemophilia A patients responsive to desmopressin undergoing a procedure were included. Desmopressin was administered intravenously (0.3 µg/kg) once a day. Based on previously determined FVIII response on desmopressin, additional FVIII concentrate dosing was calculated using PK-guidance. Modelling technique was continuously adapted and improved based on study data. Desmopressin was administered for a maximum of three consecutive days. FVIII activity was determined before and after combination therapy (trough and peak levels). Hypothetical FVIII concentrate loading dose was calculated, assuming an increase of 0.02 IU/ml per IU FVIII concentrate per kilogram bodyweight. A predicted FVIII level by the desmopressin-FVIII PK-model was considered accurate if difference between predicted and measured FVIII level was ≤ 0.2 IU/ml.
Results: Twenty-one procedures were performed in 20 hemophilia A patients, of whom 19 mild and 1 moderate. Median age was 47 years (interquartile range (IQR) 40 - 59). Model predictions were accurate in 13/21 (61.9%) pre-operative peak levels at day 0 (D0, day of surgery), 14/19 (73.7%) at day 1 (D1) and 13/17 (76.5%) at day 2 (D2) post-operative trough levels. Figure 1 describes model accuracy, comparing measured FVIII levels with predicted FVIII levels and with dotted lines signifying +/- 0.2 IU/ml. FVIII concentrate loading dose per patient was 1250 IU (median; IQR 1000 - 1750) lower than hypothetical loading dose. Two patients had bleeding complications, with both patients having supraphysiological (>1.0 IU/ml) FVIII activity at the time of bleeding.

Figure 1



Summary/Conclusion: Peri-operative combination therapy of desmopressin and FVIII concentrate under PK guidance in non-severe hemophilia A patients provides a feasible and accurate treatment in the majority of patients. This novel approach resulted in considerable FVIII concentrate savings.

EP568 APPLICATION OF THROMBOELASTOGRAPHIC MARKERS TO PREDICT THE SURVIVAL IN ACUTE TRAUMA PATIENTS.

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Background: Coagulopathic hemorrhage is one of the major modifiable causes of death in trauma. Despite its clinical significance, there is a lack of adequate tests to rapidly diagnose the various aspects of trauma-induced coagulopathy (TIC). Routine coagulation tests, such as PT, aPTT, fibrinogen, platelet count, D-dimer and FDP have a limitation in diagnosis of TIC. Thromboelastography (TEG) is the viscoelastic coagulation monitoring device that measures the entire clotting cascades from fibrin polymerization to fibrinolysis.
Aims: This study aimed to investigate factors related to mortality and blood transfusion requirements based on coagulation profile with fibrinolytic status using thromboelastrography in trauma patients.
Methods: We included 452 trauma patients who visited the trauma center of Uijeongbu St. Mary's Hospital. Citrated blood samples were

analyzed using the TEG 5000 Thrombelastography Hemostasis Analyzer (Haemonetics, Niles, IL). The following indices were obtained from the TEG: R-time, K-time, α-angle, maximum amplitude (MA), and lysis 30 minutes after MA (LY30). Patients were stratified based on LY30% results into fibrinolysis shutdown (SD) (LY30% <0.8%), physiologic fibrinolysis (0.8-3.0%), and hyperfibrinolysis groups (LY30% >3.0%) Also, we investigate transfusion requirement and mortality during hospitalization period.
Results: The mean age was 52.3 years and the mortality rate was 39/452 (8.6%). Lower GCS, longer TEG K-time, and lower TEG MA were independent factors associated with mortality. The lower MA group demonstrated the highest probability of survival (odds ratio 0.207), followed by prolonged R-time (odds ratio 0.220). The patient numbers in fibrinolysis shutdown (SD), physiologic fibrinolysis and hyperfibrinolysis groups were 219 (52.3%), 131 (31.4%), and 68 (16.3%), respectively. The mortality rates of fibrinolysis SD group (11.9%) and hyperfibrinolysis (8.8%) were higher than the physiologic fibrinolysis groups (3.8%). The cutoff obtained from ROC analysis was found to be suitable for predicting survival. R-time, MA, and LY30 were effective to predict survival or death when applying the cutoff value from the ROC analysis (Table 3A). About probability (comparison of prediction power) of survival, the lower MA group (under the cutoff level) showed the highest probability of survival (odds ratio 0.207), followed by prolonged R-time (odds ratio 0.220).The transfusion requirements were significantly higher in the fibrinolysis SD group than in the other two groups.
Summary/Conclusion: TEG based markers were shown to be more useful to make a diagnosis coagulopathies including dysfibrinolysis and predict the survival than routine coagulation tests. Dysfunctional fibrinolysis showed higher mortality than physiologic group. If multiple integration of each TEG markers are used, it would be helpful for prompt diagnosis and management of coagulopathies and to decrease a preventable death in trauma.

EP569 POPULATION PHARMACOKINETIC MODELING OF FACTOR CONCENTRATES IN HEMOPHILIA: A DETAILED OVERVIEW FOR CLINICIANS AND EVALUATION OF OUR BEST PRACTICE.

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Background: The accuracy of pharmacokinetic (PK)-guided dosing of factor concentrates in hemophilia A and B patients is dependent on the clinical and laboratory data used to construct the applied population PK model, next to the individual PK profile of the patient.
Aims: This review aims to supply a detailed overview of the data used for these models as reported in literature and to evaluate best practice, in order to enable physicians to establish which models best suit the individual patient.
Methods: A literature search was performed on PubMed; publications describing prophylactic population PK models for factor VIII (FVIII) or factor IX (FIX) concentrates based on original patient data and constructed using non-linear mixed-effect modeling (NLMEM) were included. The following data was collected: detailed demographics of study populations, severity of hemophilia, type of product, assessed and included covariates, laboratory specifications and validation of models. According to our recommendations of best practice, included models were scored on 10 criteria as complete (+), incomplete (±) or absent (-) to evaluate their quality. Figure 1 depicts the evaluation of our best practice.
Results: This review comprehended twenty and seven models for FVIII and FIX concentrates respectively. Although most models (22/27) included pediatric patient, only four models reported complete pediatric demographics. The wide range of body weight suggested that overweight and obese adults were represented in the models. However, other morphometric variables (mostly BMI) were described in only 13/27 publications. Almost all models (26/27) reported the applied assay to measure the factor level, whereas only 15 models specified the reagent. Eight models were validated using a second dataset.

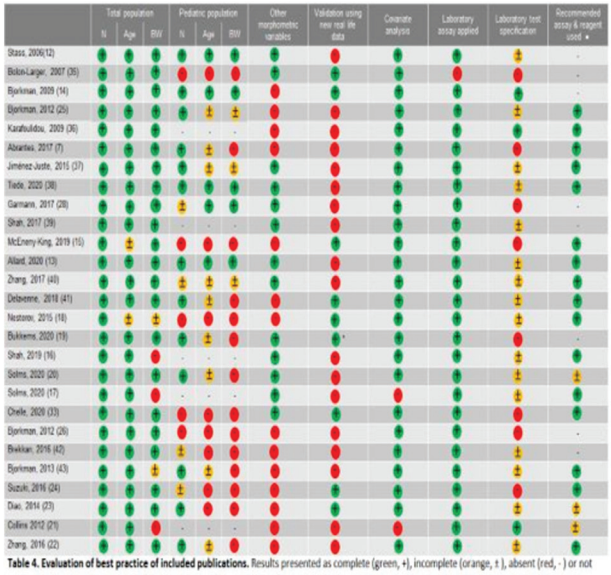


Table 4. Evaluation of best practice of included publications. Results presented as complete (green, +), incomplete (orange, ±), absent (red, -) or not applicable (-). N: Number of subjects. BW: body weight. HT: height. ● According to UK guidelines Grey et al Haemophilia 2020. * Bukkems et al. have externally validated the model of Nesterov et al.

Summary/Conclusion: This evaluation of available prophylactic population PK models for FVIII and FIX shows a wide variation in detail of included clinical and laboratory data used to construct these models. We provide an overview and give recommendations with regard to best practice to increase the reliability of PK-guided dosing of factor concentrates for prophylaxis in hemophilia A and B.

EP570 FACTOR XI DEFICIENCY IN PREGNANT WOMEN: A GENOTYPE TO PHENOTYPE CORRELATION AND ANALYSIS

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Background: Factor XI (FXI) deficiency (FXIDef) is an otherwise rare bleeding disorder that commonly affects Ashkenazi and Iraqi Jews, with a homozygous prevalence of 1:450, and a heterozygosity rate of 8%. In the general population, however, heterozygosity rate is estimated to be 1%. Pregnancy in these women poses a potential increased bleeding risk during delivery.
Aims: We describe the experience of an Outpatient Hematology Service in New York to which pregnant women with FXIDef are referred. Different genotypes of FXIDef and their impacts on patients' phenotypes were analyzed.
Methods: We identified 39 patients with FXIDef evaluated by a single provider between October/2016 and February/2020. Diagnosis was established on routine genetic screening during pregnancy. Epidemiological, clinical, and laboratory data were reviewed. Anesthetic modalities and routes of delivery were also extracted from the records. FXI activity (FXIAct) was measured at initial visit, and near term, at approximately gestational week 37. Basic statistical data for relevant parameters were calculated. Comparisons between FXIAct at first visit and near term, and between genotypes, were made with two-sample T-test.
Results: In the sample, 61.54% presented mutation c.901T>C, p.F301L (c.901); 28.20% had mutation c.403G>T, p.E135X (c.403); and 10.26% had 4 different mutations. In the c.901 group, 87.5% showed Jewish ancestry, while 72.73% in the c.403 group presented this ancestry. No statistically significant difference (p=0.43) in FXIAct at first visit was seen between the commonest mutations, also without difference near term (p=0.45). Comparing FXIAct between the first appointment and near term within the c.901 group showed no significant difference (p=0.96), and no difference was noted when comparing the same parameters within the c.403 group (p=0.29). Most patients had a normal vaginal delivery, with no complications recorded, with no need for therapeutic interventions secondary to excessive bleeding. One patient (c.901 group) received a prophylactic intervention before delivery, receiving intravenous tranexamic acid before delivery due to a FIXAct of 42%. Only a single patient from our analysis was homozygous, and she presented mutation c.901. This patient did not receive any special prophylactic or therapeutic interventions before or during delivery. See the attached table for further data.

	c.901T>C, p.F301L	c403G>T, p.E135X
Number of patients (n)	24	11
Mean Age (years)	33.12 ± 3.94	33.91 ± 3.83
Number of homozygous patients (n; %)	1; 4.2%	0; 0%
Jewish ancestry (n; %)	21; 87.5%	8; 72.73%
Mean FXI activity on 1st appointment (%)	54.92 ± 18.68	68.00 ± 51.69
Mean aPTT on 1st appointment (s) (normal range: 24.6- 34.7s)	30.90 ± 3.19	31.85 ± 2.51
Mean INR on 1st appointment (normal range: 0.9-1.1)	0.97 ± 0.07	1 ± 0.04
Mean Platelets on 1st appointment (x10⁹/L) (normal range: 150-450x10⁹/L)	234.96 ± 32.16	211 ± 40.55
Mean FXI activity near term (%)	55.26 ± 23.13	50.11 ± 11.13
Mean aPTT at birth (s)	30.04 ± 2.16	30.48 ± 2.54
Mean Blood Loss on Delivery (mL)	348.89 ± 198.60	290.25 ± 68.26
Mean Postpartum Blood Loss (mL)	103.12 ± 245.78	28.67 ± 52.60
Neuraxial Anesthesia (n; %)	15; 62.5%	5; 45.45%
Normal vaginal delivery (n; %)	20; 83.3%	11; 100%

Summary/Conclusion: No significant differences were noted between genotypes in our series. Genotypes correlate with ethnicity, with mutations c.901 and c.403 associated with Jewish ancestry. Comparing our data with other cohorts may allow for broadening of the finding that different genotypes do not affect presentation during pregnancy. Nonetheless, monitoring for FXIDef allows for prophylactic treatment in cases of increased bleeding risk, and it also contributes when deciding the best type of anesthesia for these patients, as neuraxial block is usually contraindicated in cases with FXIAct <40% in our institution. Therefore, genetic tests are valuable for counseling and diagnostic purposes, as well as measuring FXIAct is still relevant in pregnancy. However, as no significant difference in FIXAct was noted between initial visits and near term visits, similar to what has been described in other cohorts, reassessing FXIAct throughout pregnancy may not be necessary. Further studies and continuation of this project will assist in answering this question.

EP571 ACQUIRED VON WILLEBRAND DISEASE: THE DIAGNOSIS AND MANAGEMENT OF AN UNDERDIAGNOSED COAGULOPATHY

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Background: Acquired Von Willebrand Syndrome (AVWS) is a rare acquired coagulopathy, often associated to an underlying disorder (lymphoproliferative, cardiovascular, myeloproliferative, neoplastic, and autoimmune disorders). The diagnosis is not easy and relies on a negative familial and personal clinical hemorrhagic history and a late onset in life of bleeding symptoms, associated with a laboratory pattern for Von Willebrand Disease (VWD).
Aims: Aim of this study is to describe the experience on diagnosis and management of AVWS patients (pts) in two Italian centers.
Methods: Between 2004-2020 we have diagnosed and managed 14 pts [8F, 6M; median age 62.45 years (45.4-85.9)] affected by AVWS. Determination of coagulation parameters, including FVIII, were carried out on an automatic coagulometer (ACL Top 700, Werfen). VWF:antigen (VWF:Ag) and VWF:activity (VWF:RCo) were measured by chemiluminescence assays (HemosIL AcuStar, Werfen). VWF propeptide (VWFpp) level was measured by ELISA immunoassay (Sanquin, Amsterdam, NL). The screening for VWF:RCo inhibitor was made utilizing mixing studies
Results: Reasons for diagnosis were: recent onset of bleeding symptoms in 9 pts, increased aPTT in 5. At diagnosis, for all pts we observed these results: median VWF:Ag 15%, range 1.6-51% (n.v. blood group 0: 41-101%; no 0: 50-130%); median VWF:RCo 13%, range <6.25-33% (n.v. blood group 0: 41-97%; no 0: 52-124); median FVIII:C 19.2%, range 2.1-53% (n.v.58-130%)]. VWF:RCo inhibitor was searched in 4 cases: 3 were negative, 1 positive. We could study VWFpp and multimers in 9 pts. Except VWFpp median level (81.5%, range 42.9-154.3) all other VWF-related median parameters (VWF:Ag, VWF:RCo and FVIII:C) were significantly reduced in patients, respectively 7.3%, 4.5% and 15.2%. VWFpp/VWF:Ag ratio was significantly higher in all 9 patients: 20 (n.v.<3). Multimers were absent in 6 pts, normal in 2; in 1 patient were present just low molecular weight multimers. All the pts did not have either a family or past personal history of bleeding disorders/symptoms. The spontaneous hemorrhagic events presented at diagnosis and during follow up were: GI and gum bleeding, muscle hematomas, hematuria, ecchymoses, epistaxis. Three pts bled after dental extractions/procedures, although they were prophylactically treated with VWF/FVIII concentrate. Desmopressin, Tranexamic Acid, VWF/FVIII concentrate and recombinant FVIII were used as prophylaxis or treatment of bleedings in all pts, with variable responses on clinical symptoms. Thirteen/14 cases showed a concomitant disorder: 1 gastric B cell MALT lymphoma, 1 indolent B cell lymphoma, 7 MGUS, 2 Waldenstrom Disease and 2 patients with breast cancer and concomitant MGUS. In one case AVWS was idiopathic. In the table, therapies either for underlying disorders if present or AVWS and outcomes are shown.

Management of the patients with lymphoproliferative disorders		
Type	Treatment	Response
Gastric B cell MALT lymphoma	Rituximab	Complete remission of lymphoma and AVWS
Waldenstrom Disease (1st patient)	R-CVP Ibrutinib	After 2nd line, stable lymphoproliferative disease and persistent AVWS
Waldenstrom Disease (2nd patient)	Rituximab After two years for disease progression: Rituximab+- Bendamustine	Partial response Persistent AVWS and partial response of lymphoma
Indolent B cell lymphoma	watch and wait strategy Rituximab	 Complete remission of lymphoma and AVWS
Strategies to manage AVWS in all patients		
Type of disorder	Treatment	Response
MGUS 1 patient	Prednisone + cyclophosphamide and then high dose immunoglobulins	No response to either therapies
MGUS 3 patients	infusion of high dose immunoglobulins (2 cases are under chronic treatment with iv Ig every 6-8 weeks)	Transient CR as regard VW disease laboratory
MGUS 4 patients	No treatment	
1 patient with breast cancer	prednisone	Response to bleeding's symptoms
Idiopathic AVWS	Prednisone At relapse Prednisone + cyclophosphamide	CR on VW disease laboratory parameters CR on VW disease laboratory parameters

Summary/Conclusion: AVWS is a rare syndrome, probably underdiagnosed because unrecognized. AVWS must be suspected whenever a patient presents with a late onset in life of bleeding symptoms associated to laboratory characteristics compatible with VWD. The VWFpp/VWF:Ag ratio could be a valuable biomarker to be considered in these complicated diagnoses. It is mandatory to search for concomitant diseases.

EP572 INVESTIGATION OF PRETERM INTRAVENTRICULAR HEMORRHAGE-INDUCED INFLAMMATORY RESPONSE AND MICRORNA LEVELS IN HUMAN CHOROID PLEXUS EPITHELIAL CELLS

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Background: Intraventricular hemorrhage (IVH) is a severe complication of prematurity that results in an increased risk of neonatal mortality and neurodevelopmental impairment. After preterm IVH, subsequent destruction of red blood cells (RBC) and oxidation of extracellular hemoglobin (Hb) with the release of heme may cause a local inflammation with cellular dysfunction in the subarachnoid space. We have recently reported elevated expression of pro-inflammatory cell-free microRNA (miRNA) in cerebrospinal fluid (CSF)

samples obtained from preterm infants with grade III or IV IVH in correlation with high levels of oxidized Hb forms and soluble adhesion molecules.
Aims: In this study, our aim was to investigate the IVH-induced inflammatory cellular events in human choroid plexus epithelial cells (HCPEpiC) among *in vitro* conditions.
Methods: Primary HCPEpiC cell cultures were first exposed to CSF samples of preterm infants with IVH vs. clinical control samples (10 v/v %) for 24 hours. To observe the direct effect of hemorrhage, cells were treated with heme (25 µM) or TNF-α (100 ng/mL) as a positive pro-inflammatory agonist for 1-24 hours. After treatment, total RNA was extracted using TRI reagent, and HMOX1, IL8, IL1B, VCAM1 and ICAM1 messenger RNA (mRNA) expression were quantified by RT-qPCR. miR-155 and miR-223 were also analyzed intracellularly and in the supernatants of the cells using normalization to "spike-in" cel-miR-39. Concentrations of soluble IL-8, VCAM-1 and ICAM-1 were measured by ELISA. Nuclear translocation of the NF-κB p65 subunit was investigated with fluorescence microscopy. Cell viability was evaluated using MTT assay and via the measurement of LDH leakage in cell culture medium.
Results: Exposure to IVH CSF samples a substantial cell activation was triggered in HCPEpiCs with significant elevation in HMOX1, IL8, IL1B and ICAM1 mRNA expression in comparison to controls. Interestingly, VCAM1 mRNA level did not change after 24 hours. When cells were preincubated with heme, there was a time-dependent up-regulation in IL8, IL1B and ICAM1 mRNAs in the presence of induced *HMOX1* expression. Furthermore, significantly elevated protein levels of IL-8 and ICAM-1 were observed similar to TNF-α. Importantly, both mediators induced the nuclear translocation of the NF-κB p65 subunit. The expression of miR-155 and miR-223 were elevated in the cell culture supernatants after treatment with heme and TNF-α that underlines our former results in IVH CSF. In contrast, intracellular miR-223 was decreased, which may be related to up-regulated *ICAM1* expression. Based on the results of cell viability assay and LDH leakage, we did not find any substantial heme- or TNF-α-induced cellular damage in our experimental conditions.
Summary/Conclusion: In IVH, choroid plexus epithelial cells are highly affected by the consequences of bleeding that may contribute to the development of different complications of the disease.

EP573 THE ANALYSIS OF THE TREATMENT OUTCOME OF PATIENTS WITH ACQUIRED HEMOPHILIA IN CROATIA

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Background: Acquired haemophilia A (AHA) is a rare autoimmune disease, caused by antibodies (inhibitors) against coagulation FVIII and characterized by spontaneous hemorrhage in patients with no previous history of bleeding. Risk factors for the occurrence of AHA include advanced age and underlying diseases (malignancy, autoimmune disorders, pregnancy, and the postpartum period).
Aims: The aim is to analyze treatment outcomes of patients with acquired hemophilia A during the last ten years at the University Hospital Center Zagreb.
Methods: We analyzed retrospectively treatment outcomes of patients with AHA in the Department of Hematology, University Hospital Center Zagreb from 2010-2020. Response to treatment was assessed as partial (PR) or complete remission (CR).
Results: We analyzed the outcomes of twenty patients (11 (55%) male, 9 (45%) female), median age was 68 (33-81) years, and with median FVIII activity 5 (1 – 15) IU/dL and median inhibitor titer at the time of AHA diagnosis was 9 (2,3 – 2000) BU/ml. Severe bleeding had 75 % patients requiring erythrocyte transfusion. In 12 patients (60%) were identified underlying diseases: malignancies 2 (oligodendroglioma, B-CLL), autoimmune diseases 9 (autoimmune haemolytic anaemia - 2 rheumatoid arthritis - 2, polymyalgia rheumatica - 3, pemphigus -1 and myasthenia -1). One patient had postpartal AHA. The last female patient with myasthenia was diagnosed in December 2020. and she developed COVID19 bilateral pneumonia with ARDS. 90% of patients recieved hemostatic treatment (65 % - aPCC, 10% aPCC and rFVIIa, 25 % - rFVIIa). All patients were treated with immunosuppressive therapy, combination of cyclophosphamide and steroids in 18/20, steroids alone in 2/20 patients, while 3/20 patients (15%) were treated in the second line therapy. The response rate to the first line eradication therapy was 90%. Inhibitor eradication time was 18 (3-300) days, time to achieve CR was 32 (15-300) days. At follow up of 31 (1-90) months 13 patients (65%) are alive, 7 (35%) dead. No death was due to bledding. Two patients died of pneumonia, two deaths were associated with sepsis, one with progressive malignant disease and one with cardiogenic shock. One female patient died of COVID19 at the age of 55 years, 25 days after AHA was diagnosed. Higher inhibitor activity, known underlying cause of AHA with advanced age, comorbidities were unfavourable factors of survival.
Summary/Conclusion: Our treatment outcomes are very similar to the large European Registries, with the quite high response rate of eradication therapy in the first line treatment (90%). Infective complications and comorbidities were the leading causes of death. Patients with AHA and COVID19 could have a worse outcome due to immunosuppressive therapy.

EP574 HAEMOPHILIA B LEYDEN, AN AGE-RELATED MECHANISM FOR AN INCREASE OF FACTOR IX: CASE REPORT AND LITERATURE REVIEW

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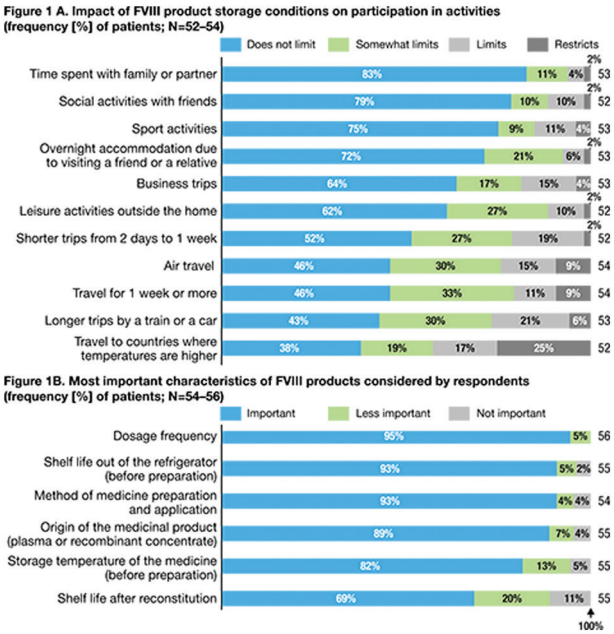
Background: Haemophilia B is a male-dominant human bleeding disorder that it is produced by mutations at the F9 gene located at Xq27; and it is characterised by reduced levels of factor IX. Haemophilia B Leyden is a subtype of haemophilia B with a phenotype of abnormal bleeding in the first period of life, increasing levels of factor IX during the puberty by an unknown and controversial mechanism. From previous assays it has been reported an 1.9% of patients with haemophilia B Leyden.
Aims: To visualize an unknown subtype of haemophilia B, and to underwrite the importance of the existence of the worldwide database to improve its knowledge.
Methods: We report clinical, phenotypical features of a clinical case of Haemophilia B Leyden in a newborn; and genotyping analysis of FIX performed by Sanger sequencing or Next Generation Sequencing according to local practice.
Results: At 2 days of age, the patient was referred to our centre because of an important bleeding after heel neonatal screening done in a regional hospital. There were no other localizations of bleeding at the time of the examination. During and after delivery no bleeding was observed. Laboratory assays revealed a prolonged activated partial thromboplastin time (APTT) with a reduced factor IX level of 1%. During follow-up the FIX:C has gradually increased (4% with 3 months and 6% with 8 months).
At 6 months of age, the patient suffered a mild head trauma after a fall. The patient waited for 24 hours to attend to the hospital. A brain computed tomography was performed, without any visible external bleeding. He was under active surveillance during 24 hours.
There was no history of haemophilia in his family. Genotyping analysis of FIX was performed by Next-Generation Sequencing (NGS) and a point mutation (c.-35G>A, variant NM¬_000133.) was detected, located in the F9 promoter region. The familiar study confirmed that his mother was a carrier. She had no history of bleeding and her FIX level was 163%.
Summary/Conclusion: Haemophilia B Leyden is an illness mediated by a genetic mechanism that produces an age-related increase in FIX levels. Patients with haemophilia B Leyden present a rise in the level of FIX, being this increase more pronounced after puberty. This mechanism is associated with growth hormone secretion, that is low during infancy and increases during early childhood until puberty, going the levels of FIX from the severe range to the mild, normal range progressively. This correction in plasma FIX levels occurs as well in female carriers of haemophilia B Leyden; according to this fact, an androgenic effect is not needed.
Thirteen different point mutations concerning haemophilia B Leyden have been identified, and just 35 cases with the c.35G>A variant have been reported in Factor IX Variant Database. Haemophilia B Leyden remains as a biological challenge, with more studies needed. In this respect, it is worth noting that the existence of a worldwide database can be very useful to improve our knowledge about this curious haemophilia.

EP575 HEMOPHILIA A SELF-MANAGEMENT – PATIENTS' PERSPECTIVES AND CHALLENGES

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Background: Despite major advances in the treatment of hemophilia A, limitations experienced by patients still remain. Good clinical treatment outcomes such as low annualized bleeding rates depend on careful patient adherence to the regimen of their factor VIII (FVIII) product. Another important aspect of patient self-management is portability and storage of recombinant FVIII (rFVIII) products. Patients with hemophilia A can benefit from the use of rFVIII products such as turoctocog alfa and turoctocog alfa pegol since, unlike other products, they can be stored at temperatures ≤40°C for ≤3 months.
Aims: To identify limitations regarding compliance, storage conditions and understanding of treatment with FVIII products among patients with hemophilia A.
Methods: Patients with hemophilia A in Slovenia who use different FVIII products completed a 10-minute, self-administered questionnaire comprising 22 questions. Questions focusing on patients' hemophilia burden, everyday limitations, their perceptions and understanding of FVIII product storage were included.
Results: Data were collected between February and July 2020. Of 63 individuals surveyed (n=61 patients, n=2 caregivers), most were >18 years old (59 patients, 94%), had severe hemophilia A (43 patients, 68%), were treated prophylactically (44 out of 60 respondents, 73%) and dosed 3 times per week (19 out of 37 respondents, 51%) with different FVIII products. Mean (median) numbers of bleeds within the current 12 months were 5.7 (3.0) and 2.3 (1.0) for prophylactically and episodically treated patients, respectively, due to severe disease for patients on prophylaxis. Almost half of the respondents (26 out of 56 respondents, 46%) reported missed or forgotten doses. Of the 21 prophylactically treated patients who had their pharmacokinetics (PK) assessed, the reported trough FVIII activity ranged from 0-24%.
Bleed frequency within the last 12 months was higher for patients reporting missed/forgotten doses (mean [median], 5.9 [4.0]) compared to those patients with no missed/forgotten doses (4.6 [3.0]) during the same period. Most patients (42 out of 53 respondents, 79%) stored their product in a refrigerator and believed that FVIII products should always be stored at ≤25°C (49 out of 54 respondents, 91%). Perceived storage conditions limited daily activities for 76% (42 out of 55 respondents) of patients; travel (business trips and work activities) was the activity most frequently impacted (**Figure 1A**). Forty-six patients (73%) indicated that treatment satisfaction would be improved by a FVIII product that could be stored at >25°C (reasons included improved convenience [29 respondents, 63%], improved quality of life [9 respondents, 20%] and fewer restrictions on activities [8 respondents, 17%]). Interestingly, there was no difference between younger and older patients. Most patients considered dosing frequency, shelf life out of the refrigerator and method of product preparation/application as the most important characteristics of their FVIII product (**Figure 1B**).



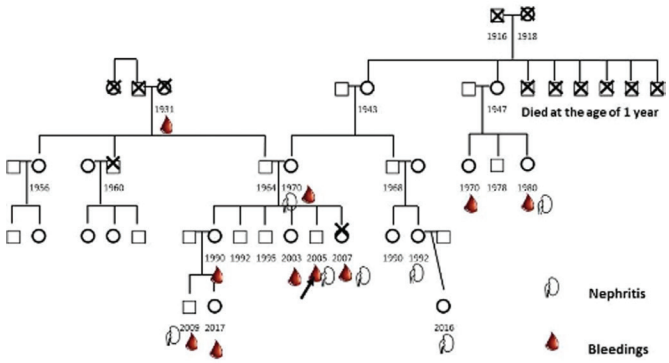
Summary/Conclusion: Patients of all ages with hemophilia A often feel restricted in their daily activities by the perceived need to store FVIII products at <25°C. These restrictions have an impact on adherence to treatment. From the patients' perspective, the most important FVIII product characteristics were dosage frequency followed by shelf life out of refrigerator. Improved patient awareness and understanding of FVIII treatment could improve compliance and treatment outcomes in patients with hemophilia A.

EP576 CONGENITAL COMBINED VITAMIN K-DEPENDENT CLOTTING FACTORS DEFICIENCY, CASE REPORTS

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Background: Congenital combined vitamin K-dependent clotting factors deficiency(VKCFD) is a very rare bleeding disorder, few cases have been described worldwide.
Aims: To describe clinical manifestations in 2 patients with bleeding disorder.
Methods: Retrospective medical chart review. Coagulation factor measurement was performed using standard kits and ACL TOP-700 coagulometer (IL, USA).
Results: 1st Patient: 12yo boy who had unexplained bleeding episodes from the age of 1 year (easy bruising, epistaxis) was admitted an outpatient unit of our Centre because of excessive bleeding. By the time of admittance he had already had recurrent episodes of joint bleedings (elbow, ankle and shoulder joint 2 times), haematuria 5 times, bleeding after tooth extraction, easy bruising, epistaxis, bleeding from oral cavity (PBQ=19). that required plasma transfusions. At the initial laboratory assessment combined PT and APTT with normal fibrinogen and vWF:Rco had been revealed. Intestinal malabsorption and severe liver dysfunction were excluded, and clotting factors activity(CFA) were measured: FII 12%(79-131), FIX 30,4%(65-150), FV 85,4%(62-139), FVII 4,8%(50-129), FX 12,5%(77-131), FXI 93,4 % (N 65-150), FXII 83,8% (N 50-150), protein S 43.1% (70-130), protein C 41% (70-140). An increase in the CFA was detected 24 hours after of subcutaneous 10 mg Vitamin K1 injection, with a rapid loss of response after 48 hours.
2nd patient, his sister, who has been suffering from recurrent mild haematuria and menorrhagia (PBQ=5) and debuted at the age of 3 years with haematuria also had low CFA: FVII 11,4%, FII 13%, FIX 24%, FX 8%. No mutations in *VKORC1* и *GGCX* genes using NGS were detected, so MLPA is planned. Other affected family members were suspected (Pic. 1).



Summary/Conclusion: The bleeding symptoms vary significantly even within the same family, despite comparable factor activity. No mutations in *VKORC1* и *GGCX* genes were found, which doesn't exclude VKCFD.

EP577 IS ANTI-NUCLEAR ANTIBODY POSITIVITY A FACTOR FOR AFFECTING TREATMENT RESPONSE IN IMMUNE THROMBOCYTOPENIA PATIENTS ON ELTROMBOPAG?

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Background: Immune thrombocytopenia (ITP) is an autoimmune disease characterized by a low platelet count which is caused by increased destruction of thrombocytes due to platelet autoantibodies and impaired platelet production.The antibodies that aim at proteins within the nucleus of a cell are called antinuclear antibodies (ANA). ANA positivity was reported between 25-39 % in studies conducted with ITP patients. Thereafter; testing for ANA was suggested as a test of potential utility according to the International consensus report on the investigation and management of primary immune thrombocytopenia. The first-line treatment of ITP consists of corticosteroids and IVIG. In patients who are corticosteroids dependent or do not have a response to corticosteroids; recommended treatment options are thrombopoietin receptor agonists (TPO-RAs), splenectomy, and rituximab. Eltrombopag and romiplostim are the currently licensed TPO-RAs for ITP. Eltrombopag is an orally available non-peptide TPO-RA and accessible in Turkey.
Aims: Despite being widely used, markers to show the response for eltrombopag are lacking and needed. In the present study, we tried to show the association between ANA positivity and eltrombopag response in ITP patients.
Methods: Patients who were diagnosed with ITP at Trakya University Faculty of Medicine Hematology Department between 01.01.2016 and 31.12.2020 and who received eltrombopag treatment due to their resistance to steroids and other treatments were included in our study. ANA measurement was made with indirect fluorescent antibody and titers of 1:160 and above were considered positive. Response criteria are listed as follows:complete response (CR): platelet count ≥100 × 10^9 / L and no bleeding, response (R): platelet count ≥30 × 10^9 / L and no bleeding, no response: defined as platelet count <30 × 10^9 / L or bleeding. For statistical analysis, SPSS 22.0 was used and a two-sided p-value below or equal to 0.05 was considered as statistically significant. Chi-square and Fisher's exact test was used in the analysis of variables. Chi-square contingency analysis was also performed due to lack of sample size.
Results: A total of 45 patients were included in our study. 33 were female and 12 were male. The mean age of the patients was 45, 73. There were 14 patients with ANA positivity and 31 patients found to be ANA negative. Response rates of the patients were evaluated according to their thrombocyte count during the treatment 1st month, 3rd month, and 6th month. One patient developed pulmonary emboli and grade 3 hyperbilirubinemia occurred in another patient while eltrombopag treatment and eltrombopag discontinued in both cases. Response rates were higher in ANA positive patients compared to ANA negative patients in the first and sixth months of the eltrombopag treatment ($p < 0.05$).

Response Rates According to ANA Positive and Negative Patients

	ANA positive N= 14	ANA negative N= 31	P value
1st Month			0,034
Complete Response	2 (14,3 %)	17 (54, 8 %)	
Response	9 (64,3 %)	9 (29, 0 %)	
No Response	3 (21,4 %)	5 (16, 2 %)	
3rd Month			0,640
Complete Response	7 (50 %)	21 (67, 7 %)	
Response	5 (35, 7 %)	6 (19, 3 %)	
No Response	2 (14, 3 %)	4 (13, 0 %)	
6th Month			0,019
Complete Response	7 (53, 8 %)	22 (73, 3 %)	
Response	4 (30, 8 %)	7 (23, 3 %)	
No Response	2 (15, 4 %)	1 (3, 3 %)	

Summary/Conclusion: Various autoimmune antibodies have been shown to be more positive in ITP patients than in people in the healthy normal population. Positive ANA test in ITP patients was associated with poor response to steroids and a more chronic disease outcome in retrospective studies. Our study population includes steroid resistant or dependent patients which could be a factor for low response rates seen in ANA positive patients. To conclude, ANA positivity in ITP may indicate unresponsiveness to eltrombopag treatment, and this should be supported by prospective studies involving more patients

EP578 NEW LIKELY PATHOGENIC VARIANTS IN THREE SPANISH PATIENTS WITH MILD HEMOPHILIA A AND B: GENETIC COUNSELING.

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Background: Mild hemophilia A (HA) and B (HB) are X-linked recessive hereditary diseases, characterized by factor VIII and IX deficiency, respectively. Patients with mild or moderate hemophilia mostly present specific mutations in *F8* gene (Xq28) or *F9* (Xq22), detectable by direct sequencing. More than 4000 mutations have been detected so far and genotype analysis should be offered in selected patients. Therefore, genetic assessment is important to provide reproductive options.
Aims: We report three new likely pathogenic variants in three male Spanish patients. Patient 1 presented asymptomatic prolonged pre-operatory aPTT and the others were studied due to hemorrhagic complications of surgery. All presented isolated reduced factor VIII or IX activity levels.
Methods: Molecular genetic studies: DNA was extracted from peripheral blood. Coding exons and adjacent intronic regions of F8 and F9 gene were amplified by polymerase chain reaction (PCR) and sequenced on Applied Biosystems® 3500DX Genetic Analyzer. The results were checked in HGMD, ClinVar, dbSNP, gnomAD, and 1000G international databases and different in silico prediction algorithms, such as: PolyPhen-2, SIFT, Mutation Taster, Align GVGD, REVEL and others were consulted.
Results: Three new missense variants were found (table 1). These variants have not been previously reported in the literature or in any of the databases consulted. They do affect the physical-chemical characteristics of the protein (*in silico* prediction). Therefore, they are classified as likely pathogenic. Because of this, we extended the study to first-degree relatives; finding carriers that were not diagnose at that time. A 20-year-old daughter (patient 1) and a sister (patient 2) received genetic counseling.

Patients	Hemophilia type	Age at diagnose (years)	Factor activity (%)	DNA variations				*In silico* prediction
				Gene	Exon	Amino acid (nucleotide) change	Genotype	
P1	A	42	13.3	*F8*	4	p.Val181Leu (c.541G>T)	hemizygous	4/4
P2	A	55	10.5	*F8*	3	p.Asp101Glu (c.303T>A)	hemizygous	4/4
P3	B	30	23.2	*F9*	7	p.Glu259Gly (c.776A>G)	hemizygous	12/16*

Table 1. **Genotypic results of the three patients.** *In silico* prediction algorithms used in the three cases: PolyPhen-2, SIFT, Mutation Taster and Align GVGD. *In patient 3 the following algorithms were also utilized: FATHMM, FATHMM-MKL, DEOGEN2, MVP, MetaSVM, MetaLR, DANN, Mut. Assessor, SIFT, SIFT4G, Provean, REVEL and GERP.

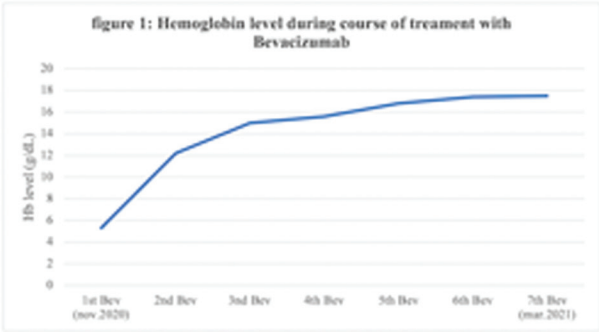
Summary/Conclusion: These new genetic variants confirm the clinical suspicion of mild hemophilia. The molecular genetic analysis in the family members helps finding asymptomatic carriers so we can provide them genetic counseling. Future reproductive options will be considered in the youngest patient and any family members if needed, firstly and foremostly, prenatal fetal sex chromosome testing by maternal plasma DNA sequencing on female carriers.

EP579 BEVACIZUMAB AND RESCUE TREATMENT FOR SEVERE GASTROINTESTINAL BLEEDING IN VON WILLEBRAND DISEASE

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Background: Von Willebrand disease (VWD) is a disorder predominantly attributable to a deficiency or dysfunction of the Von Willebrand factor (VWF) glycoprotein. It is typically characterized by recurrent episodes of mucocutaneous bleeding. Gastrointestinal (GI) bleeding associated with angiectasy is a rare but challenging complication which can result in frequent hospitalizations for red cell transfusion. Management options have been limited to off license use of anti-angiogenic and hormonal agents lacking supporting data. Since the discovery of elevated vascular endothelial growth factor (VEGF) expression in patients with VWD, reports of Bevacizumab, a monoclonal antibody against VEGF, in managing complications of VWD have emerged, with most of the reported experience in recurrent epistaxis. We present a case of VWD with refractory and progressive transfusion requirements secondary to severe GI bleeding that did not respond to conventional therapy.
Aims: Present a case of VWD with refractory transfusion requirements secondary to severe GI bleeding.
Methods: Clinical case report.
Results: A 60-year-old man with Type IIA VWD chronically medicated with VWF/FVIII prophylaxis and recurrent epistaxis, presented recurrent GI bleeding associated with small intestine angiectasies. Treatment with VWF/FVIII prophylaxis and octreotide resulted in only temporary cessation of bleeding and the patient had enduring transfusion weekly requirements with frequent need for hospitalization. Despite endoscopic and medical treatment attempts with hormonal agents and octreotide, the patient developed persistent hemorrhage and severe anemia, leading to red blood cell transfusions dependency. Subsequently he commenced on a course of Bevacizumab (5mg/kg, every 15 days). Immediately after initiating Bevacizumab, complete cessation of bleeding episodes was observed and hemoglobin levels anticipated a growing trend, as demonstrated in figure 1. The patient has been transfusion-independent since beginning anti-VEGF therapy. Currently, after 4 months of follow-up, he maintained sustained complete response without the occurrence of adverse events.



Summary/Conclusion: Our patient shown to gain noteworthy benefit from anti-VEGF therapy (Bevacizumab) with total transfusion independence and significant improvement in quality of life. This case illustrates the challenging nature of angiodysplasia-related GI bleeding in patients with VWD and shows that Bevacizumab seems to be a safe, well tolerated and efficient treatment in this group of patients. Nevertheless, the optimal dosage and duration of bevacizumab for GI bleeding in VWD, remains to be determined, and requires balancing the clinical benefits against potential adverse events of systemic treatment such as hypertension and thromboembolic events.

Bone marrow failure syndromes incl. PNH - Biology & Translational Research

EP580 ANTI-COX-2 AUTOANTIBODY AS A NOVEL DIAGNOSTIC MARKER IN APLASTIC ANEMIA

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Background: In immune aplastic anemia (IAA) severe pancytopenia results from the destruction of blood-forming cells by the patient's own immune system. Although the detailed pathomechanism is unknown, most of the experimental and clinical data point towards lymphocyte-mediated autoimmunity. A number of autoantibodies have been reported to associate with IAA, but no clinically applicable autoantibody tests are available for IAA diagnostics.
Aims: We sought to identify novel diagnostic autoantibodies in IAA.
Methods: A microarray containing more than 9000 full length proteins was used to identify autoantibodies from IAA patients' plasma samples. A sandwich immunoassay was developed to examine the presence of the novel autoantibody against cyclo-oxygenase 2 (COX-2) in a large IAA (n=334) and control cohort (n=791) including patients with other autoimmune diseases and healthy controls. Both linear and conformational COX-2 autoantibody epitopes were identified using an epitope mapping platform (PEPperPRINT). Publicly available single cell RNA-sequencing (sc-RNA-seq) datasets were reanalyzed to study COX-2 expression patterns in the bone marrow samples.
Results: The protein microarray-based screening method revealed anti-COX-2 antibodies (aCOX-2 Ab) in three out of the five tested IAA patients, but not in any of the control samples. In a larger confirmation cohort 37 % (124/334) of the adult (>18 yo) IAA patients were tested aCOX-2 Ab positive. No aCOX-2 Ab seropositivity was detected in the healthy controls (n=74), in patients with non-autoinflammatory diseases (n= 162), rheumatoid arthritis (n=51) or in LGL leukemia (n=68). Sporadic positive cases were observed in multiple sclerosis (n=2/98) and in type I diabetes (n=2/45) as well in closely related bone marrow failure diseases including myelodysplastic syndrome (MDS, n=2/75) and idiopathic thrombocytopenia (n=4/105).
Logistic regression analysis revealed that aCOX-2 Ab positivity was tightly associated with increasing age and with the HLA-DRB1*15:01 genotype. 83 % of the IAA patients over 40 years of age with the HLA-DRB1*15:01 genotype were aCOX-2 Ab positive, thus, indicating an excellent test sensitivity in this age group.
In most seropositive patients, the aCOX-2 Ab was confirmed as an IgG1 isotype antibody, while in some IAA patients an additional IgG3 isotype signal was observed. In seven out of the ten tested patients the antigenic epitope was linear, and it was mapped to the very C-terminal end of COX-2. In addition, conformational mapping with cyclic peptides revealed two additional C-terminal epitopes that were also mapped to the C-terminus of COX-2. Lastly, sc-RNA-seq revealed that *COX-2* was mainly expressed in hematopoietic stem cells (HSC) as well as in myeloid cells, mostly in monocytes. Interestingly, elevated *COX-2* expression levels were identified in IAA patients' HCSs when compared to healthy controls and MDS patients.
Summary/Conclusion: aCOX-2 Ab is a highly specific diagnostic tool for IAA and has a potential to become a routine biomarker in bone marrow failure diagnostics. HLA-association, isotype distribution, and expression pattern in the bone marrow suggest that it also may participate in the pathogenesis of IAA.

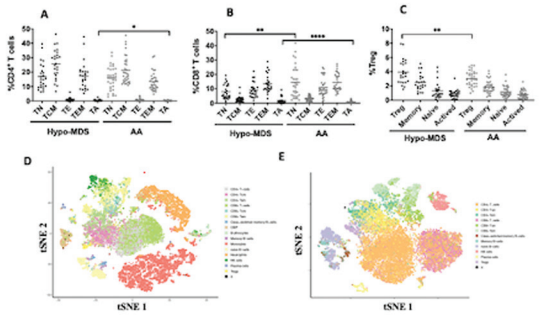
EP581 COMPARISON OF LYMPHOCYTE SUBSETS IN HYPOPLASTIC MYELODYSPLASTIC SYNDROMES AND APLASTIC ANEMIA

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Background: Both hypoplastic myelodysplastic syndrome (hypo-MDS) and aplastic anemia (AA) are bone marrow failure. Although they display multiple similarities in clinical characterizations, there are great differences in the treatment and prognosis. It is necessary to distinguish them. It is now well established that abnormal lymphocyte subsets play an important role in hypo-MDS and AA. However, there was no report about the difference of lymphocyte subsets between hypo-MDS and AA.
Aims: This study aims to compare the proportion of peripheral blood lymphocyte subsets between patients with hypoplastic myelodysplastic syndrome (hypo-MDS) and aplastic anemia (AA).
Methods: A total of 25 patients with hypo-MDS and 33 patients with AA were collected, and the proportions of peripheral blood T lymphocyte subsets, $CD3^-CD16/CD56^+$ NK cells and $CD19^+$ B cells were detected by flow cytometry. The landscape of infiltrating lymphocyte cells in hypo-MDS and AA were detected by single-cell sequencing.
Results: Although the proportions of total lymphocyte, $CD3^+$ T cells and $CD3^+CD8^+$ T cells were higher in AA patients than those in MDS patients, there was no significant difference. The $CD4^+/CD8^+$ ratio was statistically lower in AA than that in hypo-MDS ($P<0.05$). There were no significant difference in the proportions of $CD3^-CD16/CD56^+$ NK cells and $CD19^+$ B cells. Furthermore, we divided the $CD4^+$ T cells and $CD8^+$ T cells to five subgroups, which named naive T cell (TN), central memory T cell (TCM), effector T cell (TE), effector memory T cell (TEM), and activated T cells (TA), and the Treg to three subgroups, which containing memory Treg, naive Treg and activated Treg. The TA proportions of $CD4^+$ and $CD8^+$ T cells in AA patients were obviously lower than those in the hypo-MDS group ($P<0.05$ and $P< 0.0001$). The TN proportion of $CD8^+$ T cells in the AA patients was obviously higher than that in the hypo-MDS patients ($P < 0.01$). The Tregs in AA patients was obviously lower than that in hypo-MDS patients ($P<0.05$). There were no significant difference in other subgroups between AA and hypo-MDS patients. There was difference in the landscape of infiltrating lymphocyte cells in hypo-MDS and AA detected by single-cell sequencing.

Fig1



Comparison of lymphocyte subsets in Hypo-MDS and AA: $CD4^+$T cell subsets(A) ; $CD8^+$T cell subsets(B) ; Treg subsets(C);Landscape of infiltrating lymphocyte cells in hypo-MDS(D) and AA (E) by single-cell sequencing.
TN, naive T cell; **TCM**, central memory T cell; **TE**, effector T cell; **TEM**, effector memory T cell; **TA**, activated T cells

Summary/Conclusion: Changes of lymphocyte subsets and the different landscape of infiltrating lymphocyte cells can be utilized as indexes in the differential diagnosis between AA and hypo-MDS.

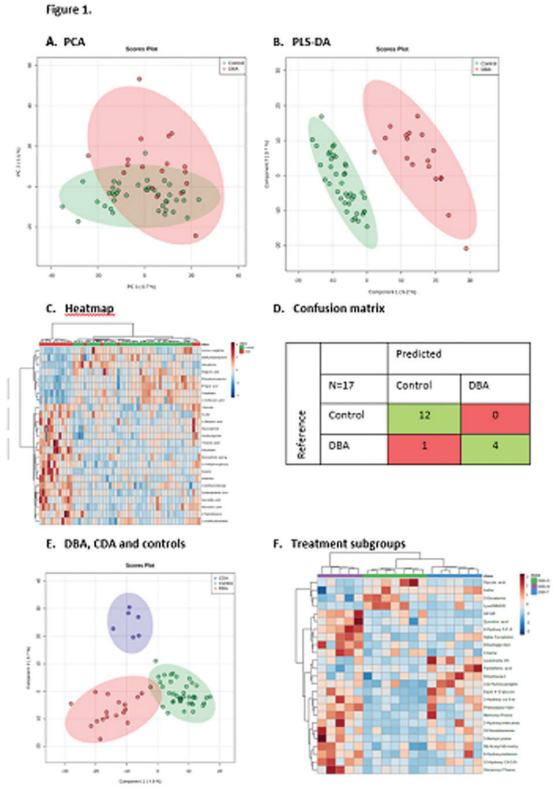
EP582 DRIED BLOOD SPOT METABOLOMICS REVEALS A METABOLIC FINGERPRINT WITH DIAGNOSTIC POTENTIAL FOR DIAMOND BLACKFAN ANEMIA

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Background: Diamond Blackfan anemia (DBA) is a rare inherited bone marrow failure syndrome characterized by erythroid hypoplasia, congenital malformations, growth defects and an increased risk of developing malignancies. From a clinical and genetic perspective the disorder is highly heterogeneous, and clear genotype-phenotype correlations are absent. Despite advances in our understanding of the genetic basis, the pathophysiology of DBA is still not fully understood. One of the major unresolved issues is how RP gene mutations result in the specific erythroid defect that characterizes DBA. Establishing the diagnosis of DBA can be particularly difficult since, in contrast to other IBMFS, no validated functional screening tests exists. Furthermore, the clinical presentation is highly heterogeneous, even within families with identical molecular defects. Currently, the diagnosis relies on consensus criteria and exclusion of other IBMFs and causes of anemia. In order to improve the diagnostic evaluation of DBA as well as our understanding of phenotypic heterogeneity and clinical severity, novel functional approaches are needed.
In this study we explore the potential of untargeted metabolomics on dried blood spots (DBS) to diagnose DBA.
Aims: Defining a metabolic signature for DBA from DBS, could **1.** Contribute to improvement of the diagnostic evaluation, and **2.** Increase our understanding of phenotypic heterogeneity and treatment response.
Methods: Untargeted metabolomics was applied on DBS samples obtained from 18 DBA patients and 40 healthy controls by direct infusion high resolution mass spectrometry using a previously established protocol (1,2). Statistical analyses were performed in MetaboAnalyst and predictive modelling was executed within R-software.
Results: A total of 1752 unique metabolite features were identified in the respective DBS samples from patients and controls. Distinct metabolic profiles were identified by principal component analysis and partial least squares discriminant analysis (Figure 1A-B). Distinctive metabolites in this metabolic fingerprint include methylmalonylcarnitine, inosine and threonic acid (Figure 1C). The metabolic fingerprint of DBA was incorporated into a machine learning algorithm, and a binary classification model was constructed using a training set. The model showed high performance characteristics (average accuracy 93.5%) and correct prediction of class was observed for all controls (n=12) and all but one patient (n=4/5) from the validation or 'test' set (accuracy 94%) (Figure 1D). Importantly, in patients with congenital dyserythropoietic anemia (CDA), an erythroid disorder with overlapping features, we observed a distinct metabolic profile, indicating the disease specificity of the DBA fingerprint and underlining its diagnostic potential (Figure 1E). Furthermore, when exploring phenotypic heterogeneity, DBA treatment subgroups yielded discrete differences in metabolic profiles, which could hold future potential in understanding therapy responses (Figure 1F).

Figure 1.



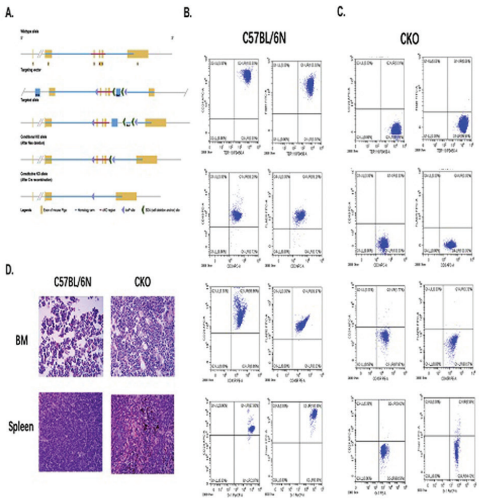
Summary/Conclusion: In this study we performed untargeted metabolomics in dried blood spots in a relatively large cohort of DBA patients with diverse genotypes and clinical phenotypes. We report here for the first time a specific metabolic fingerprint for DBA. By incorporating this fingerprint into a machine learning algorithm we demonstrate that untargeted metabolomics in dried blood spots is a promising new diagnostic tool for DBA.

EP583 A PIGA CONDITIONAL KNOCK-OUT MOUSE MODEL MEDIATED BY VAV-ICRE: STABLE GLYCOSYLPHOSPHATIDYLINOSITOL-DEFICIENT AND MILD HEMOLYSIS

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal disease caused by PIGA mutation of hematopoietic stem cells. Vav is a specific expression promoter of hematopoietic system, and hematopoietic system-specific knockout mice can be obtained by using Vav-iCre.
Aims: This study aims to construct an animal model with a PNH disease phenotype by using Vav-iCre targeted knockout of PIGA gene in the hematopoietic system.
Methods: C57BL/6N ES cells was used for gene targeting. Exon 3-5 was selected as conditional knockout region (CKO region) (Figure 1A). The KO allele was obtained after Vav-iCre-mediated recombination. Vav-iCre mediated deletion of the CKO region resulted in the loss of Piga gene function in mouse hematopoietic stem cells, thus a Piga conditional knockout (CKO) mouse model was constructed. Flow cytometry was used to detect the expressions of Glycosylphosphatidylinositol (GPI) and GPI-anchor protein (GPI-AP) on the surface of erythrocytes, granulocytes, T lymphocytes and B lymphocytes in peripheral blood of normal C57BL/6N mouse and CKO mouse. In addition, hemolysis related indicators (hemoglobin concentration (Hb), lactic dehydrogenase (LDH), total bilirubin (TBIL), indirect bilirubin (IBIL), free hemoglobin (FHb)) and mouse complement levels of C3a, C5a, and C5b-9 of normal C57BL/6N mouse and CKO mouse were measured. Finally, the spleen and bone marrow of two groups of mouse were taken for pathological examination.
Results: The expressions of GPI and GPI-AP in peripheral blood cells of normal C57BL/6N mouse were positive (Figure 1B) and were almost completely absent in CKO mouse (Figure 1C). What's more, the proportion of the deficiency remained stable from birth. In normal C57BL/6N mouse group, the Hb were (152.7±11.07)g/l, the level of LDH were (439.8±45.11)U/L, the level of TBIL were (1.868±0.646)μmol/l, the level of IBIL were (2.006±0.308)μmol/l,the level of FHb were (168.1±61.00)mg/l; in CKO mouse group, the Hb were (120.6±17.22)g/l, the level of LDH were (832.9±208.9)U/L, the level of TBIL were (3.830±0.493) μmol/l, the level of IBIL were (3.318±0.293) μmol/l,the level of FHb were (354.1±91.03)mg/l. The above hemolysis related indexes were statistically different between the two groups ($p < 0.0001$, $p=0.0034$, $p=0.0006$, $p=0.0001$, $p=0.0029$).The level of C5a,C5b-9 in normal C57BL/6N mouse group were (83.80±13.45)ng/ml and (174.3±10.79)ng/l; in CKO mouse group were (116.3±28.45)ng/ml and (217.2±26.39)ng/l, which had statistical difference between two groups($p=0.0495$,$p=0.0098$). The pathological examination showed that the volume of hematopoietic tissue(VOL) in bone marrow of CKO mouse was increased(95%VOL) compared with that of normal mice(90%VOL), and the granulosiderin cells in the spleen of CKO mouse were distributed in small clusters and aggregated in clumps(Figure 1D).



Summary/Conclusion: A Piga conditional knock-out mouse model mediated by Vav-iCre was constructed which had stable GPI-deficient and mild hemolysis.

EP584 CYTOKINE-PRODUCING ABILITY OF MESENCHYMAL CELLS OF THE BONE MARROW STROMA IN CASE OF NEUTROPENIA IN CHILDREN

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Background: Acquired idiopathic neutropenia is a rare disorder associated with impaired proliferation and differentiation of neutrophil precursors. The stromal microenvironment plays an important role in the regulation of the maturation of granulocyte colony-forming units (CFU-G). The bone marrow stroma regulates hematopoiesis locally in hematopoietic niches and by producing cytokines and growth factors in normal conditions and in various hematologic diseases. Thus, the efficiency of hematopoiesis directly depends on the functional state of the mesenchymal stromal cells (MSC) of the bone marrow. The study of the mechanisms of interaction and ways of regulating of the development hematopoietic and stromal cells` is necessary to establish the hypoplastic variant of neutropenia.
Aims: To assess the cytokine-producing ability of MSC of the bone marrow in patients with hypoplastic neutropenia.
Methods: The bone marrow of 17 patients with neutropenia at the age from 2.5 to 17 (median - 9.5) years was researched. The determination of the proliferative potential and differentiation ability of the bone marrow was carried out by counting the CFU-G formed in a 14-day culture based on the morphological recognition of their cellular elements. Cultivation of MSC carried out on the surface of plastic flasks under conditions of 5% carbon dioxide at a temperature of 37 ° C. The levels of interleukins (IL) -1β, -2, -6, tumor necrosis factor α (TNFα) and transforming growth factor β (TGFβ) determined by enzyme-linked immunosorbent assay in supernatants of MSC cultures
Results: In 13 of 17 (76.5%) patients the content CFU-G was decreased to 20-60 (with a normal range of 70-350) per $1x10^6$ nuclear cells. It made it possible to establish a hypoplastic variant of neutropenia. The absolute content of neutrophils of peripheral blood in these patients was 170-1325 (Me = 920) in 1 μl. There was no significant correlation between the number of bone marrow CFU-G and the level of neutrophils in the peripheral blood (Pearson's correlation coefficient r = 0.07). The levels of MSC cytokine production were: IL-1β 0.49-0.82 (Me = 0.70) pg / ml / day, IL-2 0.369-1.591 (Me = 0.589) pg / ml / day, IL-6 87.7-127.3 (Me = 108.0) pg / ml / day, TGFβ 5.26-28.91 (Me = 13.76) pg / ml / day. An inverse relationship between the number of CFU-G and the concentration of IL-1β, IL-6 and TGFβ was found (r = -0.59, -0.84, -0.50, respectively). The correlation coefficient between the production of IL-2 MSCs, TGFβ and the content of neutrophils in peripheral blood was -0.66 and 0.50, respectively.
Summary/Conclusion: A cultural research of the myeloid lineage of the bone marrow and the stromal microenvironment with an assessment of the functional activity of MSC is an important part of diagnostic of a hypoplastic variant of neutropenia. The depth of CFU-G decreasing is associated with the level of secretion IL-1β, IL-6 and TGFβ by of MSC, and neutrophil quantity – IL-2 and TGFβ.

Bone marrow failure syndromes incl. PNH - Clinical

EP585 BCX9930, A NOVEL ORAL FACTOR D INHIBITOR, HAS POSITIVE EFFECTS ON HEMOLYSIS AND CLINICAL OUTCOMES IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NAÏVE TO COMPLEMENT INHIBITORS

A. McDonald [1,*], J. L. R. Malherbe [2], M. Cornpropst [3], S. Dobo [3], M. Farmer [3], D. Kargl [3], J. M. Best [3], W. P. Sheridan [3], A. Risitano [4]

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Background: PNH, a rare, chronic, life-threatening disease is characterized by hemolysis due to uncontrolled activity of the complement alternative pathway (AP), and is associated with bone marrow failure,

and thrombosis. Terminal complement pathway inhibition with C5 inhibitors may not be sufficient for disease control as up to half of PNH patients remain transfusion dependent with C5 inhibitor treatment. BCX9930 is an orally administered small-molecule factor D inhibitor targeting the proximal AP with the potential to inhibit intravascular hemolysis and prevent extravascular hemolysis in patients with PNH.

Aims: The objectives of this part of the study were to evaluate the safety, tolerability, and effectiveness of BCX9930 in complement inhibitor-naïve patients with PNH.

Methods: Study BCX9930-101 (NCT04330534), an open-label dose-ranging study, enrolled PNH subjects with no prior history of C5-inhibitor treatment into one of three multiple dose cohorts. Subjects in each cohort received BCX9930 at starting doses of 50mg-400mg twice daily (BID) titrated to a maximum of 500mg BID. Safety endpoints included the incidence and severity of treatment-emergent adverse events (TEAEs). Effectiveness endpoints included clinical measurements of hemoglobin (Hb), number of transfusions, lactate dehydrogenase (LDH), absolute reticulocyte count (ARC), and percent PNH red blood cells (RBCs). Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale; a 3-point change is considered a minimal important difference. This abstract includes data from screening through data cut-off of 22 January 2021 in an open-label extension.

Results: 10 adult patients (mean age 30 years) were enrolled in 3 cohorts with starting dose regimens of 50mg BID (n=4), 200mg BID (N=4), and 400mg BID (N=2). Mean time since clinical diagnosis of PNH was 4 years. Six patients required a total of 31 transfusions in the 12 months prior to treatment. The median duration of BCX9930 treatment was 147 days (range 28-340); 9 patients remain on treatment at 400 or 500mg BID and 5 have been treated > 5 months. BCX9930 was well-tolerated. Nine subjects (90%) had TEAEs; 5 patients had 5 Grade 3 TEAEs of which 2 were considered treatment related and resolved with continued treatment. Two serious adverse events unrelated to study drug were reported (gastritis in 1 patient and fatal disseminated varicella zoster infection in 1 patient).

Hb improved in all patients with a mean improvement from baseline (BL) to the last treatment visit (LTV) of 3.3g/dL. Only 1 patient required 1 transfusion which occurred during the 100mg BID treatment period. Mean ARC decreased from 180.3 x 10^9/L to 115.8 x 10^9/L at LTV. The relative percent of PNH Type II+III RBC to percent PNH WBC increased from 56% at BL to 90% at LTV. Meaningful improvements in FACIT fatigue score were observed with an increase of 7.3 points. During the treatment period with 400mg BID/500mg BID, BCX9930 demonstrated a mean (SD) reduction of 67% (13.4) in LDH from BL.

Summary/Conclusion: BCX9930, an orally administered potent and specific factor D inhibitor, was safe and generally well-tolerated as monotherapy in complement inhibitor-naïve patients with PNH at doses up to 500mg BID. Inhibition of the AP with BCX9930 reduced hemolysis, with reduction in transfusions and improvements in laboratory parameters. Improvements in fatigue were also observed. This study successfully identified a safe and tolerable BCX9930 dose range with dose-related meaningful clinical improvement, supporting progression to controlled clinical trials of BCX9930 in PNH.

EP586 RAVULIZUMAB ADMINISTERED SUBCUTANEOUSLY VERSUS INTRAVENOUSLY IN ADULT PATIENTS WITH PNH PREVIOUSLY TREATED WITH ECULIZUMAB: RESULTS FROM A PHASE 3 RANDOMIZED, OPEN-LABEL STUDY

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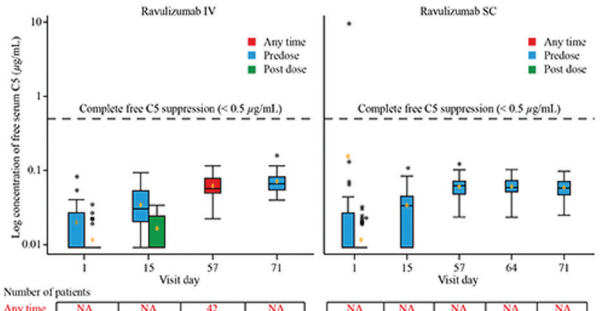
Background: The intravenous (IV) complement C5 inhibitors eculizumab and ravulizumab are the current standard of care for patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) where available. Ravulizumab self-administered via a subcutaneous (SC) on-body delivery system will offer an alternative to ravulizumab IV and allow administration outside of clinic which can improve patient independence.

Aims: Evaluate the pharmacokinetic (PK) non-inferiority of ravulizumab SC versus ravulizumab IV in adult pts with PNH.

Methods: This ongoing phase 3, multicenter, randomized, open-label study (NCT03748823) enrolled clinically stable (lactate dehydrogenase [LDH] level ≤ 1.5 upper limit of normal) adult pts (aged ≥ 18 years) with PNH treated with eculizumab for ≥ 3 months prior to entry. In the 10-week primary evaluation period, pts received a weight-based loading dose of ravulizumab IV on Day 1. On Day 15, pts on ravulizumab IV received a single weight-based maintenance dose of ravulizumab, and those randomized to ravulizumab SC received a 490mg maintenance dose and then every week (qw) thereafter. During the extension phase (up to 3.5 years), all pts will receive ravulizumab SC qw. Primary endpoint was Day 71 serum ravulizumab predose concentration (Day 71 C_{trough}). Non-inferiority was determined between the two groups using a one-sided test at an α level of 0.05, and a PK non-inferiority boundary of 0.8. Secondary endpoints included C_{trough} and free serum C5 concentration over time and incidence of anti-drug antibodies (ADA). Efficacy indicators were change in LDH level, breakthrough hemolysis (BTH), hemoglobin stabilization (Hgb-S), transfusion avoidance (TA) and PNH symptoms. Safety indicators included adverse device events (ADE), serious ADE (SADE), adverse events (AE) and serious AE (SAE).

Results: This primary analysis of PK non-inferiority of ravulizumab SC versus IV administration included 70 pts in the SC group and 43 pts in the IV group. Patient demographics were comparable between groups. Day 71 geometric mean C_{trough} concentration for ravulizumab SC demonstrated PK non-inferiority with ravulizumab IV (559.9 µg/ml and 445.3 µg/mL, respectively; ratio of geometric least squares means SC/IV: 1.26 [90% CI: 1.16–1.36; $p < 0.0001$]). All C_{trough} levels were above target trough serum concentration, and no pts tested positive for ADA at Day 71. Complete and sustained suppression of serum free C5 (mean concentration < 0.5 µg/mL) was achieved in both groups at all timepoints after the first dose (**Figure 1**). Mean (SD) percentage change in LDH from baseline was 1.7% (34.8%) and 5.1% (29.6%) in pts on ravulizumab SC and IV, respectively. Only 1 BTH event due to unknown cause was reported in a patient on ravulizumab IV. Hgb-S was achieved by 93.6% and 81.8% of pts, and TA was achieved by 94.0% and 86.7% of pts on ravulizumab SC and IV, respectively. PNH symptoms were observed in 45.2% and 46.7% of pts on ravulizumab SC and IV, respectively. Pts on ravulizumab SC with ≥ 1 ADE were 45.2% (23.8% device use), and no SADE were reported. Proportion of pts experiencing ≥ 1 AE were comparable between -ravulizumab SC and IV when ADE were excluded. Five (6.0%) pts on ravulizumab SC experienced ≥ 1 SAE versus 1 patient (2.2%) on ravulizumab IV; none were related to study treatment.

Figure 1 Free serum C5 concentration during the primary evaluation period (pharmacokinetic analysis set)



For free C5 values below the limit of quantification, lower limit of quantification/2 = 0.00915 µg/mL was utilized. Y-axis is presented on the log scale. The dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the minimum and maximum within the interval spanning 1.5 x interquartile range from each of the 1st and 3rd quartile. Outliers are represented by asterisk beyond the whiskers.
Ravulizumab SC group has samples collected at Day 1, 15, 57, 64 and 71 predose, and Day 1 and 15 postdose.
Ravulizumab IV group has samples collected at Day 1, 15 and 71 predose, and Day 57 anytime.
C5, complement component 5; IV, intravenously; NA, not available; SC, subcutaneously.

Summary/Conclusion: Ravulizumab SC C_{trough} levels were non-inferior to those obtained with ravulizumab IV. Ravulizumab SC provided complete and sustained free C5 inhibition comparable to ravulizumab IV at all timepoints.

EP587 LONG-TERM FOLLOW UP AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR IDIOPATHIC SEVERE APLASTIC ANEMIA. THE EXPERIENCE OF THE SPANISH GROUP OF HEMATOPOIETIC STEM CELL TRANSPLANT (GETH).

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is considered the only curative option for severe aplastic anemia (SAA). However, it is not currently recommended as the first choice for patients older than 40 years old, even they have a matched sibling donor. The HSCT procedures have been improved in the recent years. Therefore, updated information about the long-term results of patients who undergo HSCT for SAA may be of interest.
Aims: To determine the overall survival (OS) at 5 and 10 years after HSCT in patients with SAA, as well as and the rate of patients alive in complete remission (CR). Secondly, we evaluated the causes and factors related to mortality.
Methods: Between the years 2000 and 2019, the Spanish Group of Hematopoietic Stem Cell Transplant and Cellular Therapy (GETH-TC) performed 722 allogeneic HSCT due to bone marrow failure (BMF) syndromes. The follow-up has been updated in 333 patients, 271 due to SAA (including 188 (76%) idiopathic SAA) and 62 due to congenital disease (72% Fanconi anemia). To evaluate the factors related to mortality. Univariate analysis included: previous immunosuppressive therapy (IST) (yes or no), time from diagnosis to HSCT (< or ≥6 months), age at transplant (<20 y/o, 20-39 y/o, 40-59 y/o, >60 y/o), year of transplant (2000-2004, 2005-2009, 2010-2014, 2015-2019), stem cell source (BM, PB, CB), and the experience of the center in SAA HSCT (< or ≥10 in the last 20 years). Multivariate analysis includes all variables with p value <0.2 in the univariate analysis.
Results: We present here the updated results from the series of 188 patients with idiopathic SAA and HSCT. The median age at diagnosis was 25 years (range 2-69) and 55% were male. 108 (57%) patients were previously treated with IST (≥ 2 cycles, 36 patients; unknown 2 patients). 91 (47%) patients received the HSCT before the year 2010. The median age at HSCT was 27 years (IQR 17-40). The stem cell source was BM (62%), PB (30%) and CB (7%) and the HSCT was performed from a matched donor in 153 (81%) patients [sibling 111 (59%); unrelated 42 (22%)]. The most frequent conditioning regimen was FluCyATG (41%) followed by Cy-ATG (37%) and cyclosporine combined with methotrexate (59%) or prednisone (23%) were the most common GVHD prophylaxis. 106 (54%) patients received the HSCT ≥6 months after the diagnosis. Factors related to delayed HSCT were prior IST (p <0.001) and lack of matched related donor (p<0.001). With a median follow-up of 114 months (IQR 68-173), the OS at 5 and 10 years were 67.8±3.6% for both moments (Figure 1a). Among the 119 patients alive, 97 (82%) are currently in continued CR. 61 patients died, mainly due to infections (40 patients, 65%) and other HSCT related causes (16 patients, 26%). Cumulative incidence of TRM at 1 year was 25.4% (95% CI 19.1-32.2%) and 29% at 5 and at 10 years (95% CI 22.3-36.0%), respectively. Previous IST (HR 1.93, 95%CI 1.04-3.81, p=0.04) and the age at transplant ≥20 years (HR 2.29, 95%CI 1.21-4.35, p=0.01) were associated to mortality in the multivariate analysis. In patients older than 20 years, the use of previous IST doubles the probability of death (Figure 1b).

Figure 1a

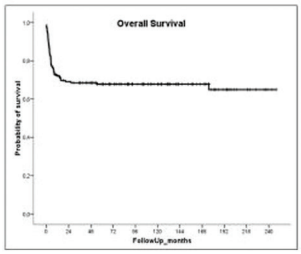
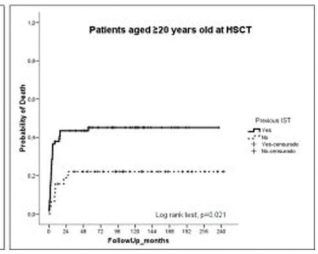


Figure 1b



Summary/Conclusion: In this large series of transplanted patients due to aplastic anemia, we observed high rates of survival in CR after a long follow-up. The major causes of death are post-HSCT infections and, since older age at transplant and the use of previous IST confers high risk of mortality, our data support the need of new strategies to prevent infectious complications and the reassessment of the role of frontline HSCT in older patients.

EP588 LONGITUDINAL CLINICAL AND LABORATORY DATA AND OUTCOME OF PATIENTS WITH CHRONIC IDIOPATHIC NEUTROPENIA

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Background: Patients with persistent, unexplained neutropenia who do not fulfil the diagnostic criteria of any underlying disease are characterized as chronic idiopathic neutropenia (CIN) cases. Real-world data based on longitudinal studies of large number of CIN patients are rare. A cooperation in science and technology (COST) Action, the EuNet-INNOCHRON, has been recently launched, aiming to promote the research on chronic neutropenias, including CIN, across and beyond Europe.
Aims: We present longitudinal laboratory and clinical data from adult patients with CIN registered in a database within EuNet-INNOCHRON aiming to provide insights in the natural history and outcome of patients with this rare disease.
Methods: Patient data are registered in the "NeutroReg" electronic registry hosted in the University of Crete Data Center in compliance with the European General Data Protection Regulation. The enrolment is based on previously described diagnostic criteria for CIN, i.e. absolute neutrophil counts (ANC) below 1800/μl of blood for more than 6 months and no evidence of any underlying disease/condition associated with neutropenia following a defined clinical/laboratory investigation including bone marrow biopsy and karyotype. In all registered patients we performed targeted next generation sequencing (NGS) of myeloid genes for identification of clonal hemopoiesis (MiSeq, Illumina) and genotyping of the *DARC/ACKR1* gene for identification of the single nucleotide polymorphism (SNP) rs2814778 (-46T>C) associated with benign ethnic neutropenia.
Results: We present data from 200 adult CIN patients, 159 females and 41 males (79.5% and 20.5%, respectively), aged 19-90 years (median 60 years), registered from one center that accepts patients from all over Greece. Seven patients were non-Greek white Europeans and 193 were Greeks. The median time from the initial identification of neutropenia until last follow-up was 179 months (range 12-420 months) and the median time of follow-up was 133 months (range 12-396 months). The patients

had mean ANCs 1370±420/µL (median 1600, range 200-1700/µL), lymphocytes 1640±475/µL (median 1600, range 700-3700/µL), monocytes 336±134/µL (median 300, range 100-800/µL), platelets 221±48 x103/µl (median 219, range 150-336 x103/µl), haemoglobin 13.3±0.99 g/dL (median 13.25, range 10.6-16.5 g/dL) and MCV 88.15±5.76 fl (median 89, range 63.4-98.1 fl). Clonal hemopoiesis in NGS analysis was identified in 40 patients (20%) and these patients were further characterized as cases with clonal cytopenia of undetermined significance (CCUS). The most frequently mutated genes were DNMT3A and TET2 involving more than 50% of CCUS patients followed by BCOR/BCORL1, IDH1/2, ASXL1, SRSF2, TP53, WT1. Five patients (2.5%) were homozygous for the DARC/ACKR1 SNP rs2814778. Overall, five patients transformed into MDS/AML, four from the CCUS and one from the non-clonal group (P<0.0001) with a relative risk 20 for transformation in the presence of clonal disease. Nine patients developed a non-hematologic malignancy, three from the CCUS and six from the non-clonal group (non-significant difference). The patients had rare infections and only one patient presented a mild covid-19 infection so far.
Summary/Conclusion: This is the first study presenting longitudinal clinical/laboratory data and disease outcome in CIN. The coordinated collection of common data from CIN patients from different backgrounds under EuNet-INNOCHRON is anticipated to enrich further the knowledge on the natural history of this rare disease.

EP589 BCX9930, AN ORAL FACTOR D INHIBITOR, CONTROLS EXTRAVASCULAR HEMOLYSIS AND ALLEVIATES ASSOCIATED SYMPTOMS IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA INADEQUATELY CONTROLLED ON C5 INHIBITORS

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening disorder characterized by red blood cell (RBC) hemolysis, resulting from uncontrolled activity of complement leading to episodes of intravascular hemolysis (IVH), extravascular hemolysis (EVH), chronic hemolytic anemia, and thromboembolism. Administration of C5 inhibitors reduces IVH, but PNH RBCs become opsonized and susceptible to EVH. Complete normalization of hemoglobin (Hb) is only seen in a fraction of patients, while most continue to experience some degree of anemia and fatigue. BCX9930 is a potent, selective inhibitor of complement Factor D that blocks the initiation of the alternative pathway (AP) and has the potential to treat both IVH and EVH as an oral therapy.
Aims: To evaluate the safety, tolerability, and effectiveness of BCX9930 on EVH and residual IVH in PNH patients with an inadequate response to C5 inhibitors in an open-label, dose-ranging Study BCX9930-101 (NCT04330534).
Methods: Six patients receiving a C5 inhibitor with an inadequate response (received a transfusion within 3 months of screening or Hb < 10 g/dL) were enrolled. Oral BCX9930 was added to the C5 inhibitor for 28 days with an increase in BCX9930 dose on Day 15; treatment was with either 200mg BID escalated to 400mg BID (n= 2) or 400mg BID escalated to 500mg BID (n = 4). On Day 28, patients deriving benefit could continue BCX9930 in a long-term extension study.
Results: Two patients are receiving ravulizumab and 4 eculizumab (>900mg every 2 weeks in 3). At baseline, mean Hb was 8.9 g/dL, absolute reticulocyte count (ARC) was 196.3 x10^3/µL, and proportion of PNH Type II + III RBCs was 48%. Five patients received RBC transfusions (range 1-15) in the 3 months prior to screening. As of the last follow-up visit, all 6 patients have continued in the long-term study with a total duration of BCX9930 therapy of ≥58 days. Meaningful improvements across hemolysis biomarkers and fatigue scores were demonstrated. After the first week of dosing with 400mg BID, all 4 patients had a ≥ 1g/dL increase in Hb. As of the last treatment visit, the mean Hb in the absence of transfusions increased by 3.4 g/dL to a mean of 12.3 g/dL and mean ARC decreased to 86.4 x10^3/µL. Increased EVH control was further demonstrated by the increase in proportion of PNH Type II+III RBCs to a mean of 71%. One patient received 3 RBC transfusions during the treatment period, as compared to 15 transfusions in the 3 months prior to screening. No other patients have been transfused since initiating BCX9930. Self-reported fatigue (FACIT-fatigue total score) improved by a mean of 7.5 points, well above the minimal important difference (3 points). Five patients reported adverse events (AEs); the most common drug-related AEs were self-limited rash (3) and dizziness (2). No serious or Grade 3 or 4 AEs were reported and there were no trends in safety laboratory values
Summary/Conclusion: Oral BCX9930 at doses up to 500mg BID was safe and generally well-tolerated over at least 58 days in PNH patients with inadequate response to a C5 inhibitor. Following initiation of BCX9930, notable improvements were observed in Hb, ARC, abundance of PNH RBC, fatigue scores and RBC transfusion requirements. Both proximal AP inhibition of Factor D and demonstrated improvements in hemolysis support future evaluation of BCX9930 monotherapy for patients who are inadequately responding to C5 inhibitors.

EP590 PHARMACOKINETICS, PHARMACODYNAMICS, EFFICACY AND SAFETY OF RAVULIZUMAB IN CHILDREN AND ADOLESCENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: INTERIM ANALYSIS OF A PHASE 3, OPEN-LABEL STUDY

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) typically manifests during adulthood, with pediatric patients accounting for ~14% of reported cases. Ravulizumab is a terminal complement component 5 (C5) inhibitor shown to have a similar efficacy and safety profile to eculizumab in adults with PNH, and a study in pediatric patients is ongoing.
Aims: To assess the pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of ravulizumab in a pediatric population with PNH.
Methods: This ongoing phase 3, multicenter, single-arm, open-label study (NCT03406507) enrolled complement-inhibitor-naïve and eculizumab-experienced pediatric patients (aged < 18 years) with a diagnosis of PNH, at 9 sites in 6 countries. Naïve patients received a weight-based loading dose (LD) of ravulizumab on Day 1 followed by weight-based maintenance dose (MD) on Day 15, and then once every 8 weeks [LD (mg)/MD (mg)]: ≥ 30 to < 40 kg bodyweight [1200 mg/2700 mg]; ≥ 40 to < 60 kg bodyweight [2400/3000]; ≥ 60 to < 100 kg bodyweight [2700/3300]. For patients switching from eculizumab therapy, ravulizumab Day 1 was 2 weeks after the last eculizumab dose. All analyses were performed to the end of the primary evaluation period (Day 183). Primary endpoints included ravulizumab maximum and trough serum concentration (C_{max}, C_{trough}; at the end of dosing interval at steady state), accumulation ratio and change in free C5 concentration. Secondary endpoints included percentage change in lactate dehydrogenase (LDH) from baseline, transfusion avoidance (TA), breakthrough hemolysis (BTH) and hemoglobin stabilization (Hgb-S). Safety endpoints included incidence of treatment-emergent adverse events (TEAE) and serious adverse events (SAE).
Results: In total, 13 patients were enrolled, 12 (4 complement-inhibitor-naïve) were included in the interim analysis (1 patient did not complete Day 183 evaluation by database lock: 27 May 2020; **Table 1**). Ten (83.3%) patients were aged ≥ 12 years, with a median (range) age at first ravulizumab infusion of 15.0 (9–17) years. Steady-state therapeutic serum concentrations of ravulizumab were achieved immediately following the first dose and maintained throughout the primary evaluation period with no

evidence of accumulation (mean [SD] C_{max} and C_{trough} accumulation ratios of 1.1 [0.1] and 1.1 [0.2], respectively). Complete terminal complement inhibition was attained by the end of first ravulizumab infusion (defined as mean serum free C5 concentration < 0.5 µg/mL) and was sustained through Day 183 in all patients (**Table 1**). Mean (SD) percentage change in LDH was –42.1% (59.0) in complement-inhibitor-naïve patients and remained stable in eculizumab-experienced patients at +4.65% (44.7). Overall, 10 (83.3%) patients achieved TA, 8 (66.7%) achieved Hgb-S and no patients experienced BTH. TEAE were reported in 10 patients; the most frequent were abdominal pain and nasopharyngitis. No meningococcal infections, deaths or discontinuations due to TEAE were reported. Three patients had ≥ 1 SAE during the study and no SAE were assessed to be treatment-related.

Table 1 Pharmacokinetics/pharmacodynamics and secondary efficacy parameters up to Day 183: patient narratives

	Patient 1 F	Patient 2 F	Patient 3 F	Patient 4 M	Patient 5 F	Patient 6 F	Patient 7 F	Patient 8 F	Patient 9 M	Patient 10 M	Patient 11 F	Patient 12 M
Age at study entry (years)												
	17	17	12	17	13	9	17	13	17	15	11	15
Day 1 body weight (kg)												
	68.8	59.3	44.5	68.7	51.3	36.7	69.0	51.7	72.0	55.2	39.5	59.0
C_{max} (µg/mL)												
D1	855	1070	1120	784	761	611	876	1000	695	813	589	716
D127	1450	1770	1840	1570	1530	1880	1850	1750	1020	1520	1990	1430
C_{trough} (µg/mL)												
D15	425	452	547	439	419	330	475	531	318	419	292	375
D183	495	646	541	593	472	513	629	636	117	515	630	382
Free C5 (µg/mL) predose[a]												
D15	0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	0.1	0.0	0.1	0.0
D183	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.3	0.1	0.0	0.1
LDH (U/L) [individual reference range][b]												
BL	230.5	250	275	487	304.5	253	161.5	140.5	543.3	588.5	444	2269.7
D183	221 [100–220]	NA[c] [100–220]	235 [140–280]	286 [100–242]	611[d] [100–275]	236 [140–280]	154 [100–220]	145 [100–275]	195 [100–242]	257 [100–242]	637[e] [140–280]	195 [120–290]
Hemoglobin (g/L) [individual reference range]												
D15	71	98	93	105	118	101	114	119	82	145	114	92
D183	76 [120–160]	NA[c] [120–160]	132 [114–151]	NR [135–175]	116 [114–151]	NR [114–151]	122 [120–160]	114 [114–151]	109 [135–175]	143 [135–175]	106 [114–151]	122 [135–175]
Units of packed red blood cells received												
	0	0	0	0	0	0	0	0	3	0	0	2
Breakthrough hemolysis												
	0	0	0	0	0	0	0	0	0	0	0	0

Ravulizumab (10 mg/mL solution) loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg were administered by IV infusion. Data shaded grey are from complement-inhibitor-naïve patients.
[a]Lower limit of quantitation for free C5 = 0.0183 µg/mL. [b]Multiple LDH reference ranges are present depending on pediatric age and gender group: 100–220 U/L, 100–242 U/L, 100–275 U/L, 120–290 U/L and 140–280 U/L. [c]Day 183 samples were not analyzed at the central laboratory owing to internal Eurofins issue with process of registration samples; the samples were considered as missing. [d]At Day 183, the LDH level of patient 5 was greater than at baseline; however, the blood sample was reported to be hemolyzed and the patient did not have any new or worsening PNH signs or symptoms. [e]At Day 183; the LDH level of patient 11 was greater than at baseline; however, the blood sample was reported to be hemolyzed and the patient did not have any new or worsening PNH signs or symptoms.
BL, baseline; BLOQ, below limit of quantification; C5, complement component 5; C_{max}, max ravulizumab serum concentration; C_{trough}, trough ravulizumab serum concentration; D, day; F, female; IV, intravenous; LDH, lactate dehydrogenase; M, male; NA, not analyzed; NR, not reported; PNH, paroxysmal nocturnal hemoglobinuria.

Summary/Conclusion: These interim results are from the largest study of pediatric patients with PNH to date. In this rare population, ravulizumab was effective, well-tolerated, and provided immediate, complete, and sustained terminal complement inhibition irrespective of prior treatment with eculizumab. These PK, PD, efficacy and safety findings suggest that pediatric patients can be initiated on ravulizumab or switched from eculizumab to ravulizumab.

EP591 REAL - WORLD SCENARIO OF RESPONSE WITH LONG - TERM USE OF ANDROGENIC STEROIDS IN PATIENTS WITH ACQUIRED APLASTIC ANEMIA: REPORT FROM A TERTIARY CARE HOSPITAL IN WEST BENGAL, INDIA

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Background: Aplastic anemia (AA) is a disease characterised by pancytopenia and it may be inherited or acquired (immune) in nature. Though the definitive treatment is allogeneic stem cell transplant, use of Anti Thymocyte Globulin (ATG), Cyclosporine (Cx) or TPO agonists as first line therapy have greatly improved the disease prognosis. Though androgenic steroids are used upfront in Inherited Bone marrow failure syndromes (IBMFS), sometimes they are also used in Acquired AA. The efficacy is lower than the first line agents (70%).
Aims: Though androgens are used commonly in patients who have failed first line therapy or as first-line in patients with logistic constraints, there is very little real-world data regarding the response outcomes with these drugs. The target of our study is to address this void.
Methods: This analysis was conducted among patients who attended NRS Medical College in West Bengal, India in the span of 1 year (1st January-31st December, 2020). Patients with AA, both Severe AA (SAA) and Non-SAA (NSAA) (according to the Camitta criteria), were considered and the patients who relapsed / did not respond to / could not be given first-line therapy, either due to logistic reasons or side effects (such as, rising creatinine or gum hypertrophy necessitating stoppage of cyclosporine), were included for the analysis (Table 1). Patients having features of IBMFS have been excluded from the analysis.
Second-line therapy was given with androgenic steroids such as, Stanozolol (St), Danazol (Da) or Oxymetholone (Ox), in addition to supportive care. The drug dosages were as follows: St 1 mg/kg/day; Da 10 mg/kg/day; Ox 2 mg/kg/day. First-line therapy comprised of ATG, Cx or Eltrombopag.
The improvement was assessed according to criteria in published literature, as follows: a) lesser requirement of transfusions; b) increase in haemoglobin (Hb) levels; c) increase in absolute neutrophil count (ANC); d) increase in platelet count
Results: Out of a total of 388 patients with Acquired AA, 108 required second-line therapy with ≥1 androgen (Table 1). Most of the patients were aged ≥ 40 years age (61.1%) and there was a male preponderance (1.5:1). Majority of patients had SAA (75.9%).
The most common cause for starting a patient on androgens was logistic, followed by starting the drug due to no response with frontline agents. Many patients had ≥1 reason for starting androgenic steroids. The most commonly used steroid was St, followed by Da and Ox. Many patients have received more than one type of steroid at different time periods, due to reasons ranging from cost to side effects (Table 1).
Overall response (OR), which included both Complete response (CR) and Partial response (PR), was noted in 47.2% patients (Table 1). The median time of OR was 2 years.

Number of patients with AA		388
Patients requiring second-line treatment with androgenic steroids (*n=108*) [Some patients received androgenic steroids due to more than one reason]	Relapsed after having responded to first-line therapy	14
	Did not respond to first-line therapy	45
	First-line therapy had to be stopped due to side effects	5
	Not given first-line drugs due to logistic reasons	67
Median age (range) in years		46.5 (8-78)
Number of patients ≤ 20 years age		13 (11.8%)
Number of patients 21-40 years age		29 (26.4%)
Number of patients ≥ 40 years age		66 (61.1%)
Sex (male: female)		1.5:1 (65:43)
Mean duration of AA from diagnosis (range) in years		4.4 (1-23)
Median duration of AA from diagnosis		3
Severe AA		82 (75.9%)
Non-Severe AA		26 (24.1%)
Baseline symptoms		Fever, transfusion requirement
First-line therapy		ATG, Cx, Eltrombopag
Median time after which androgenic steroids started (range) in years		1 (0-20)
Number of patients who received Stanozolol		89
Mean duration of Stanozolol use (range) in years		1.9 (0.1-6); 2 patients intermittent
Number of patients who received Danazol		26
Mean duration of Danazol use (range) in years		2.74 (0.25-6)
Number of patients who received Oxymetholone		4
Mean duration of Oxymetholone use (range) in years		1.75 (1-2)
Overall Response (CR+PR)		51 (47.2%)
Median time to attain response (range in years)		2 (0.25-10)
Continuing requirement for transfusions		57 (52.8%)

Table 1: Tabular representation of patients with Acquired AA, who received androgenic steroids as second line therapy. *11 patients received both Stanozolol and Danazol.* Abbrev: AA= Aplastic anemia, ATG= Anti Thymocyte Globulin, Cx= Cyclosporine, Hb= haemoglobin, CR= Complete response, PR= Partial response

Summary/Conclusion: Androgens are not considered as first line agents in Acquired AA, however 47.2% OR was seen in patients who had taken androgens for variable time periods. In this analysis, it was seen that the time required to attain OR was quite long, median time being 2 years. Thus, in situations where ATG/Cx/TPO agonists fail or cannot be used due to logistic reasons, androgens may be a good alternative. St or Da are the most commonly used agents and the superiority of one over the other cannot be decided. However, the choice of androgen used may depend on the expense or side effects. St is more expensive than Da and mainly used in IBMFS, while Da is preferred in male patients.

EP592 MANAGEMENT OF MENINGOCOCCAL DISEASE RISK IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) ON COMPLEMENT INHIBITORS: 18 YEARS' EXPERIENCE FROM THE UK NATIONAL PNH SERVICE IN LEEDS

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Background: Eculizumab, treatment for Paroxysmal Nocturnal Hemoglobinuria (PNH) C5 inhibitors increase susceptibility to encapsulated microorganisms, (*Neisseria meningitidis)*. The PNH National service, has 18 years of experience. The risk of *N. meningitidis* is mitigated by vaccination, ciprofloxacin (500 mg bd) days 1-13 we moved to vaccination day one of complement inhibitor, and prophylaxis (penicillin / erythromycin). Since a case of sepsis with penicillin-resistant meningococci, patients also have course ciprofloxacin. Education, prompt action in case of fever and a 24 hour on-call service are equally important.

Aims: Until 2010 patients were revaccinated with MenACWY 3 yearly. Bexsero (MenB vaccine) vaccination added in 2015. In collaboration with Public Health England Meningococcal Reference Unit a program was developed to monitor titers after vaccination, to revaccinate if titers below protective levels. It is technically not possible to assay for meningoccal serogroup B antibody titers when on Eculizumab therapy.
Methods: Methods: Antibody titers were assayed following vaccination. Unprotective titers led to revaccination. We evaluate practice of 9 meningococcal infections in 8 patients. Present disease characteristics, serogroup and outcome, vaccination history and antibody status.
Results: Between 2002 and 2020, 324 patients commenced complement inhibitor treatment for PNH. 801 vaccinations with MenACWY were administered: median 2 vaccinations per patient (range 1 - 10). A total of 1,671 antibody titer assessments conducted in 294 patients, median of 4 tests per patient (range 1 - 15). Every test assessed antibodies against all four serogroups.
Titers were not assessed in 9% of patients (30), due to vaccination prior to change in practice or recent commencement.
Protective response after first vaccination was observed in 170 / 294 patients (57.8%) and a partial response (3 serotypes) in 51 /294 (17.3%). Revaccination of 51 partial responders resulted an additional 21 patients with a full response. Revaccination of 73 non-responders (antibodies to 0-2 serotypes) resulted in 32 more partial / full responses. 287 of 324 patients received MenB vaccinations: median 2 vaccinations per patient (range 1 - 4). 8 of 324 (2%) median age 22.5 years developed meningococcal sepsis (see table); patient 5 had 2 episodes. 3 of 5 cases with serogroup B infection were before serogroup B vaccination. 4 episodes in 3 patients were due to Y, C, W meningococci, in one the serogroup is unknown. All except patient 1 were compliant with antibiotic prophylaxis. Patient 7 died from meningococcemia, a delay in seeking medical attention may have contributed, (a penicillin resistant strain).
Results: Discussion:
The largest experience of managing meningococcal risk in complement inhibitor for PNH. Despite proactive management we had 9 cases of meningococcal sepsis,1 fatal infection. Recently practice of prompt treatment with ciprofloxacin if pyrexic on prophylaxis will prevent cases - patient 7 with a penicillin resistant strain. 3 patients had a meningococci sepsis serogroups C, W and Y;1 patient had no titers due to recent commencement on treatment, titres of 2 suggested protective immunity.

Table 1: Meningococcal infections from 2002-July 2020

Patient	Age	Eculizumab start date	Vaccination status with reference to the meningitis episode	*Neisseria meningitidis* diagnosed	Serogroup identified	Penicillin sensitivity	Fatal
1	40	Jun 2005	Before introduction of Men B vaccination*	Oct 2009	B	Sensitive	No
2	20	Aug 2008	Before introduction of Men B vaccination*	Oct 2008	B	Sensitive	No
3	20	Sep 2011	Before introduction of Men B vaccination*	Sep 2011	B	Sensitive	No
4	25	May 2016	Jun 2016 Full ACWY response	Jan 2017	Y	Sensitive	No
5	19 22	Mar 2016	Apr 2017 Partial (ACY) Mar 2020 Partial (ACY)	Sep 2017 May 2020	C NG	Sensitive Sensitive	No
6	23	Jan 2017**	Unavailable***	Mar 2017	W	NG	No
7	37	Jun 2013	Most recent Men B vaccination: Jan 2015	Sep 2019	B	Resistant	Yes
8	28	Dec 2017	Most recent Men B vaccination Feb 2018	Jan 2020	B	Sensitive	No

*meningococcal B vaccination was commenced in 2015

** commenced clinical trial with C5 inhibitor in Dec 2016, changed to eculizumab Jan 2017

*** Most recent MenACWY vaccination date Dec 2016 at start of C5 inhibitor clinical trial; no titers available prior to meningococcal event

NG: not known as PCR only confirmed

Summary/Conclusion: A full antibody response can be obtained on second vaccination in most if first one failed. If no response is achieved, then MenACWY vaccination is not likely to be successful. Current practice significantly mitigates risk of meningococcal disease; however, it is essential patients are vigilant for fever, seeking immediate medical attention stating their diagnosis of PNH on complement inhibitor therapy.

EP593 ELTROMBOPAG PLUS IMMUNOSUPPRESSIVE THERAPY VERSUS MATCHED SIBLING DONOR TRANSPLANTATION AS FIRST-LINE THERAPY FOR SEVERE APLASTIC ANEMIA – A META-ANALYSIS

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Background: Eltrombopag (ELT) is a thrombopoietin agonist which has been recently applied with immunosuppressive therapy (IST) for untreated severe aplastic anemia (SAA) patients. This new combination therapy was reported to be effective, yet no study has compared ELT+IST with matched sibling donor bone marrow transplantation (MSD-BMT), the traditional first-line therapy for SAA.
Aims: This meta-analysis aimed to compare the efficacy and survival benefit of ELT+IST and MSD-BMT for newly-diagnosed SAA patients.
Methods: Databases of Pubmed, Embase, Cochrane Library and Web of Science were searched. Studies published in recent 10 years, with a topic of ELT+IST and/or MSD-BMT and a record of patient overall response (OR) rate/myeloid engraftment rate, 1, 2 and 2.5-year overall survival (OS) rate and causes of death were included. Patients were separated into ELT+IST group and MSD-BMT group for data analysis. Baseline characteristic-compatible subgroup were selected for further analysis. OR rate, OS rate, failure-free survival (FFS) rate and the proportion of adverse events (AE) were pooled and compared.
Results: 8 clinical trials or cohort studies with 1004 patients (113 patients receiving ELT+IST, and 891 receiving MSD-BMT) were selected. The pooled age of patients receiving ELT+IST was significantly older than that of MSD-BMT group (45.2±20.5 vs 21.6±15.6 years old, P=0.000). For ELT-IST group, the pooled OR rate was significantly lower (86% *vs* 94%, P=0.002), yet the 1, 2 and 2.5-year OS rate was significantly higher (99% to 99% *vs* 92% to 90% from 1 to 2.5-year OS, P<0.05). No significant difference was observed in 1 and 2-year FFS rate between 2 therapy groups. The major cause of death was infection for MSD-BMT, while no treatment-related death was recorded in ELT+IST group. The pooled relapse rate was 16%, and 8.4% for pooled clonal evolution rate for ELT+IST, while no record of relapse or clonal evolution was available for MSD-BMT. In the subgroup with compatible patient baseline characteristics (mean age: 33 years old), 92 patients were included in ELT+IST group and 213 patients were in MSD-BMT group. The pooled OR rate was lower (87% vs 95%, P=0.017), and the pooled 1, 2 and 2.5-year OS rate was higher (P<0.05) for ELT+IST. For ELT+IST, the relapse rate was 14%, and the clonal evolution rate was 7.6%, while there was no relevant data for MSD-BMT group.
Summary/Conclusion: ELT+IST had potential advantage in survival benefit but lower OR rate for newly-diagnosed SAA patients when compared with MSD-BMT during 2.5 years of follow-up. Treatment-related death and relapse/clonal evolution needed to be balanced when ELT+IST was considered for SAA patients.

EP594 SAFETY OF RAVULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: STUDY 301/302 2-YEAR RESULTS

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Background: Patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) often present with chronic intravascular hemolysis and clinical sequelae due to uncontrolled terminal complement activation, leading to an increased risk of thrombosis and death. In two phase 3 randomized trials of pts with PNH, ravulizumab (administered every 8 weeks; q8w) was shown to be non-inferior to eculizumab (every 2 weeks; q2w) for all efficacy endpoints with a similar safety profile and no unexpected safety signals. Each study had a 26-week randomized primary evaluation period followed by an extension period during which all pts received ravulizumab. Safety results from the 27 weeks–2-years extension period for both studies were analyzed.
Aims: Describe the 2-year safety profile of ravulizumab in pts with PNH from two phase 3 trials.
Methods: Clinical trials 301 (NCT02946463) and 302 (NCT03056040) were phase 3, randomized, open-label, noninferiority, multicenter studies of adult pts with confirmed diagnosis of PNH. Pts in study 301 were naïve to complement C5 inhibitor therapy, with lactate dehydrogenase (LDH) levels ≥ 1.5 × ULN and ≥ 1 sign or symptom of PNH at screening, and generally referred to as pts with high disease activity. Pts in study 302 had been stable on eculizumab treatment for ≥ 6 months prior to study entry, with LDH levels ≤ 1.5 × ULN at screening. Pts received weight-based dosing of ravulizumab q8w or the approved eculizumab dose (900 mg, q2w) for 26 weeks; eligible pts could continue on, or switch to, ravulizumab in

the extension period. The incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), breakthrough hemolysis (BTH) and anti-drug antibody (ADA) status were assessed in the extension period.
Results: Patient demographics were similar across both studies. In total for combined studies, 434 pts received ravulizumab treatment in the extension period. Of these, 214 were complement C5 inhibitor-experienced having received eculizumab prior to switching to ravulizumab in the extension period. Total exposure for ravulizumab (27 weeks–2-years) was 662 patient-years for the studies. Ninety-eight pts (22.6%) reported treatment-related TEAEs, 10 pts (2.3%) reported treatment-related SAEs, and 3 pts (0.7%) had an SAE that led to study drug discontinuation (unrelated to treatment). Six pts (1.4%) had a major adverse vascular event (MAVE). The most commonly reported TEAEs (in ≥ 10% of pts) were upper respiratory tract infection, nasopharyngitis, headache and pyrexia, n (%): 80 (18.4); 70 (16.1); 56 (12.9); 44 (10.1), respectively (**Table 1**). The percentage of pts with BTH events in the 18-month follow-up extension periods were similar with 15 (6.2%) and 11 (5.6%) in pts naïve to complement C5 inhibitor therapy (study 301) and those with prior eculizumab use (study 302), respectively. Immunogenicity at 2 years was low across both studies, with treatment-emergent non-neutralizing ADA-positivity in 5 pts. Four deaths unrelated to treatment were reported during the extension period. Meningococcal infection was not observed up to the 2-year extension period; there was one fatal case of meningococcal sepsis in a patient at 2.2 years after receiving first dose of ravulizumab. More than 90% of pts in both studies continued ravulizumab treatment beyond the 2-year data cut of the extension periods.

Table 1 Safety outcomes from the combined 301 and 302 studies

	27 weeks – 2-year data cut (N = 434)	
Variable	**n (%)**	**Events (event rate)**
Total patient-years of exposure	-	**662.0**
Treatment emergent adverse events (TEAEs)		
Any TEAE*	391 (90.1)	2327 (351.5)
Related TEAEs	98 (22.6)	236 (35.6)
Unrelated TEAEs	381 (87.8)	2091 (315.8)
Grade 1	333 (76.7)	1347 (203.5)
Grade 2	280 (64.5)	794 (119.9)
Grade 3	100 (23.0)	159 (24.0)
Grade 4	19 (4.4)	25 (3.8)
Grade 5	2 (0.5)	2 (0.3)
TEAE considered as a MAVE	6 (1.4)[§]	8 (1.2)
Most common TEAEs in ≥ 10% of patients		
URTI	80 (18.4)	103 (15.6)
Nasopharyngitis	70 (16.1)	108 (16.3)
Headache	56 (12.9)	75 (11.3)
Pyrexia	44 (10.1)	52 (7.9)
Serious adverse events (SAEs), n (%)		
Any serious SAE	86 (19.8)	121 (18.3)
Related SAE	10 (2.3)	12 (1.8)
Unrelated SAE	80 (18.4)	109 (16.5)
SAE leading to study drug discontinuation	3 (0.7)[†]	3 (0.5)
Death	4 (0.9)[‡]	-

Rate = rate of AE adjusted by patient-years of exposure, defined as (number of events)/100 patient years. Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening, Grade 5 = fatal.
*TEAEs are AEs with a start data and start time on or after the date and time of the first infusion of study drug.
§Eight MAVEs were recorded: 1 patient had 2 events of pulmonary embolism, 1 patient had 2 events of cerebral infarction; the other MAVEs included thrombophlebitis, deep vein thrombosis, jugular vein thrombosis and peripheral artery thrombosis. Six events were considered to be unrelated to treatment and two events were unlikely related to treatment. None of these events led to change in dose.
†Three discontinuations were recorded: acute myeloid leukemia, myelodysplastic syndrome and lung adenocarcinoma.
‡Four deaths unrelated to study drug were reported: pulmonary sepsis, acute myeloid leukemia, lung adenocarcinoma and lung neoplasm malignant; the two deaths leading to study drug discontinuation were acute myeloid leukemia and lung adenocarcinoma.
AE, adverse event; MAVE, major adverse vascular event; SAE, serious adverse event, TEAE, treatment emergent adverse event; URTI, upper respiratory tract infection.

Summary/Conclusion: Ravulizumab was well tolerated in pts with PNH who were complement C5 inhibitor therapy naïve or experienced, with no new safety signals reported up to 2 years of treatment.

EP595 EFFECT OF PEGCETACOPLAN ON QUALITY OF LIFE IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: WEEK 48 OF PEGASUS PHASE 3 TRIAL COMPARING PEGCETACOPLAN TO ECULIZUMAB

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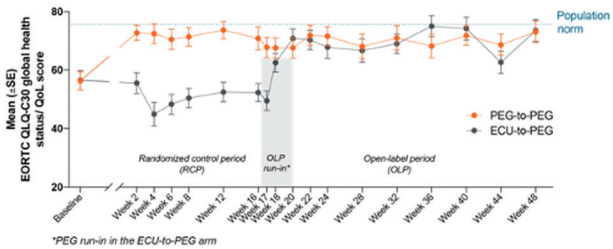
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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening hematologic disease characterized by chronic complement-mediated red blood cell hemolysis. Current standard treatments for PNH are the C5 inhibitors eculizumab (ECU) or ravulizumab. Despite their proven efficacy in the control of intravascular hemolysis (IVH), up to 72% of patients experience persistent hemolysis leading to suboptimal hemoglobin (Hb) levels and 36% require transfusions despite ECU treatment which results in significant impact on quality of life (QoL), including persistent fatigue. Pegcetacoplan (PEG) is a C3 inhibitor that provides broad hemolysis control (including IVH and extravascular hemolysis) in patients with PNH.
Aims: This analysis evaluates QoL measures in the PEGASUS study (NCT03500549), a phase 3, open-label, randomized, active-comparator trial evaluating the efficacy and safety of PEG compared with ECU.
Methods: This study is an extension of the PEGASUS trial. PEGASUS enrolled patients ≥18 years of age with PNH and Hb levels <10.5 g/dL despite receiving treatment with ECU for ≥3 months. Patients entered a 4-week run-in period in which they received ECU plus twice-weekly PEG (1080 mg, administered subcutaneously) and were then randomized 1:1 to monotherapy with PEG or ECU for 16 weeks. Patients receiving ECU during the randomized controlled period entered another 4-week run-in period (ECU+PEG), before PEG monotherapy (groups: PEG-to-PEG and ECU-to-PEG). This was followed by an Open Label Period (OLP), in which all patients received pegcetacoplan monotherapy. The primary endpoint was change from baseline in Hb levels at Week 16, where PEG demonstrated superiority to ECU *(Hillmen P et al, EHA 2020)*. Secondary endpoints included the QoL measures by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC QLQ-C30) and Linear Analog Scale Assessment (LASA). The EORTC QLQ-C30 contains 30 questions comprising 5 functional, 9 individual symptom, and one global health status/QoL item(s). The LASA consists of 3 sections asking to rate the perceived level of functioning (scale 0-100) and contains specific domains for activity level, ability to carry out daily activities, and overall QoL.
Results: PEGASUS enrolled 80 patients (Peg, n=41; ECU, n=39). Overall, mean baseline scores of the EORTC QLQ-C30 functional and symptom scales were similar between groups. At Week 16, patients in the PEG group typically scored better than ECU (ECU only to Week 16) patients on various scales of the EORTC QLQ-C30 (Figure A). After receiving PEG monotherapy for 28 weeks (OLP), both groups showed improvements in all functional scales (Figure A) and the global health status/QoL at Week 48 (Figure B) and as indicated by an increase in the score from baseline. Improvements in the fatigue (Figure B) and dyspnea scales were also observed in both groups at Week 48 as indicated by a reduction in the symptom score close to the population norms (fatigue general population norm: 24.1 [22.7], dyspnea general population norm: 10.9 [20.6]). Mean total LASA scores increased in the PEG-to-PEG group as compared to the ECU-to-PEG group to Week 16 and after 28 Weeks of open-label PEG monotherapy the mean score was comparable between both groups at Week 48 (Figure A).

A

All observed, mean (SD)	PEG-to-PEG n=41			ECU-to-PEG n=39		
	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48
EORTC QLQ-C30						
Global Health Status/QoL	56.30 (20.39)	70.83 (23.70)	73.06 (20.38)	56.53 (20.24)	52.31 (18.6)	73.51 (19.78)
Functional Scales						
Physical functioning	71.38 (20.23)	87.96 (14.93)	85.11 (16.02)	72.11 (20.14)	72.79 (21.34)	86.44 (16.95)
Role functioning	63.82 (29.56)	78.70 (26.01)	78.33 (25.58)	59.65 (33.92)	54.95 (33.07)	82.76 (21.59)
Emotional functioning	72.36 (25.38)	79.63 (25.62)	77.78 (22.03)	69.59 (22.67)	69.44 (24.23)	79.76 (17.04)
Cognitive functioning	76.02 (24.45)	83.33 (22.89)	80.00 (27.12)	75.23 (25.95)	69.44 (28.59)	80.95 (17.40)
Social functioning	69.51 (28.84)	82.41 (24.54)	81.67 (26.02)	64.86 (32.82)	66.20 (32.49)	84.52 (22.19)
Symptom Scales						
Fatigue	49.59 (29.09)	28.40 (22.61)	31.48 (26.28)	50.29 (24.74)	49.25 (25.60)	24.52 (24.56)
Nausea and vomiting	3.66 (8.75)	3.24 (7.79)	2.22 (7.24)	5.26 (11.69)	10.81 (21.23)	1.72 (5.17)
Pain	19.51 (26.85)	19.91 (26.67)	20.56 (31.77)	15.79 (25.10)	26.58 (27.35)	16.67 (19.42)
Dyspnea	33.33 (27.96)	15.74 (24.54)	18.89 (20.87)	43.86 (32.05)	36.94 (26.97)	17.24 (21.12)
Insomnia	32.52 (34.55)	23.15 (35.47)	33.33 (36.09)	29.82 (29.80)	25.23 (28.77)	25.29 (34.10)
Appetite loss	12.20 (17.88)	5.56 (14.91)	5.56 (12.64)	13.16 (23.94)	12.61 (24.03)	6.90 (18.64)
Constipation	11.38 (20.56)	15.74 (24.54)	14.44 (25.80)	10.81 (22.30)	5.56 (18.69)	4.76 (11.88)
Diarrhea	11.38 (23.11)	12.96 (21.50)	13.33 (20.72)	11.71 (21.11)	20.37 (21.50)	17.86 (27.94)
Financial difficulties	18.70 (26.93)	8.33 (16.67)	7.78 (16.80)	24.32 (37.39)	22.22 (33.81)	11.90 (22.62)
LASA						
Total LASA score	161.00 (67.99)	213.37 (69.36)	215.97 (67.14)	156.66 (61.27)	148.14 (65.26)	218.41 (60.11)

B



Summary/Conclusion: Although no statistical tests were performed on these QoL endpoints based on the trial protocol, substantial and clinically relevant improvements in QoL were consistently observed with PEG across both LASA and EORTC QLQ-C30 scores.

EP596 RISK OF SERIOUS INFECTIONS IN PATIENTS WITH OR WITHOUT PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A REAL-WORLD MATCHED COHORT ANALYSIS

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Background: Due to complement-associated defects and the use of C5 inhibitors, the risk of infection may be high in patients with paroxysmal nocturnal hemoglobinuria (PNH). However, there are only limited data on comparative rates of hospitalized serious infections (SI) in patients (pts) with PNH vs pts without PNH.
Aims: To compare the incidence rate (IR) of SI, including bacterial, viral, or opportunistic infections in pts with or without PNH in a real-world setting.
Methods: Using the IBM MarketScan Commercial Database, a cohort of pts with PNH was identified with confirmed diagnosis of PNH between Jan 1, 2000 and Dec 31, 2019 and ≥3 claims for PNH within 365 consecutive days. The earliest claim that satisfied this criterion was assigned as the index. A cohort of individuals with no evidence of PNH in the study period was randomly selected from the database and matched (without replacement) to the PNH cohort by age, sex, insurance type, region, enrollment length, HIV status, diabetes status, and chemotherapy status at a 1:3 ratio. In this analysis, cases and controls were followed up for ≥6 months. Cases of SI were identified via validated algorithms (Pawar 2019 [PMID: 30679153]; Dommasch 2019 [PMID: 31075163]; Khan 2020 [PMID: 30980714]). We limited our analysis to SI to reduce surveillance bias associated with assessing outpatient infections. The analysis used all infections with discharge diagnosis codes, and a sensitivity analysis was performed by restricting to only SI with primary discharge diagnosis code. The SI discharge dates were required to be separated by ≥28 days to reduce the risk of counting readmissions for same infection (Feldman 2017 [PMID: 27589220]). A sensitivity analysis was performed using ≥14 days. Mean cumulative function (MCF) was used to characterize the cumulative number of infections. A Poisson regression model was fitted to estimate the incidence rate ratio (IRR) and 95% CI. The hazard of first infection was compared between groups via Cox proportional hazards model. Subgroup analyses were performed for infection subtypes and for pts with PNH with or without aplastic anemia (AA).
Results: Overall, 1083 pts with PNH (200 [18.5%] with AA; 322 [29.7%] who received anti-C5 agents during follow-up) and 3249 control pts were identified. In all, 20.9% of pts with PNH and 4.7% of control pts experienced ≥1 SI during a follow-up of 3196.9 and 12,596.0 person-years, respectively. The IR of SI was 12.7 (95% CI: 11.5, 14.0) and 1.7 (95% CI: 1.5, 2.0) per 100 person-years for pts with PNH and control pts, respectively, translating into an IRR of 7.27 (95% CI: 6.17, 8.57). The overall IR for SI was not significantly different between PNH patients with or without AA. Subgroup analyses showed higher IR in pts with PNH compared with control pts across all infection subtypes (Fig. 1A) and sex and age groups (Fig. 1B). The hazard of first infection was higher in pts with PNH vs control pts (HR, 6.08; 95% CI: 4.95, 7.48). The MCFs suggested that for every 100 pts with PNH, there were 15, 26, and 57 excess SI compared with control pts within 1, 2, and 5 years, respectively. The IR did not change when the allowable gap between discharge dates was ≥14 days. The higher IR of SI in pts with PNH remained consistent when the analysis was restricted to only SI with primary discharge diagnosis status (IRR, 6.75; 95% CI: 5.16, 8.84).

Table: Incidence of SI in PNH patients versus control patients. A, By infection subtype. B, By sociodemographic group.

A

Infection subtype	Cases				Controls					
	N	Events	Person-years	IR (95% CI)[a]	N	Events	Person-years	IR (95% CI)[a]	RD (95% CI)[a]	IRR (95% CI)
Serious bacterial infection	1083	292	3196.9	9.1 (8.1-10.2)	3249	165	12,596.0	1.3 (1.1-1.5)	7.8 (7.2-8.5)	6.97 (5.76-8.44)
Septicemia/ bacteremia	1083	142	3196.9	4.4 (3.7-5.2)	3249	44	12,596.0	0.3 (0.3-0.5)	4.1 (3.7-4.5)	12.72 (9.07-17.83)
Pneumonia/ URTI	1083	170	3196.9	5.3 (4.5-6.2)	3249	77	12,596.0	0.6 (0.5-0.8)	4.7 (4.2-5.2)	8.7 (6.65-11.39)
Pyelonephritis/ UTI	1083	91	3196.9	2.8 (2.3-3.5)	3249	76	12,596.0	0.6 (0.5-0.8)	2.2 (1.8-2.6)	4.72 (3.48-6.40)
Opportunistic infection	1083	69	3196.9	2.2 (1.7-2.7)	3249	20	12,596.0	0.2 (0.1-0.2)	2.0 (1.7-2.3)	13.59 (8.26-22.36)
Skin and soft tissue infection	1083	57	3196.9	1.8 (1.4-2.3)	3249	56	12,596.0	0.4 (0.3-0.6)	1.3 (1.0-1.8)	4.01 (2.77-5.80)

B

Population	Cases				Controls					
	N	Events	Person-years	IR (95% CI)[a]	N	Events	Person-years	IR (95% CI)[a]	RD (95% CI)[a]	IRR (95% CI)
All	1083	406	3196.9	12.7 (11.5-14.0)	3249	220	12,596.0	1.7 (1.5-2.0)	10.9 (10.2-11.7)	7.27 (6.17-8.57)
Age group										
<18 years	66	16	225.1	7.1 (4.1-11.5)	198	5	898.5	0.6 (0.2-1.3)	6.6 (4.6-8.6)	12.77 (4.68-34.87)
≥18 years	1017	390	2971.8	13.1 (11.9-14.5)	3051	215	11,697.5	1.8 (1.6-2.1)	11.3 (10.5-12.1)	7.14 (6.05-8.43)
Gender										
Male	505	190	1502.4	12.6 (10.9-14.6)	1515	113	5845.7	1.9 (1.6-2.3)	10.7 (9.6-11.9)	6.54 (5.18-8.26)
Female	578	216	1694.5	12.7 (11.1-14.6)	1734	107	6750.3	1.6 (1.3-1.9)	11.2 (10.1-12.2)	8.04 (6.38-10.14)
Insurance type										
Commercial	922	310	2666.4	11.6 (10.4-13.0)	2766	103	10,753.3	1.0 (0.8-1.2)	10.7 (9.92-11.4)	12.14 (9.71-15.17)
Medicare	161	96	530.4	18.1 (14.7-22.1)	483	117	1842.7	6.3 (5.3-7.6)	11.8 (8.9-14.6)	2.85 (2.18-3.73)

CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; RD, rate difference; SI, serious infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.
[a] Per 100 person-years; [b] RD is the incidence rate difference (incidence rate in cases-controls) per 100 person-years.

Summary/Conclusion: This analysis revealed substantial burden of SI in pts with PNH compared with pts without PNH. Measures to minimize the risk of SI could improve health outcomes of pts with PNH and reduce infection-related healthcare costs.

EP597 REAL WORLD DATA OF PATIENTS WITH ACQUIRED PURE RED CELL APLASIA: A SINGLE INSTITUTION EXPERIENCE

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Background: Pure red cell aplasia (PRCA) is a rare condition characterised by absent erythropoiesis within the bone marrow. The acquired form may present as a primary haematological disorder in the absence of other diseases and is classified as idiopathic PRCA. Occasionally, it can present secondary to other conditions and can be associated with various medications, viral infections, immune disorders, ABO-incompatible haematopoietic stem cell transplantation (HSCT) and malignancies such as thymomas.
Aims: This is a retrospective audit of all adult patients diagnosed with PRCA from 2010 to 2020 to evaluate underlying causes, treatment administered, time to response and survival outcomes.
Methods: A retrospective review of all the patients diagnosed with PRCA above the age of 18 at NUH from 2010 to 2020 was performed. Clinical data recorded include patient's age at diagnosis, gender, laboratory values at diagnosis, associated conditions, treatment administered, time to response and survival outcomes.
Results: A total of 31 patients were diagnosed with PRCA from our clinical database. There were 20 male and 11 female patients identified. Median age at diagnosis was 58 years (range: 27 – 83 years old). 11 patients were diagnosed with idiopathic PRCA and the rest were diagnosed with secondary PRCA (64.5%). Secondary PRCA was associated with conditions such as thymomas (n=3), autoimmune disease (n=3), drug-related (n=3), ABO-mismatched HSCT (n=7), haematological malignancies (n=2) and parvovirus-induced (n=1). Median haemoglobin at presentation was 6.1 g/dL (range: 3.3 – 12.3 g/dL) and median absolute reticulocyte count was 4.7 X 10^9/L (range: 1.7 – 27.8 X 10^9/L). 22 patients were started on immunosuppressive therapy (IST) and 87.5% achieved a complete response. 7 patients were unevaluable for treatment response due to patient's demise, lost to follow-up or short duration of follow-up. 1 patient was unable to tolerate IST and another patient subsequently lost response and now has refractory PRCA. 14 patients had sustained response to IST but only 14.3% were able to stop IST successfully without relapse. Amongst 4 patients with PRCA associated with thymomas, 2 were diagnosed post-thymectomy and all required adjuvant IST post-thymectomy for sustained response. A total of 26 patients were assessed for survival outcome. 21 patients were alive and 4 were deceased from underlying conditions such as end-stage renal failure (ESRF), relapsed acute leukaemia and infective complications. The cause of death for 1 patient was unknown but likely related to the underlying metastatic thymic carcinoma.

Summary/Conclusion: Given that PRCA is a rare diagnosis, the treatment initiated, associated response rates and long- term follow-up for evaluation of the sustainability of those responses are needed to help haematologists better manage these patients.

EP598 CLINICAL CHARACTERISTICS OF 512 ECULIZUMAB-NAIVE PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS IN CHINA: A SINGLE-CENTER OBSERVATIONAL STUDY

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Background: The characters update of patients with paroxysmal nocturnal hemoglobinuria (PNH) in China has not been well addressed. We retrospectively reviewed patients with complete data who visited Peking Union Medical College Hospital from 2009 to 2018 and had been followed up for more than 2 years.
Aims: To update the characters of patients with PNH in China.
Methods: Retrospectively analyzed 512 patients diagnosed with PNH in the past ten years from a single center in China.
Results: There were 512 patients, including 56.3% males and 43.8% females. The median age at disease onset was 33 (9~80) years. Classic PNH, bone marrow failure (BMF)/PNH and subclinical PNH accounted for 52.3%, 46.3% and 1. 6% of the patients, respectively. Most of the patients were at 21~40 years (50.6%) and 41~60 years (25.4%). The most common symptoms and positive lab findings were hemolytic and BMF related. Most of the patients had >50% of Flare- granulocytes. PNH clone size correlated with hematoglubinuria (R2=0.038, P=0.001), erectile dysfunction (R2=0.03, P=0.019), reticulocyte (R2=0.164, P<0.01) and LDH level (R2=0.268, P<0.001). Thrombosis events (TEs) occurred in 18.0% of patients. 88.8% were venous and 11.2% were arterial events. 77.2% of the patients had single-site thrombosis with the abdominal vein (44.8%) the most common site. 22.8% of patients experienced repeated or multiple-site thrombosis. Renal deficiency happened in 16.9% of patients. Patients with classic PNH had longer disease duration, bigger PNH clone size, higher LDH, TBil, DBil, AST, Scr, and blood cell count, lower ferritin compared with those with BMF/PNH. Although the rate of thrombosis was similar for patients with classic PNH (17.3%) and BMF/PNH (19.1%, P=0.66), patients with larger PNH clone and BMF/PNH had higher chance of renal impairment (P<0.05). Immunosuppressive agents, glucocorticoids were the most common treatments and only 39.1% of patients with thrombosis received anticoagulants. The chance of pregnancy was rare and the abortions were high for women in need of fertility. More evolution from BMF/PNH into classic PNH (26.2%) and less from classic PNH into AA/PNH (2.2%) and even less into malignancies were observed at a median of 93.5 (24~144) months follow-up. The major causes of deaths were thrombosis (29.6%), hemorrhage (18.5%) and infections (18.5%). Thrombosis (HR, 3.462; P =0.013) and renal deficiency (HR, 2.105; P =0.032) were the independent risk factors for overall survival (OS).
Summary/Conclusion: Although most PNH patients survived without complement inhibitors, more hemolytic features of PNH in China might be greatly improved with complement inhibitors in the future.

Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

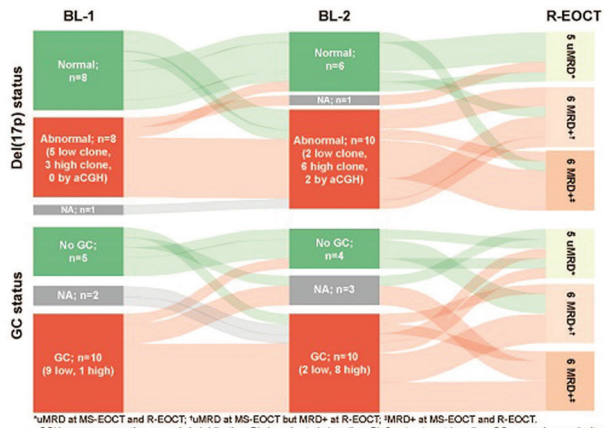
EP599 IMPACT OF UNFAVORABLE GENETICS ON MINIMAL RESIDUAL DISEASE (MRD) RESPONSE TO VENETOCLAX+RITUXIMAB RETREATMENT IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL): PHASE 3 MURANO SUBSTUDY

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Background: At the 5-yr update of the Phase 3 MURANO trial (NCT02005471), median (95% CI) progression-free survival (PFS) was 54 (48–57) mo with venetoclax-rituximab (VenR) or 17 (15–22) mo with bendamustine-rituximab (BR) treatment, while 36% of VenR-treated patients (pts) and 63% of BR-treated pts had received new anti-CLL therapy. A substudy from 2018 onward enrolled 34 R/R CLL pts who progressed after initial treatment to receive VenR as retreatment (n=25) or crossover from BR (n=9). We report on the VenR-treated pts who had progressive disease (median [range] PFS 46 [36–58] mo), were eligible for anti-CLL therapy, and were retreated with VenR.
Aims: Evaluate molecular profile changes from the MURANO main study baseline (BL-1) to the retreatment baseline (BL-2), describe the genetic features at BL-2 and assess their association with MRD response to VenR.
Methods: Pts on retreatment received VenR (Ven 400mg/d for 2 yrs + monthly R for the first 6 mo). Genomic complexity (GC; defined by copy number alterations [CNA]: 0–2 non-complex, 3–4 low, ≥5 high) was assessed by array comparative genomic hybridization (aCGH). Chromosomal abnormalities were analyzed by aCGH and fluorescence *in situ* hybridization (high clone ≥20%, low clone 7–<20%). Peripheral blood MRD was analyzed by allele-specific oligonucleotide PCR and/or flow cytometry, with a $<10^{-4}$ threshold for undetectable (u)MRD.
Results: At data cutoff (13 Oct 2020), 25 pts were retreated with VenR; median (range) follow-up 12.1 (2.5–21.2) mo, median (range) treatment-free interval 28.3 (12.4–38.1) mo. Unfavorable genetic characteristics were enriched from BL-1 to BL-2. At BL-2, 14/24 pts had del(17p), including 11 high clones, with 3 newly acquired and 4 who shifted from low to high clone. An increase in CNA from BL-1 to BL-2 was observed; median (range) was 3 (1–6) at BL-1 and 4 (1–15) at BL-2 (P<0.05). Overall, 11/20 pts had GC (8 with high GC) at BL-2, with either new chromosomal abnormalities or increased clone size in poor prognostic lesions such as 2p and 8q gain, and 7q, 8p, 11q and 18p loss.
Investigator-assessed objective response rate to VenR retreatment was 70% (14/20 evaluable pts; 50% [14/25] among intent-to-treat pts; 5 complete response, 9 partial response, 5 non-evaluable). Of 17 pts with available MRD data at the retreatment end of combination treatment (R-EOCT), 5 achieved uMRD and 12 were MRD+ (Figure). Sixteen pts had evaluable del(17p) results. Of 6 pts without del(17p) at BL-2, 4 attained uMRD at R-EOCT while all 10 with del(17p) at BL-2 were MRD+ at R-EOCT. Of these, 4/10 had new del(17p) from BL-1 or had evolved from del(17p) low clone to high clone. GC status was available for 14 pts. Of 4 pts without GC at BL-2, 2 attained uMRD at R-EOCT. Of 10 pts with GC at BL-2, 8 were MRD+ and 2 had uMRD at R-EOCT. Of the pts with GC at BL-2, 5/10 had new or increased GC from BL-1. Ten pts attained uMRD at main study EOCT; 4/10 re-attained uMRD at R-EOCT and 6/10 did not. Among the 6 who were unable to re-attain uMRD, 83% (5/6) had del(17p) at BL-2 (3/5 were newly evolved from BL-1) compared with 40% (2/5) at BL-1.

Figure. Increased del(17p) clonality and GC negatively impact MRD response at R-EOCT



*uMRD at MS-EOCT and R-EOCT; †uMRD at MS-EOCT but MRD+ at R-EOCT; ‡MRD+ at MS-EOCT and R-EOCT.
aCGH, array comparative genomic hybridization; BL-1, main study baseline; BL-2, retreatment baseline; GC, genomic complexity; MRD, minimal residual disease; MS-EOCT, main study end of combination treatment; NA, not available; R-EOCT, retreatment end of combination treatment; uMRD, undetectable minimal residual disease.

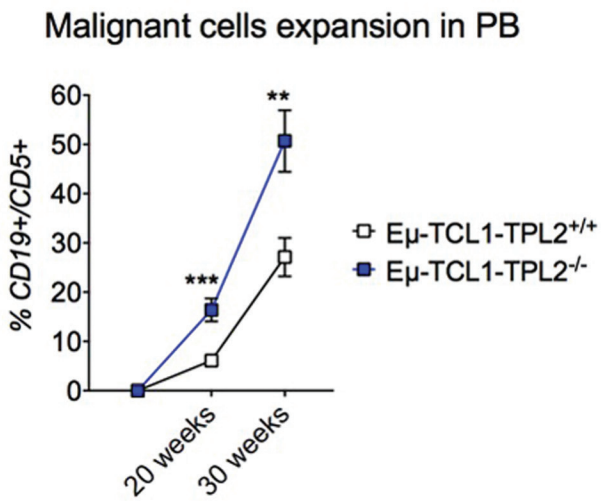
Summary/Conclusion: Pts who relapsed after initial VenR therapy were highly enriched for unfavorable characteristics at BL-2. We observed a genetic profile shift from BL-1 to BL-2, with greater GC as well as higher prevalence and increased clonality in del(17p). Increased prevalence of unfavorable genetic risk factors negatively impacted MRD response of retreatment pts at the R-EOCT. Deep initial response alongside favorable BL-2 characteristics predict attainment of uMRD with VenR retreatment.

EP600 TPL2 ABLATION ACCELERATES DISEASE DEVELOPMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA EU-TCL1 MOUSE MODEL

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Background: Tumor progression locus 2 (TPL2; also known as MAP3K8) is a serine-threonine kinase that regulates innate/adaptive immunity and inflammation, through ERK activation and cytokines gene expression. Upon inflammatory signals, TPL2 modulates the expression of cytokines and chemokines that promote immune cell recruitment, differentiation, and activation, and in turn, the establishment of an inflammatory microenvironment. Increased TPL2 kinase activity is involved in inflammatory diseases and operates as a potent tumor promoter in most cancers, in association with known oncogenes. However, suppressed TPL2 expression has also been reported in some tumor types, such as lung cancer, and its ablation is associated with increased tumorigenesis in several experimental cancer models, being required for optimal p53 response to genotoxic stress. In line with the latter cases, we have observed, using gene expression datasets, that TPL2 expression is also lower in leukemic cells from patients with chronic lymphocytic leukemia (CLL) as compared to normal B cells, suggesting that TPL2 reduction might be also involved in the pathogenesis of this disease.
Aims: We aimed at investigating the *in vivo*effects of TPL2 ablation in the disease development of CLL, taking advantage of the Em-TCL1 mice, a validated animal model for CLL, and at focusing our attention on the molecular pathways affected by the absence of TPL2.
Methods: We crossed TPL2$^{-/-}$mice with Eμ-TCL1 mice to generate Eμ-TCL1-TPL2$^{-/-}$animals. We analyzed disease expansion by assessing the percentage of CD19^{+}CD5^{+}malignant cells in the peripheral blood (PB), spleen, and bone marrow (BM) using flow cytometry. Malignant cells were collected from the spleen, sorted by flow cytometry, and analyzed for gene expression using RNAseq. We validated the expression levels of selected genes by qRT-PCR.
Results: Eμ-TCL1-TPL2$^{+/+}$mice develop CLL-like disease with aging. Analysis of CD19^{+}CD5^{+}cells at 20 and 30 weeks of age showed increased malignant cell expansion in all relevant tissues. In particular, in the PB of Eμ-TCL1-TPL2$^{-/-}$mice we observed 16% malignant cells at 20 weeks and 51% at 30 weeks at variance with control Eμ-TCL1-TPL2$^{+/+}$mice where malignant cells were 6% and 27%, respectively ($p<0.01$) (Figure 1). In the absence of TPL2, disease expansion was also accelerated in the BM ($p<0.05$) and spleen ($p<0.01$) analyzed at the same time points.
Gene expression profiling of B cells purified from Eμ-TCL1-TPL2$^{-/-}$and Eμ-TCL1-TPL2$^{+/+}$mice showed upregulation of genes involved in cytokine/chemokine production and leukocyte activation in the former. Validation by qRT-PCR confirmed higher expression of genes implicated in CLL pathogenesis and tissue homing in the Eμ-TCL1-TPL2$^{-/-}$animals, including CCL4 ($p<0.05$), CCL3 ($p<0.05$), CCR5 ($p<0.01$), Zap70 ($p<0.05$) and BAFF ($p<0.01$). We also observed, in Eμ-TCL1-TPL2$^{-/-}$mice, downregulation of genes involved in cell death regulation, including pro-apoptotic factors such as NOXA ($p<0.01$), PUMA ($p<0.01$), GADD45 ($p<0.01$), and ATF-3 ($p<0.01$). The expression of all these genes was not altered in either Eμ-TCL1 or TPL2$^{-/-}$parental mice as compared to wild type mice.



Summary/Conclusion: Ablation of TPL2 expression accelerate CLL development in Eμ-TCL1-TPL2$^{-/-}$mice. The absence of TPL2 leads to the inhibition of pro-apoptotic genes in malignant cells and the upregulation of genes with major pathogenetic roles in CLL, including tissue invasion and dissemination. Our data suggest that loss of TLP2 might synergistically contribute to disease development under pro-tumorigenic conditions.

EP601 LONG NON-CODING RNA LINC00525 PROMOTES PROLIFERATION AND INHIBITS APOPTOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS BY TARGETING MIR-338-3P/ WWP1 AXIS

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Background: Emerging evidences have indicated that long noncoding RNAs (lncRNAs) play essential roles in the development and progression of cancers. LncRNAs were aberrantly expressed in most hematological malignancies including leukemia, participating in tumor suppression or promoting oncogenesis and modulating key genes in different pathways. Dysregulation of LINC00525 has recently been reported in several types of cancers, and researches on the function of LINC00525 in cancers suggested that LINC00525 could act as an oncogene. But the functional involvement of LINC00525 has not been studied in chronic lymphocytic leukemia (CLL).
Aims: In order to explore the expression and biological function of LINC00525 in CLL.
Methods: In our study, CCK8 assays, cycle assays, apotosis experiments were used to identify biological effects of LINC00525 on CLL cells in vitro. The expression of LINC00525, microRNA-338-3p (miR-338-3p) were detected by qRT-PCR. Dual-luciferase reporter assay and RNA immunoprecipitation (RIP) assay were performed to show the interactions of LINC00525 and miR-338-3p. The bioinformatics methods were completed to find the target genes of miR-338-3p. And Dual-luciferase reporter assay and Western blot analysis were further used to confirm the target gene of miR-338-3p.
Results: We found that LINC00525 knockdown obviously suppressed CLL proliferation and increase apoptosis in vitro. Besides, silencing of LINC00525 significantly increased the expression of microRNA-338-3p (miR-338-3p), which could play a tumor suppressor role in CLL. Moreover, dual-luciferase reporter assay and RNA immunoprecipitation (RIP) assay revealed that LINC00525 exerted tumor-suppressive functions by binding directly to miR-338-3p, and there was a reciprocal inhibition between LINC00525 and miR-338-3p in the same RNA induced silencing complex (RISC). Furthermore, overexpression of LINC00525 enhanced the expression of suppression of the E3 ubiquitin ligase (E3) WWP1, which was identified as a downstream target gene of miR-338-3P. Thus, LINC00525 positively regulated WWP1 expression through sponging miR-338-3P, and acted as tumor suppressor in CLL.
Summary/Conclusion: LINC00525 promotes cell proliferation through LINC00525/miR-338-3p/ WWP1 axis in CLL.

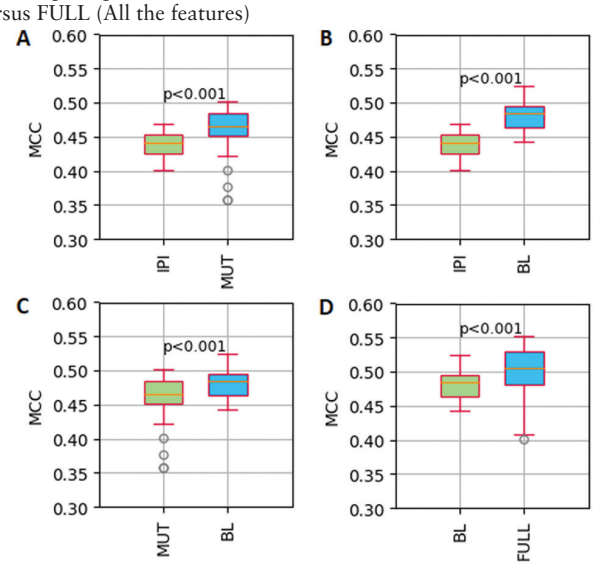
EP602 COMPARING MACHINE LEARNING-BASED PREDICTION OF TREATMENT IN CLL USING RECURRENT GENE MUTATIONS VERSUS (PARA)CLINICAL FEATURES

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Background: The international prognostic index for patients with chronic lymphocytic leukemia (CLL-IPI) is the current standard for prognostication. We previously improved the CLL-IPI by 1) using a Treatment and Infection Model (CLL-TIM) and 2) by the number of signaling pathways impaired by recurrent mutations. In this study, we compare the performance of Machine Learning models trained on CLL-IPI variables plus baseline (para)clinical variables with CLL-IPI plus recurrent mutations in patients with newly diagnosed CLL.
Aims: 1) Investigating the predictive performance of CLL-IPI variables, recurrent gene mutations, and (para)clinical variables for Treatment at time of CLL diagnosis.
2) Studying the impact of data-driven selection of the Machine Learning algorithm as well as the interaction between data variables and the algorithms.
Methods: In a cohort consisting of 314 patients with newly diagnosed CLL, CLL-IPI variables, recurrent gene mutations, and (para)clinical variables were extracted and used as features in a predictive framework in which a variety of Machine Learning algorithms (Linear SVM, AdaBoost, CatBoost, XGBoost, LightGBM, RandomForest, ExtraTrees, and Bagging) were used to predict CLL treatment as the outcome.
By using different combinations of feature sets, four models were defined as following:
1. CLL-IPI features only (IPI),
2. CLL-IPI features plus recurrent mutations (MUT),
3. CLL-IPI features plus (para)clinical baseline features (BL),
4. All the above features (FULL).

Patients were randomly split into a 60% train set and a 40% blinded validation set. The train set was further split 40 times into training set (75%) and test set (25%) to perform hypothesis testing, whereas the validation is still blinded. We here report the preliminary results on the train set.
Results: The preliminary results showed that adding either data on recurrent mutations (MUT) or (para)clinical baseline data (BL) improved the predictive performance significantly compared to the CLL-IPI only (Fig. 1A and 1B). Comparing the BL and MUT models, showed that adding baseline (para)clinical features (BL) predicted CLL treatment better than adding recurrent mutations (MUT) (Fig. 1C). As expected, including all the three feature sets (FULL) outperformed the BL model. For all four hypotheses, the *Bagging* algorithm achieved the best performance (Fig. 1D).
Fig. 1 illustrates the distribution of MCC (Mathew Correlation Coefficient) values of each model. **A**) IPI (CLL-IPI features) versus MUT (CLL-IPI plus recurrent mutations features), **B**) IPI versus BL (CLL-IPI features plus (para)clinical baseline features), **C**) MUT versus BL, **D**) BL versus FULL (All the features)



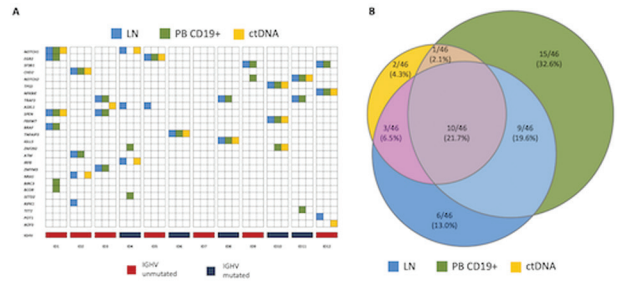
Summary/Conclusion: We here demonstrate that including data on recurrent mutations and (para)clinical features on top of CLL- IPI can improve the predictive performance in a Machine Learning model predicting CLL treatment. Furthermore, a data driven selection of the optimal Machine Learning algorithm improves the predictive power. Upon confirmation of these findings in a blinded internal validation set and in external cohorts, these data indicate that combined modelling of multidimensional OMICs and (para)clinical data can pave the way for truly personalized management of CLL.

EP603 MULTIREGIONAL SEQUENCING AND CIRCULATING TUMOR DNA ANALYSIS PROVIDE COMPLEMENTARY APPROACHES FOR COMPREHENSIVE DISEASE PROFILING OF SMALL LYMPHOCYTIC LYMPHOMA

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Background: Spatial heterogeneity is a hallmark of metastatic solid cancer, while it is less obvious in leukemic B-cell tumors that systemically involve secondary lymphoid organs and circulate in blood. Small lymphocytic lymphoma (SLL) is a model that can inform on whether spatial heterogeneity exists in leukemic B-cell tumors, as it is the sole entity that markedly involves both blood and lymph nodes in all cases. Circulating tumor DNA (ctDNA) recapitulates disease genetics in aggressive lymphomas but its role advantage multiregional sequencing of peripheral blood and lymph node biopsy is unexplored.
Aims: To dissect the genetics of different anatomical compartments in SLL with a multiregional sequencing and liquid biopsy approach.
Methods: Patients with SLL (n=12) were referred to our institution and provided with: i) tumour gDNA extracted from fresh frozen lymph node cells or formalin-fixed paraffin-embedded (FFPE) lymph node biopsies; ii) tumour gDNA extracted from sorted peripheral blood (PB) CD19+/CD5+ cells; iii) ctDNA from plasma; and iv) germline gDNA extracted from CD3+ T-cells and/or granulocytes for comparative purposes. The CAPP-Seq assay was used for the mutational profiling and comprised a panel of 124 genes relevant in B cell malignancies. Copy number variants (CNVs) were identified with the GATK4 CNV workflow.
Results: Overall, the analysis of the three SLL compartments analyzed (i.e. lymph node biopsy, circulating PB CD19+ cell compartment, and plasma ctDNA) identified a total of 46 mutations in genes known to be mutated in B cell malignancies. At least one mutation was found in 11 out of 12 (91.7%) patients with a median number of 3 mutations per patient (range 0-6). The most frequently mutated genes were *TRAF3* and *ASXL1* in 3/12 (25.0%) patients each, followed by *NOTCH1*, *EGR2*, and *SF3B1* in 2/12 (16.7%) patients each (Fig 1A). By comparing the representation of gene mutations in the different anatomical compartments investigated in SLL, 10/46 (21.7%) mutations were identified in all three compartments, whereas the remaining mutations were differently distributed among the three examined compartments. More precisely, 6/46 (13.0%) mutations were exclusive of the lymph node biopsy, 15/46 (32.6%) were exclusive of the circulating PB CD19+ cell compartment, and only a small fraction of mutations (2/46; 4.3%) were detectable uniquely in the plasma ctDNA (Fig 1B). Interestingly, from a translational perspective, a *BIRC3* mutation that may harbor potential predictive value, has been identified only in the circulating PB CD19+ cell compartment. In addition, a bioinformatic algorithm for CNVs analysis has been applied to 8 patients in order to identify potential additional differences between the lymph node biopsy and the circulating PB CD19+ cell compartment. This algorithm showed 100% concordance with FISH karyotype and allowed the detection of at least one CNVs difference in 3/8 patients (37.5%).



Summary/Conclusion: These results suggest that the multiregional sequencing of the different anatomical compartments of SLL is essential to gain a comprehensive view of the disease mutational landscape. Consistently, mutational analysis of the SLL lymph node biopsy should be coupled to analysis of the circulating PB CD19+ cell compartment, and eventually with ctDNA analysis. This observation may have clinical relevance when treatment tailoring is based on specific gene mutations used as molecular predictors that might be present in only one specific anatomical compartment of the disease.

EP604 CFOS/MIR-181A CIRCUITRY IS INVOLVED IN BCR SIGNALLING AND DEATH OF CLL CELLS.

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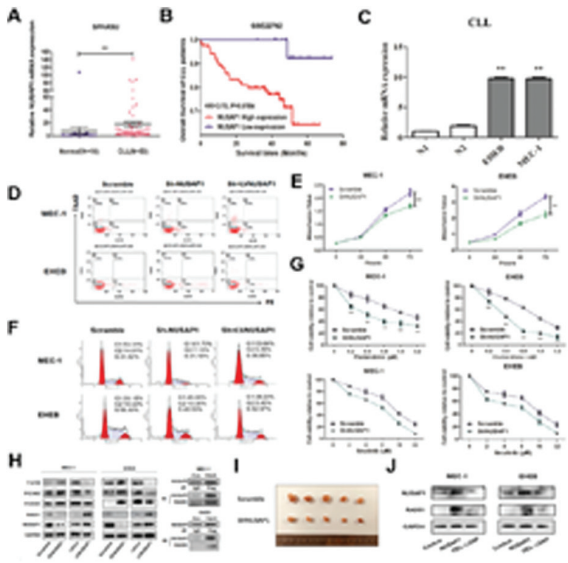
Background: B-cell receptor (BCR) signalling plays a pathogenic role in Chronic Lymphocytic Leukemia (CLL); in CLL, there is constitutive activation of the BCR, and the CD40L-CD40 signalling is impaired. We have recently demonstrated that miR-181b is a downstream effector of B and activated T cells' interaction. Indeed, miR-181b is an effector of the CD40L-CD40 pathway, which induces death of CLL cells by increasing the cytotoxic activity of T cells versus the leukemic clone. We thus hypothesized that also miR-181a could stimulate this process. Considering the crosstalk between the CD40L-CD40 and the BCR pathway, we speculated the involvement of the miR-181a also in the BCR pathway.
Aims: Assess the involvement of miR-181a in BCR signalling pathway; evaluate the ability of miR-181a to induce the cytotoxic activity of T cells.
Methods: Since the BCR stimulation induces an heterogeneous response in the expression of miRNAs due to BCR stereotype, to assess the involvement of miR-181a in BCR signalling pathway, CLL cells were treated in vitro with Ibrutinib, a BCR inhibitor. The expression of the miR was then analysed in CLL samples from patients treated with Ibrutinib. To evaluate whether the transcription factor cFOS take part in BCR signalling, its expression was analysed after Ibrutinib treatment. To test whether the transcription factor cFOS regulates the miR-181a, the expression of the miR was analysed after overexpression or silencing of cFOS. To assess if the miR-181a could promote the cytotoxic activity of T cells, Cytotoxic T lymphocytes (CTLs) were generated by mixing CD40L-stimulated and miR-181a-overexpressed CLL cells with autologous T cells.
Results: We observed an increase in miR-181a expression after in vitro inhibition of BCR signalling; we observed the same effect also in vivo in most of CLL patients treated with Ibrutinib. The increased expression of miR-181a inversely correlated with the amount of White Blood Cells (WBC) and, specifically, it was higher in those patients for which the WBC decreased more than 50%. To explain a possible mechanism by which the expression of miR-181a increase, we focused on the transcription factor cFOS, which we already found involved in the transcriptional regulation of miR-181b in CLL; we found that cFOS expression decreased after Ibrutinib treatment in vitro and that overexpression of cFOS downregulated miR-181a, while its silencing increased the expression of the miR in CLL cell line.
Since the overexpression of miR-181a was associated with a reduction of the WBC in vivo, we sought to identify a mechanism by which the miR could affect cell survival. To this end, we focused on the IL10, whose downregulation through miR-181b increase the cytotoxic activity of CTL. We found that miR-181a overexpression downregulated the levels of IL10 after the CTL generation assay in half of the analysed patients, and this was associated with the increase in the percentage of CTL. Conversely, in those patients for which we did not observed a reduction of IL10, there were no effect on CTL amount. Previous studies demonstrated that the IL10 was upregulated by cFOS protein and that cFOS was a target of miR-181a. Considering that cFOS negatively regulates miR-181a, we suggest that the circuitry consisting of cFOS/miR-181a could play a role in BCR signalling and CLL cells death.
Summary/Conclusion: MiR-181a is upregulated by BCR signalling inhibition in vitro and in vivo. The overexpression of miR-181a promotes the generation of autologous cytotoxic T cell versus the leukemic clone through the downregulation of IL10.

EP605 NUSAP1 ENHANCES DRUG RESISTANCE BY BINDING TO RAD51 THROUGH DNA DAMAGE REPAIR PATHWAY IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Enhanced DNA damage repair effect is an important mechanism for drug-resistance in chronic lymphocytic leukemia (CLL). Previous studies reported that nucleolar and spindle associated protein 1 (NUSAP1) was involved in DNA damage repair process and played important roles in the development, progression, and metastasis in several types of cancer. However, its role and mechanism in the development of CLL are still unclear.
Aims: We aim to further explore the expression and exact role of NUSAP1 in CLL development, providing theoretical basis for new molecular markers and targeted therapy.
Methods: Expression levels of NUSAP1 mRNA and protein in CLL cell lines and patient specimens were detected by qRT-PCR and Western blot, and Kaplan-Meier survival curve and overall survival were analyzed by log-rank test. Peripheral blood samples from *de novo* CLL patients and healthy volunteers were collected with informed consents at the Department of Hematology in Shandong Provincial Hospital Affiliated to Shandong University (SPHASU). Microarray datasets GSE22762 were obtained from Gene Expression Omnibus. With altering NUSAP1 expression by lentivirus-transfected cells in vitro, the effects of NUSAP1 on cell proliferation, apoptosis and cycle were detected by CCK8, Annexin V-PE /7AAD staining and PI/RNase staining respectively.
Results: To study the role of NUSAP1, CLL specimens were chosen for qRT-PCR analysis. The expression level of NUSAP1 gene in samples of CLL patients was significantly increased than that of healthy donors ($P<0.05$) (Figure A). Besides, the results indicated that the overall survival (OS) of patients with highly expressed NUSAP1 was significantly worse than in patients with low expression with the statistical analysis database GSE22762 (Figure B). mRNA and protein expression levels of NUSAP1 were significantly higher in CLL cell lines than in PBMCs from healthy donors (Figure C). Moreover, the amounts of DNA fragmentation of the apoptotic cells were remarkably increased in shNUSAP1 transfection cells compared with the Scramble group (Figure D). Our findings indicated that NUSAP1 knockdown notably suppressed cell proliferation (Figure E). In addition, after downregulating NUSAP1, MEC-1 and EHEB cells were blocked in G0/G1 phase (Figure F). Treatment with fludarabine or ibrutinib in shNUSAP1 group showed enhanced cytotoxicity in CLL cells (Figure G). Suppression of NUSAP1 inhibited the action of proteins in DNA damage repair pathway (Figure H). Through COIP, NUSAP1 was identified to bind with RAD51 (Figure H). After CLL cells were subcutaneously injected into (SCID) beige mice for 45 days, tumor volumes were significantly reduced in mice treated with ShNUSAP1 cells compared to scramble group (Figure I). Compared with the NUSAP1 upregulated group, the NUSAP1-ΔSAP transfection group suppressed RAD51 expression as expected (Figure J). Hence, NUSAP1 participates in the DNA damage repair process and enhances the drug resistance in CLL.



Summary/Conclusion: Collectively, our findings demonstrate that NUSAP1 contributes to DNA damage repairing by binding with RAD51 and promoting stable proliferation of CLL cells both *in vitro and vivo*. Therefore, NUSAP1 is expected to be a potential target for the treatment of CLL with drug-resistance.

EP606 CLINICAL VALIDATION OF A NGS CAPTURE PANEL TO IDENTIFY MUTATIONS, COPY NUMBER ALTERATIONS AND CHROMOSOMAL REARRANGEMENTS IN MATURE B-CELL NEOPLASMS

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Background: At a research level, next-generation sequencing (NGS) techniques have provided a large amount of new information, sometimes with clinical implications. In mature B-cell neoplasms (MBCN) the main applications are focused on the identification of somatic variants, while there are limited applications including rearrangements and copy number alterations (CNAs), which are crucial in clinical practice.
Aims: Thus, we designed an NGS capture panel to analyze in a single assay all key genetic aberrations including single nucleotide variants (SNVs), indels, CNAs and chromosomal rearrangements.
Methods: A total of 173 samples from 170 patients diagnosed of different MBCN (55 DLBCL, 43 MZL, 37 CLL, 14 FL, 12 MCL, 5 BL, 4 HCL) were analyzed. DNA was extracted from peripheral blood (n=88), bone marrow (n=7) or other tissues (n=78). Samples were tested in two sequentially designed versions of a custom targeted panel (PV1 and PV2) (Roche Nimblegen) covering 4 rearrangement genes (*BCL2*, *BCL6*, *MYC* and *CCND1*), 35 frequently mutated genes, and 13 CNA regions (Figure). PV1 also included 9,111 SNPs to assess CNAs genomewide (size=4.6Mb). In PV2 the size was significantly reduced (1.4Mb), and the design for *BCL2* and *MYC* optimized. Sequencing was performed using Illumina NextSeq500. Data were analyzed for SNVs and small indels (MUTECT2), rearrangements (DELLY and Smoove) and CNAs (CopywriteR). Results were validated using different genetic techniques (chromosome banding analysis, FISH, genomic arrays, PCR, Sanger and other NGS panels).
Results: High sensitivity and specificity were achieved (Figure). Regarding mutations, variants with a mean coverage >110x, ≥10 supporting variant reads, and variant allele frequency ≥ 6.4% for PV1 and ≥ 4.2% for PV2 were considered. Besides 107 mutations identified in clinical practice (107/108, 99%), 461 variants affecting the cellular pathways typically described in MBCN were detected, of which 14.1% were classified as pathogenic and 38.7% as likely pathogenic. Regarding rearrangements, optimization of the PV2 design for *BCL2* and *MYC* allowed an improvement in sensitivity. Both panels identified the translocation partners in all patients [including 31% (20/65) in which the partner could not be identified by conventional techniques]. While *BCL2* and *CCND1* were always rearranged with IGH, 42% of *BCL6* rearrangements involved non-IG genes, which were highly variable. *MYC* was rearranged with IG genes in 72% of cases. In three cases, double rearrangements involving two different translocation partners were detected. Furthermore, a MCL was identified carrying a double rearrangement of *MYC* with chromosomes 4 and 11, besides *CCND1*-IGH rearrangement. Regarding CNAs, both panels were highly concordant in terms of size and location of the detected aberrations with those previously defined by genomic arrays. The NGS panels achieved a similar sensitivity than genomic arrays (cut off detection: 20-30% aberrant cells) but the removal of SNPs from PV2 compromised it (Figure).

Panel design						Sensitivity and specificity	
						PV1	PV2
Single nucleotide variants (SNVs) and indels		*TNFRSF14* *XPO1* *CARD11* *BIRC3* *TP53* *NOTCH2* *TNFAIP3* *NOTCH1* *MAP2K1*	*ARID1A* *MYD88* *EZH2* *CCND1* *CD79B* *CXCR4* *ARID1B* *TRAF2* *EP300*	*BCL10* *NSD2* *POT1* *MLL2* *CD79A* *SF381* *BRAF* *ATM* *CREBBP*	*ID3* *CCND3* *UBR5* *FOXO1* *KLF2* *CHD2* *MEF2B* *TCF3*	Sensitivity= 100% Specificity= 100%	Sensitivity= 97% Specificity= 100%
Copy number alterations (CNAs)	Losses	1p36 11q22.1-q24	6q13-q26 13q14	7q22.1-q35 8p21.1-p23.1	9p21 17p13 (TP53)	Sensitivity= 83% Specificity= 100%	Sensitivity= 66% Specificity= 99%
	Gains	2p12-2p16 Chr18	Chr3	8q24 (MYC)	Chr12		
Rearrangements		*BCL2*				Sensitivity= 70% Specificity= 100%	Sensitivity= 86% Specificity= 100%
		BCL6				Sensitivity= 100% Specificity= 100%	Sensitivity= 86% Specificity= 100%
		MYC				Sensitivity= 50% Specificity= 100%	Sensitivity= 75% Specificity= 100%
		CCND1				Sensitivity= 100% Specificity= 100%	Sensitivity= 100% Specificity= 100%

Figure. Summary of the target alterations analyzed in the NGS panels, as well as the sensitivity and specificity achieved in each of the designed versions (PV1 and PV2)

Summary/Conclusion: Our NGS panel allows a more comprehensive evaluation of the genomic landscape of MBCN patients in a single assay by (a) detecting the most important and recurrent mutations, translocations and CNAs with high sensitivity, (b) identifying rearrangement partners not detected by FISH and (c) identifying other clinically relevant genetic alterations not included in clinical guidelines. Although further studies are required to improve its performance, it could potentially be implemented in clinical practice.

EP607 INFLUENCE OF THE STATE OF THE "TELOMERE-TELOMERASE" SYSTEM ON THE COURSE OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Chronic lymphocytic leukemia (CLL) is a prevalent lymphoproliferative disease characterized by a high heterogeneity of the course. The variability of CLL is directly related to the immunobiological characteristics of cell clones in each patient, differences in the survival of leukemia cells, their activation, proliferation and interaction with the microenvironment. Telomeres, which are located at the ends of chromosomes and represent nucleoprotein structures, serve as protection against "replicative aging" of cells during division. In tumor cells, genomic instability is associated with pronounced telomere dysfunction, at the same time critical telomere contraction and, ultimately, chromosome degradation with loss of cell viability are prevented by the activation of cellular telomerase.
Aims: To evaluate the influence of the length of telomeric fragments (LTF) of lymphocytes and telomerase activity in CLL on the nature of the disease course.
Methods: We examined 95 patients at the onset of CLL and 22 healthy individuals (comparison group), comparable in age and gender. The length of telomeric fragments in CD19-positive peripheral blood lymphocytes was determined using the multi-color flow cytometry method with the stage of fluorescent in situ hybridization ("FACS Canto II", Becton Dickinson). The activity of cellular telomerase was evaluated by the level of expression of the matrix RNA gene of the catalytic unit of the human telomerase reverse transcriptase (hTERT) enzyme, for which the content of complementary DNA in the reactions of reverse transcription and quantitative polymerase chain reaction was determined in the peripheral blood in real time («DT-96», DNA Technology). The significance of the differences in the parameters was

determined using the Mann-Whitney test. The time from the diagnosis of CLL to the start of specific treatment was calculated by the Kaplan-Meyer method.
Results: LTF in peripheral blood B-lymphocytes in patients was significantly shorter than in donors (3,7 [2,8; 4,6] kb vs. 6,8 [5,6; 8,7] kb, p < 0,01). In all patients with CLL, cellular hTERT was in an activated state. Reduction of LTF below 5,0 kb, corresponding to less than 1,5 standard deviations from the mean value in the comparison group, was found in 35,7 % of cases, moderate activation of hTERT (up to 15,2 copies per µl) - in 74,7 %, high activation (more than 15,2 copies per µl) - in 25,3 %. There were 4 groups of patients, depending on the levels of LTF and the degree of hTERT activation. Group I included 9 patients with shortened LTF and high hTERT activation, group II - with shortened LTF and moderate hTERT activation (n=25), group III - without a decrease in LTF with high hTERT activation (n=15), and group IV - without a decrease in LTF with moderate hTERT activation (n=46). The median duration of the time period from the diagnosis of CLL to the start of specific therapy in groups I, II, III and IV of patients was 4,0; 22,0; 30,0 and 36,0 months, respectively. The time interval before the start of therapy in patients of group I was significantly shorter than in other groups (p≤ 0,001). No statistical differences were found between groups II, III, and IV.
Summary/Conclusion: A significant influence of the state of the "telomer-telomerase" system on the nature of the CLL course was established. A decrease of LTF in B-lymphocytes, combined with a high activation of cellular telomerase, correlates with earlier initiation of therapy.

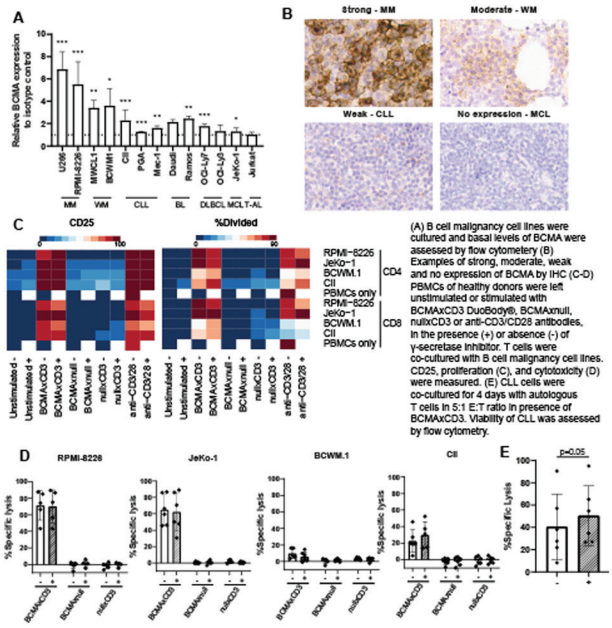
EP608 BCMA AS A TARGET FOR T-CELL REDIRECTING BISPECIFIC ANTIBODIES IN B-CELL LYMPHOMAS AND CLL

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Background: B-cell maturation antigen (BCMA) is highly expressed on normal and malignant cells and is a feasible target for multiple myeloma (MM) immunotherapy, which is currently clinically exploited with Teclistamab (Tec, BCMAxCD3 DuoBody®, JNJ-64007957; NCT03145181). BCMA is expressed on late stage B-cells, and whether BCMA can serve as immunotherapeutic target for earlier stage B-cell malignancies is currently unknown. Data regarding BCMA expression on B-cell malignancies are limited. Increased serum levels of soluble BCMA in chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia (WM) have been observed, indicating that these B-cell malignancies do express BCMA which is subsequently cleaved off the membrane by γ-secretase (γ-sec).
Aims: We assessed BCMA expression on B-cell lymphoma cell lines and primary malignant cells and explored effects of T-cell activation and killing of B-NHL mediated by Tec *in vitro*.
Methods: B-NHL cell lines or CLL cells were cultured in presence or absence of γ-sec inhibitor. BCMA expression was assessed by flow cytometry or immunohistochemistry (IHC). To assess Tec function, cell lines or primary CLL were co-cultured with healthy donor (HD) T-cells in presence of Tec. Cytotoxicity, T-cell activation and cytokine production were assessed by flow cytometry.
Results: BCMA expression varied among different B-NHL cell lines while Jurkat (T-cell line) did not express BCMA. Highest BCMA expression was observed in MM cell lines (RPMI-8226 and U266), followed by WM (MWCL1 and BWCM.1), Burkitt lymphoma (BL, Daudi and Ramos), CLL (CII, PGA and Mec-1), diffuse large B-cell lymphoma (DLBCL, OCI-Ly3 and OCI-Ly7) and mantle cell lymphoma (MCL, JeKo-1) (Fig 1A). γ-sec inhibition increased BCMA expression, even when basal levels of BCMA were low, indicating active BCMA shedding. These data were corroborated in primary B-cell lymphoma by IHC and showed moderate levels in WM, and weak or undetectable expression in MCL, DLBCL and CLL (Fig 1B). BCMA membrane expression could be detected at low levels on primary CLL cells by flow cytometry and could be marginally increased by γ-sec treatment.

Next, potency of Tec against lymphoma cell lines was studied. Co-culture of HD T-cells with RPMI-8226, CII, BWCM.1 or JeKo-1 in the presence of Tec resulted in T-cell activation, proliferation and cytotoxicity (Fig 1C-D), independent of the level of BCMA expression. Response to Tec therefore seems to be dependent on a threshold BCMA expression level, but is likely also influenced by tumor intrinsic factors, since WM cell lines with high expression are not efficiently killed.
Efficacy of Tec on primary tumor cells was studied using CLL cells. Despite low BCMA levels, HD T-cells lysed CLL cells up to 40% in presence of Tec. Furthermore, Tec induced activation, degranulation and efficient cytotoxicity by CLL-derived T-cells upon coculture with autologous CLL cells (Fig 1E).



Summary/Conclusion: In conclusion, BCMA expression is variable on B-cell lines, which can be enhanced by γ-sec inhibition, and Tec induces cytotoxicity independent of BCMA expression levels. Despite low BCMA expression in primary CLL, Tec induced cytotoxicity and autologous T-cell activation. Further studies to understand the determinants of response to Tec will be required to identify which other diseases might be suitable targets for Tec treatment.

EP609 IN SILICO PREDICTION REVEALS PUTATIVE T-CELL CLASS I NEOEPITOPES WITHIN THE CLONOTYPIC BCR IG OF CLL PATIENTS

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Background: Chronic lymphocytic leukemia (CLL) is characterized by the existence of subsets of patients carrying stereotyped i.e. quasi-identical B-cell receptor immunoglobulins (BcR IG), strongly suggesting restricted antigenic selection. Data showing autonomous BcR signaling through homotypic interactions between BcR IG molecules, distinctive for each subset, suggest that the selecting epitopes may lie within the clonotypic BcR IG itself. Antigenic drive appears relevant also for T cells in CLL, where published evidence supports that CLL T cells are selected by restricted, subset-specific tumor antigens. That said, whether the antigens selecting CLL progenitors and T cells are the same remains obscure.

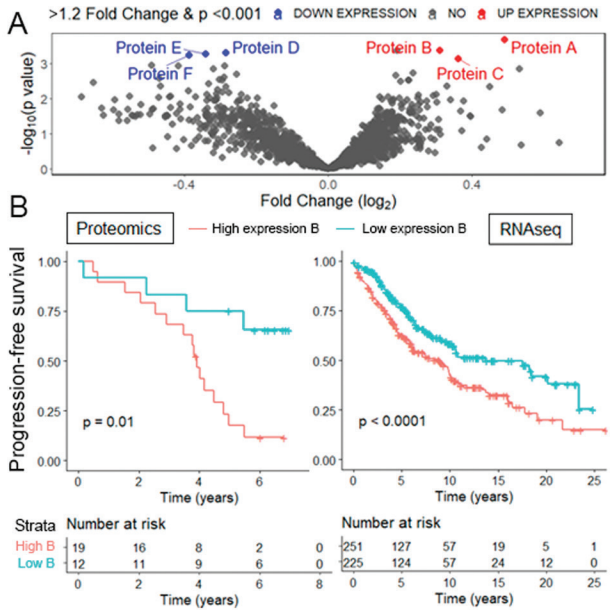
Aims: We performed *ad hoc* prediction of putative T-cell class I neoepitopes contained within the clonotypic BcR IGs of CLL patients, with an intended bias towards major stereotyped subsets.
Methods: We selected 27 patients to represent the full spectrum of CLL: (i) with mutated IGHV genes (M-CLL, n=5), (ii) with unmutated IGHV genes (U-CLL, n=5), (iii) assigned to major stereotyped subsets (subset #1, n=7; subset #2, n=5; subset #4, n=5). RT-PCR was performed for the heavy (H) and the light (K/L) IG chain using subgroup-specific leader primers for the IGHV/IGK/LV gene and universal primers annealing to the constant region (IGHG, IGHM, IGKC, IGLC), in order to produce a full-length V-(D)-J gene rearrangement sequence, plus the start of the constant domain. PCR products were subjected to direct double-strand Sanger sequencing with a quality-optimized protocol. The amino acid sequences were subsequently parsed in peptides and subjected to NetMHCpan. The rank score was calculated, considering the 4-digit HLA-A and -B typing for each patient separately. Only high-binding peptides (rank score <.5%) were selected. Exact matches to germline and/or proteome databases were excluded.
Results: Overall, 202 predicted neoepitopes were identified in 22/27 patients. All 22 patients had predicted $CD8^+$ T-cell epitopes within the heavy chain, and 19/22 also within the light chain. Half of the peptides (n=106, 52.5%) resulted from somatic hypermutations (SHMs) at the intersections of FR and CDR3 regions (FR1/CDR1, n=14; CDR1/FR2, n=28; FR2/CDR2, n=6; FR3/CDR3, n=17; CDR3/FR4, n=41). The remaining mostly involved the FR3 (n=52) and CDR3 (n=21). Overall, the majority of peptides involved (at least part of) the CDR3 (79/202, n=39.1%), which is particularly relevant given its small length (9-27 aa) within the full sequence (331-660 aa). There was no statistically significant difference in the rank score of peptides involving the CDR3 vs. all others. Peptide clustering revealed similar or identical predicted neoepitopes among different patients (17 clusters of two, 2 clusters of three, 1 cluster of four). Importantly, these clusters involved: (i) shared CDR3 patterns in patients assigned to the same subset, but also (ii) subset-specific recurrent SHMs in the IGHV gene, e.g. G to E SHM at position 28 in the CDR1 of subset #4, which was previously reported to be present in 114/265 (43%) subset #4 cases.
Summary/Conclusion: *Ad hoc* prediction with established bioinformatics algorithms identified a significant number of putative T-cell class I neoepitopes contained within the clonotypic BcR IG of CLL patients. Many of them culminate from subset-specific ('stereotypic') CDR3 patterns or recurrent SHMs, suggesting that the targeted SHM which shapes the CLL BcR IG repertoire may produce immunogenic $CD8^+$ T-cell epitopes. Their actual immunogenicity has to be tested in *ex vivo* studies, currently underway by our group.

EP610 SWATH-MS PROTEOMICS AS A NEW TOOL FOR DISCOVERING POTENTIAL DRUG TARGETS AND BIOMARKERS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Genomic and transcriptomic studies in chronic lymphocytic leukaemia (CLL) have significantly improved our understanding of disease biology and drug resistance mechanisms whilst simultaneously identifying new biomarkers. Despite the ability of such biomarkers to predict treatment response and survival, the prognostic/predictive information they provide is not absolute. Since disease phenotype is determined at the protein level and given the imperfect correlation between mRNA and protein expression, we hypothesised that a proteomic approach might shed new light on pathogenetic mechanisms and indicate potential drug targets and biomarkers.
Aims: Using SWATH-MS (Sequential Window Acquisition of All Theoretical Mass Spectra), the study aimed to elucidate differences in the pre-treatment CLL proteome that correlated with response to fludarabine-based chemo-immunotherapy defined by post-treatment minimal residual disease (MRD) status.
Methods: Pre-treatment cryopreserved peripheral blood mononuclear cells collected from patients as part of the ARCTIC and AdMIRe trials were lysed and protein extracted using published protocols. After trypsin digestion, the peptides were processed and mass spectrometry (Sciex TripleTOF 6600) performed. Data was normalized within DIA-NN software and proteins were identified (q<0.01) using our published CLL-specific SWATH library. Data was visualized in R and the inter-batch variation removed along with an outlier. Differential protein expression analysis was performed between MRD positive (MRD+, defined as ≥1 CLL cell in 10,000 leukocytes in the bone marrow) and negative (MRD-) groups measured three months after the end of treatment. Receiver operating characteristic (ROC) analysis was performed to split patients into low- and high-expression groups for each protein using thresholds that gave the optimum sensitivity and specificity. Functional analyses were performed using Ingenuity Pathway Analysis and Gene Set Enrichment Analysis tools.
Results: Thirty-two patients were included in the study. Bone marrow MRD data was available for 29 patients, of which 17 (59%) were MRD+ and 12 (41%) MRD-. The median age was 64 (IQR 59-68.5), with a male preponderance (75%). Of the 4696 proteins identified, 2357 were consistently detected and used for subsequent analysis. Using >1.2 fold change and p<0.001 cut-offs, six differentially expressed proteins were identified (proteins A-F; Fig. A). Unsupervised clustering and principal component analysis plots of the six proteins showed clustering of samples based on their MRD status. In univariate analysis, high expression of protein B along with a low expression of proteins D and E were associated with increased risk of progression or death (HR 4.17 [p=0.012], HR 2.75 [p=0.041] and HR 2.53 [p=0.046], respectively). The findings were corroborated using an external RNAseq dataset of 476 patients (The International Cancer Genome Consortium), which confirmed that protein B and its mRNA expression were associated with worse progression-free survival (PFS) in both datasets (p=0.01 and p<0.0001; Fig. B). Functional analyses of proteomic data revealed enrichment of pathways related to mTOR along with processes related to Golgi vesicle transport and protein localization to endoplasmic reticulum, suggesting a possible drug resistance mechanism.



Summary/Conclusion: Proteomic analysis using SWATH-MS provides a novel approach to elucidating pathogenetic mechanisms in CLL. In this study, protein B was identified as a potential drug target and biomarker for therapy response.

EP611 CHARACTERIZATION OF STAT5B MUTATIONS AND TCRB REPERTOIRE IN CD4+ T LARGE GRANULAR LYMPHOCYTE LEUKEMIA

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Background: T-cell large granular lymphocyte leukemia (T-LGLL) is a rare lymphoproliferative disease whose etiology is still unknown. T-LGLL includes two subtypes of lymphoproliferation: the most frequent CD8+ T-LGLL (70% of cases) and the less common CD4+ T-LGLL (30% of cases). In the CD4+ variant, the leukemic T-LGLs express the CD4 determinant (either alone or together with CD8), the α/β T-cell receptor (TCR), and display a typical mature cytotoxic and activated/memory T-cell phenotype. Previously, in small series of cases, up to 55% of CD4+ T-LGLL patients have shown to be characterized by *STAT5B* mutations, at variance from CD8+ T-LGLL cases, who frequently harbor *STAT3* mutations and only seldom *STAT5B* mutations.
Aims: In this study, we collected the largest cohort of CD4+ T-LGLL (n=35) so far described at molecular level in the literature. We evaluated the presence of *STAT5B* mutations and their correlation with patients' clinical data. In addition, we characterized the clonal landscape, publicness, and structural similarities of TCRβ repertoire in CD4+ T-LGLL in comparison to healthy TCR repertoires.
Methods: CD4+ T-LGLL patients were enrolled from Hematology Units of 3 Academic Institutions, i.e., Padova (Italy; n=22), Helsinki (Finland; n=6), and Shinshu (Japan; n=7). Buffy coats from healthy controls (n=37) were supplied by the Finnish Red Cross Blood service (Helsinki, Finland). *STAT5B* deep amplicon sequencing was performed for each patient in LGL or PBMC using Illumina platform on MiSeq instrument. The evaluation of differential *STAT5B* transcriptional activities was measured through *STAT5B* luciferase reporter assay. TCRβ sequencing was obtained from genomic DNA (the same DNA used for amplicon sequencing) with Adaptive Biotechnologies' ImmunoSEQ assay.
Results: We observed 63% (23/35) of the patients harboring *STAT5B* mutations. In addition to the gain-of-function *STAT5B* mutations previously described in T-LGLL (*N642H, Y665F, Q706L, S715F*), we found 6 novel mutations (*Q220H, E433K, T628S, P658R, P702A, V712E*) located not only in hot spot regions but also in other gene domains. In 22% (5/23) of *STAT5B* mutated CD4+ T-LGLL cases, multiple *STAT5B* mutations were either coexisting in one clone or in distinct clones. On clinical grounds, patients with *STAT5B* mutations were distinguishable from *STAT5B* wild type patients for increased lymphocyte and LGL counts.
The deep sequencing of TCRβ repertoire was obtained on 27 patients. We demonstrated that as well as large LGL expansions, also the non-leukemic TCR repertoires exhibited higher clonality in CD4+ T-LGLL patients than in healthy controls. Considering clones with the size exceeding 5% of the repertoire, we identified 59 different clonotypes and 24% of them were also found among the non-expanded TCR repertoires of other CD4+ T-LGLL patients. In 44% of the patients, the LGL clonal expansion was characterized by TRBV06 (TCRVβ13.1) expression. Nevertheless, structural similarities among LGL clonotypes were infrequent and direct viral antigen matches were not identified.
Summary/Conclusion: *STAT5B* mutations are the hallmark of CD4+ T-LGLL and they associate with higher lymphocyte and LGL counts. Despite the gain-of-function nature of the mutations, patients rarely have any symptoms, and the disease is indolent. TCR repertoire of both leukemic and non-leukemic CD4+ T cells is more clonal than in healthy individuals and TRBV06 is overrepresented hinting towards an initial immune response to an antigen as a likely triggering event of LGL expansion.

EP612 AUTOPHAGY-RELATED GENETIC VARIANTS INFLUENCE THE RISK OF DEVELOPING CHRONIC LYMPHOCYTIC LEUKEMIA: A STUDY IN THE CONTEXT OF THE CRUCIAL CONSORTIUM

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Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in Western countries and remains as an incurable disease. Despite the information provided by genome-wide association studies (GWAS), the genetic component underlying CLL has not been completely unravelled and multiple susceptibility loci remain to be identified. An aberrant expression of autophagy-related genes has been associated with cancer development (1,2) and it has been observed that autophagy shapes anti-tumoral immune responses by acting at multiple levels including the promotion of signals to activate phagocytosis of tumour cells but also signals to induce MHC-class-I and -II presentation (3,4), T-and B-cell activation, development and maintenance (5).
Aims: Considering this background, we investigated whether autophagy-related variants might influence the risk of developing CLL.
Methods: We conducted a population-based case–control study including 1285 Caucasian CLL cases and 1386 healthy controls ascertained through the Consortium for Research in Chronic lymphocytIc LeukemiA (CRuCIAL). Sixteen single nucleotide polymorphisms (SNPs) within autophagy-related loci were selected on the basis of their previous associations with other haematological malignancy (at P<0.01 level) (6). Hardy–Weinberg equilibrium (HWE) was assessed in the control group (P>0.01) and the association between CLL risk and the autophagy-related SNPs was tested using unconditional logistic regression analysis. A P-value of 0.0010 (0.05/16/3 inheritance models) was set to be the multiple testing significance threshold. Functional characterization of the most interesting markers was tested using cytokine quantitative trait loci (cQTL) data after stimulation of peripheral blood mononuclear cells (PBMCs), whole blood or monocyte-derived macrophages (MDMs) from 408 healthy subjects from the Human Functional Genomics Project (HFGP) cohort with LPS, PHA, Pam3Cys, CpG and B. burgdorferi and E. coli, as experimental model for cytokine production capacity. We also analysed the correlation between selected SNPs with data on 91 annotated immune cell populations, 103 serum inflammatory proteins, 7 steroid hormones and autophagy flux.
Results: Selected SNPs were in HWE. Logistic regression analysis showed that the $ATG5_{rs12527992}$, $BIRC6_{rs12992095}$, $KLHDC7B_{rs140522}$, and $NAMPT_{rs62481378}$ SNPs were associated with CLL risk at P<0.05 level. The strongest association was found for the $KLHDC7B_{rs140522}$ SNP that remained significant after correction for multiple testing. Each copy of the $KLHDC7B_{rs140522A}$ allele increased the risk of CLL by 25% (OR=1.25, 95%CI 1.11-1.40, P=0.0001; Table 1). Furthermore, we

found an association for the $NAMPT_{rs62481378}$ SNP with an increased risk of CLL that remained marginally significant after multiple testing correction. Each copy of the $NAMPT_{rs62481378A}$ allele increased the risk of the disease by 36% (OR=1.36, 95%CI 1.10-1.67, *P*=0.0044; Table 1). Functional experiments trying to shed some light into the biological mechanisms underlying these associations have been conducted and statistical analyses are currently ongoing.

Table 1. Association of autophagy-related SNPs and CLL risk.

SNP_rsID	Gene	Risk allele	OR(95% CI)[§]	*P*
rs12527992	ATG5	T	**1.27 (1.04-1.56)**	**0.021**
rs149103600	BAG3	A	1.02 (0.69-1.51)	0.93
rs12992095	BIRC6	A	**1.15 (1.01-1.30)**	**0.041**
rs26864	CASKIN1||GBL	A	1.06 (0.95-1.19)	0.29
rs146749265	CHMP2B	C	1.38 (0.87-2.18)	0.17
rs55967915	EIF4G1	C	1.03 (0.92-1.16)	0.56
rs148155729	FAS||FAS-AS1	T	1.12 (0.78-1.60)	0.54
rs2241369	GNB2L1	C	1.00 (0.72-1.38)	0.99
rs117867844	HSPB8	G	1.01 (0.59-1.71)	0.98
rs113424540	ITGB4	A	1.16 (0.89-1.51)	0.26
rs17041030	ITPR1	C	1.06 (0.94-1.19)	0.32
rs140522	KLHDC7B	A	**1.25 (1.11-1.40)**	**0.00018**
rs62481378	NAMPT	A	**1.36 (1.10-1.67)**	**0.0044**
rs72831075	NBR1	C	1.08 (0.86-1.35)	0.50
rs10736174	NRG3	C	1.09 (0.95-1.24)	0.22
rs6599175	ULK4	C	1.05 (0.92-1.20)	0.46

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio.
[§] Logistic regression analysis assuming a log-additive model of inheritance.
Significant results in bold (P<0.05).

Summary/Conclusion: This study suggests that the *KLHDC7B* locus is involved in determining the risk of CLL and points to a modest effect of the *NAMPT* gene. Additional studies are warranted to establish the role of *ATG5* and *BIRC6* loci in modulating disease risk.

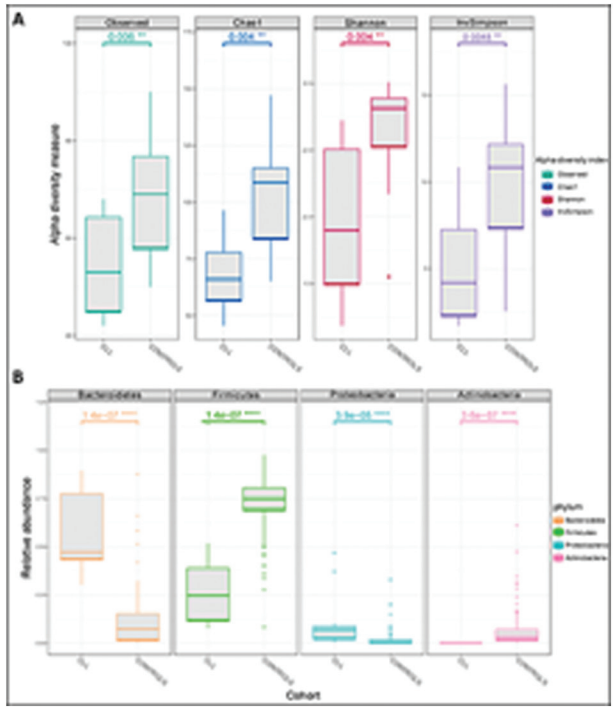
References: [1] Maiuri et al. Cell Death Differ, 2009;
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EP613 THE GUT MICROBIOME IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The human gut microbiome may impact both immune function and carcinogenesis. Previous studies have reported potential associations between gut microbiome constitution and both the incidence and progression of a wide array of cancers. The gut microbiota in patients with chronic lymphocytic leukemia (CLL) remains to be characterized.
Aims: Our research aims to investigate whether gut dysbiosis, i.e. the loss of "health-promoting" commensal gut microbes and/or the overgrowth of pathogenic bacteria, distinguishes patients with CLL from that of the background population.
Methods: Feces samples were collected, immediately fixated and frozen within 72 h; total genomic DNA was sequenced using Next Generation Sequencing (NGS). Control cohorts were selected from an array of previously published cohorts. Taxonomical profiling was done using an in-house bioinformatics pipeline. Data analysis was performed using standard Compositional Data Analysis (CoDA) methods.
Results: In total 10 CLL patients were included in the study. The control cohort included 124 healthy individuals. We observed that the gut microbiome alpha diversity in bacterial genera was reduced among the CLL patients (Figure 1A). Lower number of observed species (P = 0.006) and a lower diversity (Shannon index, P = 0.004; Inverse Simpson index, P = 0.0048) was observed in the CLL cohort versus healthy controls. Finally, the abundance of Bacteroidetes and Proteobacteria was increased while the abundance of Firmicutes was decreased in the CLL patients compared to healthy controls (Figure 1B).



Summary/Conclusion: Our data indicate that the microbiome in CLL patients is less diverse than that of the background population. The gut dysbiosis in CLL includes an increase in Proteobacteria and an increase abundance of other specific bacterial genera. Further investigations are crucial for our understanding of the interplay between the gut microbiome and CLL development. The aim of such studies should be to identify possible interventions modulating the microbiome to change the course of CLL and the adjoined immune dysfunction.
Figure 1. Comparison between the CLL cohort and control cohorts. A) Box plots of Observed number of genera, Chao 1, Shannon and Inverse Simpson indices in CLL cohort and a control cohort. Six controls were randomly sampled from each of the two control cohorts and pooled as CONTROLS. B) Relative abundance of four major bacterial phyla in microbiota in CLL cohort and a control cohort. All samples from each of the two control cohorts were pooled as CONTROLS. The P-values (adjusted for multiple testing with the Benjamini-Hochberg procedure) obtained upon Wilcoxon rank-sum tests are indicated.

EP614 EX VIVO DRUG SENSITIVITY IDENTIFIES COMBINATION TREATMENT WITH PI3K/BCL-2 INHIBITORS FOR MONOTHERAPY-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The phosphatidylinositol 3-kinase inhibitors (PI3Ki) idelalisib and duvelisib are approved for relapsed chronic lymphocytic leukemia (CLL). However, treatment intolerance and resistance remain clinical challenges. Strategies to overcome these challenges include targeting bypass mechanisms by using a different PI3Ki and combining different classes of targeted therapies. Direct drug testing on patient-derived primary cells may provide insights into patient-tailored therapeutic options.
Aims: The aims of this study were to (i) characterize the efficacy, selectivity, and synergy of 10 clinically relevant PI3Ki alone and in combination

with the B-cell lymphoma-2 (BCL-2) antagonist venetoclax in primary CLL cells, (ii) investigate whether signaling molecules can serve as early biomarkers for drug sensitivity, and (iii) identify clinically relevant treatment options for CLL patients who have failed on a PI3Ki monotherapy.
Methods: We performed high-throughput drug sensitivity screens with 72h drug treatment of primary cells from 18 CLL patients and 3 healthy blood donors. A phospho-flow cytometry assay was applied to study intracellular signaling changes in primary CLL cells after 30 min of drug treatment *ex vivo*.
Results: The pan-PI3Ki buparlisib, copanlisib and pictilisib were most active in 72h assays, with up to 97% reduction in cell viability at 10 000 nM. However, treatment with the p110d-selective PI3Ki umbralisib plus venetoclax showed more selective targeting of CLL cells compared to normal B cell and T cells than combinations involving a pan-PI3Ki. Interestingly, distinct changes in cell signaling induced by 30 min of drug treatment predicted cell viability in 72h assays. AKT (pS473) and S6-ribosomal protein (pS235/S236) correlated with drug sensitivity to p110d-selective PI3Ki plus venetoclax, while BTK (pY551) correlated with sensitivity to pan-PI3Ki. Samples from patients no longer responding to idelalisib *in vivo* (n=4) showed high sensitivity to pan-PI3Ki *ex vivo*. Drug sensitivity assessment of an ibrutinib (BTK inhibitor), idelalisib and venetoclax refractory CLL patient indicated combination of idelalisib and venetoclax as a promising therapeutic option. The patient was treated with the combination, and obtained a good clinical response. Unfortunately, the patient experienced unacceptable gastrointestinal adverse effects as she had with idelalisib monotherapy, and the treatment was stopped. Interestingly, the patient continued to show a strong *ex vivo* response to the pan-PI3K inhibitors buparlisib, copanlisib and pictilisib, suggesting that these therapies may be considered for CLL patients who relapse on currently available targeted therapies.
Summary/Conclusion: These data provide insights into efficacy, selectivity, and synergy of combinatorial strategies in CLL, and indicate a potential for signaling molecules as early biomarkers for patient stratification. *Ex vivo* drug sensitivity assessment of CLL cells from a patient who had failed on all available targeted therapies in Norway indicated combined PI3K/BCL-2 inhibition as an effective treatment option. This demonstrates that *ex vivo* drug sensitivity assessments can guide clinical decisions in CLL. We further showed that CLL cells from refractory patients remain sensitive to pan-PI3Ki *ex vivo*, suggesting pan-PI3Ki as potential treatment options to be explored for relapsing CLL patients.

EP615 THE IGLV3-21 LIGHT CHAIN ANALYSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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Background: Unmutated (UM) immunoglobulin heavy chain variable region (IgHV) status or subset #2 stereotyped Ig receptor (IgHV3-21/IgLV3-21) expression is associated with poor prognosis in chronic lymphocytic leukemia (CLL). It is considered that the light chain also can affect CLL outcome. The IgLV3-21 light chain usage was shown to confer unfavourable prognosis irrespective of IgHV mutational status or subset #2 stereotyped receptor.
Aims: To analyse the presence of IgLV3-21 in CLL cohort and corelate it with clinical outcome and poor prognosis molecular markers.
Methods: A total of 166 CLL patients with available IgHV data and clinico-biological information were included in the study. All patients gave written informed consent. Patient characteristics were as follows: 72% males; median age: 57; Binet stages B or C: 55%; IgHV status: 73% IgHV-unmutated (more or equal 98% identity to germline, UM); 27% IgHV-mutated (less than 98% germline identity, M), recurrent mutations: *TP53*: 12.9% (13 of 101 cases), *NOTCH1*: 10.3% (15 of 145 cases); *SF3B1*: 18.3% (17 of 93 cases); major stereotyped subsets assigned using the ARResT/AssignSubsets tool: 20.5%, the most frequent: subset #1 (4.2 %), subset #2 (3.0%), subset #3 (2.4%), subset #6 (2.4%). In 115 patients the Ig light chain rearrangements were analysed by Sanger sequencing using BIOMED-2 protocol, in 51 patients the IgLV3-21 chain presence was tested with real-time PCR method and primer strategy developed by Stamatopoulos et al. [2018]. Time-to-first-treatment (TTFT) and overall survival (OS) were analyzed by Kaplan-Meier statistic.
Results: The IgLV3-21 light chain expression was found in 16 (9.6%) patients in studied group, among them 5 cases (31.3%) belonged to subset #2 (IgHV3-21/IgLV3-21). Non-subset #2 IgHV3-21 cases were not represented. Besides of stereotyped subset #2, only subset #5 was represented (one case). More than half of the IgLV3-21 expressing cases (9 of 16) were IgHV M, largely due to subset #2 cases, all of which were IgHV M. In accordance with previous studies a higher frequency of *SF3B1* mutations was seen in IgLV3-21 patients ($P = 0.061$), they were presented irrespective of subset #2 stereotyped Ig expression (subset #2: 50% and non-subset #2: 33.3%, $P = 0.548$). At that, *SF3B1* mutations did not affect significantly neither OS ($P = 0.525$), nor TTFT ($P = 0.831$). Patients with the IgLV3-21 chain demonstrated a significantly shorter median OS compared to IgHV M (70 vs. 277 months, $P = 0.005$), but comparable to IgHV UM cases (75 months, $P = 0.688$). Similarly, TTFT was shorter in IgLV3-21 compared to IgHV M cases, although did not reach statistical significance (15 vs. 33 months, $P = 0.161$), and did not differ significantly from IgHV UM cases (8 months, $P = 0.255$). Upon dividing IgLV3-21 group into subset #2, non-subset #2/IgHV M and IgHV UM, we did not find a significant difference regarding both OS ($P = 0.714$) and TTFT ($P = 0.259$).
Summary/Conclusion: Our results in line with previous publications suggest that the IgLV3-21 light chain expression identifies unfavourable CLL subgroup independent of the IgHV mutational status and is associated with presence of *SF3B1* mutations. Subsequent studies in a larger CLL cohort will clarify the significance of IgLV3-21 for risk stratification of patients.

EP616 ANALYSIS OF GENOMIC COMPLEXITY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) USING OPTICAL GENOME MAPPING

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Background: Complex karyotype (CK) is a predictor of poor prognosis in patients with chronic lymphocytic leukemia (CLL). CK is defined as the presence of ≥3 chromosomal aberrations in the same clone by chromosome banding analysis (CBA). However, recent studies have suggested that the best cut-off to predict an adverse outcome in CLL should be established at 5 abnormalities detected by either CBA or chromosomal microarrays (CMA) (Baliakas et al, 2019; Leeksma et al, 2021). Both methods are useful for risk stratification of CLL patients, but they are not equivalent due to limitations intrinsic to each technique (Ramos-Campoy et al, 2021). Optical genome mapping (OGM) is a novel method that relies on the imaging of long DNA molecules (>250 kb) labeled at specific sites. The unique pattern of labels throughout the genome allows to map the genomic location of every molecule and detect both balanced and unbalanced abnormalities with high resolution and sensitivity. This is as promising technology that overcomes most of the limitations of CBA and CMA.
Aims: 1. To compare the results obtained by OGM with previous CBA and CMA information. 2. To analyze the usefulness of OGM in the assessment of genomic complexity in CLL patients.
Methods: A total of 22 CLL patients were included, 12 carried CK by CBA and 10 were non-CK. Tumor DNA extracted from peripheral blood was analyzed by OGM (Bionano Genomics). Abnormalities found by OGM were compared with available CBA, FISH and CMA (12 CytoScan HD and 10 CytoScan 750K, ThermoFisher) results, and complexity detected by OGM in each group was assessed.
Results: OGM detection rate of previously known abnormalities was 93% (14/15) and 86% (119/138) in non-CK and CK groups, respectively.

Discordances were mainly small copy number alterations (CNAs) detected by CMA and subclonal aberrations in the karyotype expanded during CBA culture but represented in a minor proportion, also below CMA sensitivity. Size and coordinates of CNAs detected by OGM were highly concordant with those defined by CMA. Moreover, OGM provided additional structural information associated with some microarray CNAs or helped to identify unknown cytogenetic elements reported by CBA in 11/22 (50%) patients. Additional new abnormalities, including balanced rearrangements and CNAs, were found by OGM in both groups. The median number of abnormalities by OGM was 72 (range: 38-103) in non-CK and 120 (range: 50-249) in CK patients. They were highly enriched in insertions, duplications or deletions of unknown clinical significance displaying sizes smaller than CMA resolution (from only 3 to 100Kbp). When polymorphic variants and unbalanced abnormalities smaller than 100Kbp were filtered, CK group displayed significantly a more complex genome than non-CK patients [median 22 (6-77) vs 5 (2-8), P<0.01]. Globally, OGM detected a higher complexity, although a good correlation between the number of aberrations recorded by OGM and CBA or CMA was observed (r_p=0.831 and r_p=0.935, respectively) (Figure).

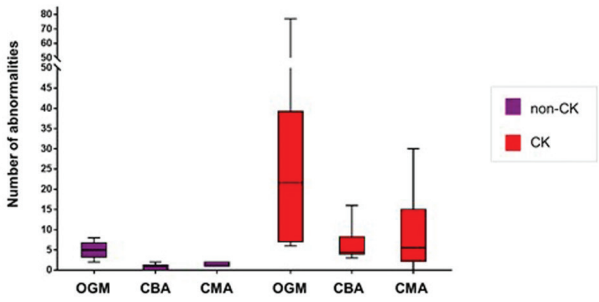


Figure. Total number of abnormalities detected by optical genome mapping (OGM, filtered data), chromosome banding analysis (CBA) and chromosomal microarrays (CMA) in non-CK and CK groups.

Summary/Conclusion: 1. OGM is a valuable tool to assess genomic complexity in CLL. It effectively detects the vast majority of the abnormalities defined by standard methods, allowing a comprehensive interpretation of some of the alterations; 2. Several additional abnormalities of unknown clinical significance are identified by OGM; 3. Further studies are required to define genomic complexity criteria by OGM and implement this technique in the routine management of CLL patients.

EP617 THE IDO-KYN-AHR PATHWAY PROMOTES CHRONIC LYMPHOCYTIC LEUKEMIA CELLS SURVIVAL AND MITIGATES THE APOPTOTIC EFFECT OF ABT-199

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Background: Chronic Lymphocytic Leukemia (CLL) accounts for about 30% of all adult leukemia and is common in Western countries. In the clinical treatment, although innumerable advances have been made, the disease is still incurable. To identify new treatment strategies it is necessary to take into account that leukemic cellsentertaina complex crosstalk with the surrounding tumor microenvironment (TME) and for this reason is important to consider a "double hit" therapeutic approaches.
The indoleamine 2,3-dioxygenase (IDO)-kynurenine (Kyn)-aryl hydrocarbon receptor (AhR) pathway is active in several types of human cancer, including hematologic malignancies, that pathologically exploit tryptophan (Trp) metabolism along the kynurenine pathway (KP) to promote growth and escape immune surveillance. IDO-derived kyn produced during cancer progression and inflammation have both autocrine and paracrine action and seem to be one of the pathways that link the leukemic cell and the TME.
Aims: We wondered to investigate the functional role of the KP and the effects of its inhibition in CLL.
Methods: Gene transcription and protein expression were evaluated by real time PCR and western blot. Enzymatic activity was assessed through ELISA. Survival was measured with annexinV/PIassay. Overexpression and silencing of target genes was obtained by nucleofection.
Results: Previously we have demonstrated that CLL cells expressed IDO at variable levels and we found that several TME stimuli were able to up-regulate IDO mRNA and protein. We have showed that IFNγ induced an active IDO protein through STAT1 signaling as assessed measuring Kyn production and Trp consumption by ELISA. Interestingly, when we up-regulated IDO in CLL cells they showed an increased survival. Same results were obtained treating cells with Kyn. We also observed that Kyn mediated AhR translocation from the cytoplasm to the nuclei, inducing its activation as assessed by up-regulation of CYP1A1, a known AhR target gene. Analyzing the anti-apoptotic proteins of the Bcl2 family after Kyn treatment, we found the induction of Mcl1, that was affected by adding CH-223191, an antagonist of AhR. Then we decided to silence AhR in CLL cells and we found that the survival of leukemic cells was compromised as they had reduced levels of Mcl1.We then analyzed to what extent KP-induced survival could affect ABT-199 sensitivity in CLL samples. Our results indicated that pre-treatment with Kynmitigated the effect of ABT-199, which produced less apoptosis, while the use of CH-223191 has been shown to have a synergistic effect in inducing apoptosis of leukemic cells.
Summary/Conclusion: Our data demonstrated that IDO-Kyn-AhR axis is active in CLL cells and promotes Mcl1 expression,sustaining the survival of leukemic cells. Our results indicated the KP as a new potential therapeutic target in the CLL microenvironment.

EP618 LNCRNA LANDSCAPE ANALYSIS IDENTIFIED LNCRNA LEF-AS1 AS AN ONCOGENE THAT UPREGULATES LEF1 AND PROMOTES SURVIVAL IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Chronic lymphocytic leukemia (CLL) is a malignant disorder of mature B lymphocytes, and the precise pathogenesis is unknown at present.
Aims: This study set out to screen the differential expression profile of long non-coding RNA (lncRNA) by microarray and explore the underlying mechanism, biological function, and clinical significance of lncRNA in CLL cells.
Methods: We performed microarray detection to screen the differential expression profile of lncRNA and related experiments to explore the underlying mechanism, biological function, and clinical significance of the lncRNA of interest.
Results: Compared to the lncRNA expression profiles of the control group, we picked out lncRNA LEF1-AS1 for further exploration. By quantitative real-time polymerase chain reaction, we validated that primary CLL cells harbor higher lncRNA LEF1-AS1 levels than normal B cells. Expression of LEF1 on RNA and protein level elevated in the two cell lines with stable overexpression of LEF1-AS1. In the term of biological functions, proliferation rates increased, and apoptosis rates decreased in the LEF1-AS1 overexpressed cell lines, as well as a trend of shortened G0/G1 phase and prolonged G2/M phase in the cell cycle. In primary CLL cells, mRNA expression of LEF1 decreased after negatively regulating the expression of LEF1-AS1. RNA Binding Protein Immunoprecipitation and RNA pull-down demonstrated that LncRNA LEF1-AS1 and LEF1 protein could combine especially. However, we have not determined the prognostic significance of lncRNA LEF1-AS1 in CLL patients.
Summary/Conclusion: The thesis concludes that LEF1-AS1 may be a potential oncogenic lncRNA that regulates the expression of the target gene LEF1 by interacting with protein LEF1, which promotes proliferation and suppresses apoptosis of CLL cells.

EP619 DISCOVERY OF HBW-3-10: A POTENT, ORALLY ACTIVE, REVERSIBLE BRUTON'S TYROSINE KINASE (BTK) INHIBITOR WITH ANTITUMOR ACTIVITIES IN MICE

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Background: The first generation irreversible BTK inhibitor ibrutinib has been approved for the treatment of B cell-related diseases, including chronic lymphocytic leukemia (CLL), for several years. However, CLL patients who used ibrutinib may develop drug resistance due to acquired

mutations, in particular C481S in BTK that directly impacts the binding of ibrutinib. In recent years, efforts have been made to develop the second generation reversible BTK inhibitors that are effective against both wild-type and C481S mutated B-cell malignancies. LOXO-305 and ARQ-531 are two examples of the second generation reversible BTK inhibitors in advanced clinical trials for ibrutinib-resistant CLL.
Aims: Discovery of Potent, Orally Active, Reversible Bruton's Tyrosine Kinase (BTK) Inhibitors
Methods: New reversible BTK inhibitors were designed, synthesized and tested for enzymatic activities against wild-type and C481S-mutated BTK. Highly active compounds were confirmed for growth effects in diffuse large B-cell lymphoma derived TMD8 cells. Their microsomal stability and ADME properties were also assessed. Potent and bioavailable compounds were further evaluated for in vivo efficacy using a TMD8 xenograft tumor model in mice. A 14-day toxicity study in rats was performed to examine compound safety.
Results: As shown in the table, HBW-3-10 has greater potency and pharmacokinetic profile (rats, 10mg/kg PO) than ARQ-531. In a TMD8 mouse xenograft study, HBW-3-10, ARQ-531 and ibrutinib were compared directly, all dosed at 10mg/kg QD, and the resulting tumor growth inhibition rates (TGI) are 38.3%, 9.3% and 22.5%, respectively. Based on our data, HBW-3-10 is more efficacious than ARQ-531 and ibrutinib. In a 14-day preliminary toxicity experiment in rats, both HBW-3-10 and ARQ-531 were dosed 100mg/kg QD. Animals in ARQ531 group started showing signs of sickness on day 3, and all died on day 6 due toxicity; in contrast, no animal in HBW-3-10 group showed any sign of sickness or died during the entire course of study.

compound	BTK IC_{50} (nM)	BTKc481s IC_{50} (nM)	TMD8 IC_{50} (nM)	hERG (uM)	Cmax (ng/mL)	AUC $_{0-\infty}$ (ng·hr/mL)	$T_{1/2}$ (hr)
ARQ-531	4.1	2.2	82.2	3.53	2414	12963	4.0
HBW-3-10	2.8	1.6	13.9	9.88	25721	211031	3.4

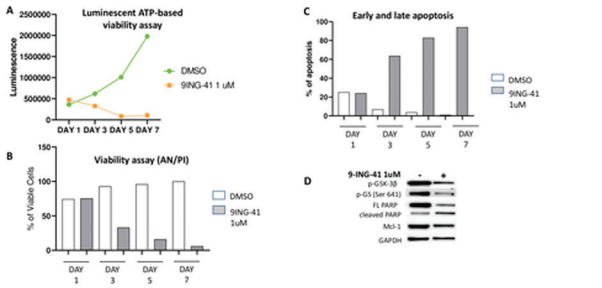
Summary/Conclusion: We have discovered a novel second generation reversible BTK inhibitor HBW-3-10, that has a superior preclinical profile, efficacy and safety than other known ones. HBW-3-10 provides a valuable clinical candidate for treating Ibrutinib resistant CLL and beyond!

EP620 TARGETING CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) CELLS WITH THE GLYCOGEN SYNTHASE KINASE-3 BETA (GSK-3B)-SELECTIVE SMALL MOLECULE INHIBITOR, 9-ING-41

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Background: GSK-3β is a serine/threonine kinase that plays a role in several disease processes, including cancer. Aberrant overexpression of GSK-3β promotes survival in B cell lymphoma cells. By contrast, little is known about the role GSK-3β in CLL and its potential as a new therapeutic target. 9-ING-41 is a selective GSK-3β inhibitor with significant pre-clinical and clinical activity in advanced malignancies. Its modes of action include direct induction of apoptosis, reversal of chemoresistance, immune-modulation, and reversal of fibrosis. 9-ING-41 induces apoptosis in B lymphoma cell lines. We hypothesized that targeting GSK-3β with 9-ING-41 may be a new CLL treatment strategy via interference with tumor survival through novel pathways.
Aims: To explore the effects of single agent 9-ING-41 on viability and apoptosis in a preclinical in vitro model of CLL.
Methods: Experiments were conducted in the PGA1 CLL cell line. 9-ING-41 was obtained from Actuate Therapeutics, Inc. Cell viability/apoptosis were assessed using Celltiter-Glo assay and flow cytometry after Annexin V-APC/propidium iodide (PI) staining. Real-time PCR and western blotting were used to measure apoptotic markers.
Results: In PGA-1 cells, 1 μM 9-ING-41 concentration resulted in reduction of the phosphorylation levels of GSK-3β and its substrate glycogen synthase (GS) (Fig. 1D). Sensitivity to 9-ING-41 was evaluated using a luminescent *ATP-based viability* assay to measure the killing efficacy of the GSK3 inhibitor. Starting at day 3, 9-ING-41 caused a reduction in cell viability, with the highest impact on intracellular *ATP* concentration observed after 7 days of treatment (Fig. 1A). *Annexin V*/PI *labeling* further supports the anti-leukemic effects of 9-ING-41. The percentage of double negative viable PGA-1 cells decreased at day 3, 5 and 7 in the presence of 9-ING-41 compared to vehicle control (33.2% vs 92.3%, 16.1% vs 96% and 6.1% vs 99%, respectively; Fig. 1B). The cytotoxicity induced by 9-ING-41 was due to apoptosis, as indicated by a significantly increased percentage of Annexin V/PI apoptotic cells compared to vehicle. Early and late apoptosis increased at day 3, 5 and 7 treatment with 9-ING-41 compared to vehicle (63.9% vs 6.8%, 82.9% vs 3.8%, 94.2% vs 1%, respectively; Fig. 1C). 9-ING-41 treatment was associated with a 1.5-fold and 2.4-fold upregulation of the pro-apoptotic family members BAX and NOXA at the mRNA level (N=2; p<0.01). At day 3, *BCL2* anti-apoptotic expression *was 1.4-fold lower in* 9-ING-41 treated cells compared with the vehicle control. In vitro studies are ongoing to investigate the potential association of 9-ING-41 with the BCL2 inhibitor Venetoclax. The apoptotic effects of 9-ING-41 were further supported by the detection of increased degradation of PARP protein to its inactive fragment (Fig. 1D). Cleavage of PARP suggests caspase activation contributed to 9-ING-41 induced apoptosis of CLL cells. Treatment with 9-ING-41 resulted in increased active cleaved products of caspase-3, concurrent with a decrease in its pro-form (Fig. 1D). Additionally, 9-ING-41 treatment was associated with reduction of MCL-1 protein expression.



***In vitro* effects of 9-ING-41 in the PGA-1 cell line.** PGA-1 cells were treated with 1uM of 9-ING-41 at the indicated time points (1, 3, 5 and 7 days). (A) Luminescent cell viability assay. The orange and green points indicated PGA-1 cells treated with 9-ING-41 or DMSO control, respectively. PGA-1 cells were labeled with Annexin-V /PI and classified as (B) viable (Ann-/PI-) and (C) early (Ann+/PI-) and late apoptotic (Ann+/PI+). (D) Western blot analysis of PGA-1 cells treated with 9-ING-41 1uM. Protein bands of p-GSK-3β, p-GS (Ser 641), PARP (Full length-FL and Cleaved), Mcl-1 and GAPDH. Figure 1

Summary/Conclusion: Our study is the first to explore the relevance of 9-ING-41 as a therapeutic strategy in CLL. 9-ING-41 has significant single agent activity with the ability to induce apoptosis in a cell line-dependent manner. Targeting GSK-3β may expand therapeutic options for CLL patients. Ongoing work continues to assess combinations with approved targeted agents in order to overcome drug-induced resistance.

EP621 INFLUENCE OF POLYMORPHISMS OF CODON 72 OF TP53 IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Predictors of a transformation of chronic lymphocytic leukemia (CLL) into Richter syndrome (RS) have not been yet established, although biomarkers that have been reported as associated with risk of DLBCL-type RS development include the mutational status of NOTCH1, TP53 abnormalities, and the use of subset 8 immunoglobulin genes (IGHV4-39). On the other hand, second malignancies are frequent complications in patients with CLL, and immune defects associated with this disease have been suggested as the main cause. The possibility was raised that some germline TP53 polymorphisms in healthy populations may also affect p53 function. Because of this, much research has been done on the ability of SNPs to cause alterations in p53 function in many types of cancer. One of the most studied polymorphisms is codon 72 (R72P), due to its potential effect on the risk of cancer.
Aims: In this study, we will analyze the relationship of the genotypes of the TP53 codon 72 polymorphisms in a large cohort of patients with

CLL, to demonstrate the association of codon 72 with the evolution of the disease.
Methods: 558 patients diagnosed with CLL were included from a group of hospitals for the study of chronic lymphoproliferative disorders, with clinical data at diagnosis, including immunophenotype, FISH, IgHV, and karyotype studies. RT-PCR and Sanger sequencing techniques analyzed the codon 72 Arg/Arg, Arg/Pro, and Pro/Pro genotypes of TP53.
Results: The Pro/Pro genotype was significantly associated with Binet stage B and C CLL, Richter transformation, and a shorter time to the first treatment. Besides, Pro/Pro and Arg/Arg genotypes was associated with a risk of have secondary neoplasms (p=0,016). Follow-up assessments showed secondary neoplasms in 19.7% (n=110) of the patients, with the tumors appearing in the bladder, skin, and colon (14.5% each), prostate (13.6%), and the lung (12.7%). During the study period, 335 patients died. Analyses of overall survival demonstrated that patients with the Pro/Pro genotype lived significantly less than those with the other genotypes (p=0,028) (Figure 1). In the subgroup of patients with RS, no significant differences were found, although a trend of lower survival was observed in patients with the Pro / Pro genotype, and that in turn, the patients with RS with Pro/Pro genotype have much shorter survival than those without RS. Finally, in the multivariate analysis, the Pro/Pro homozygous genotype at TP53 codon 72 was identified as an independent variable associated with a 1,728-fold increased risk of death (95% CI: 1.062-2.810; P = 0,028) in comparison with the Arg/Pro heterozygous genotype.

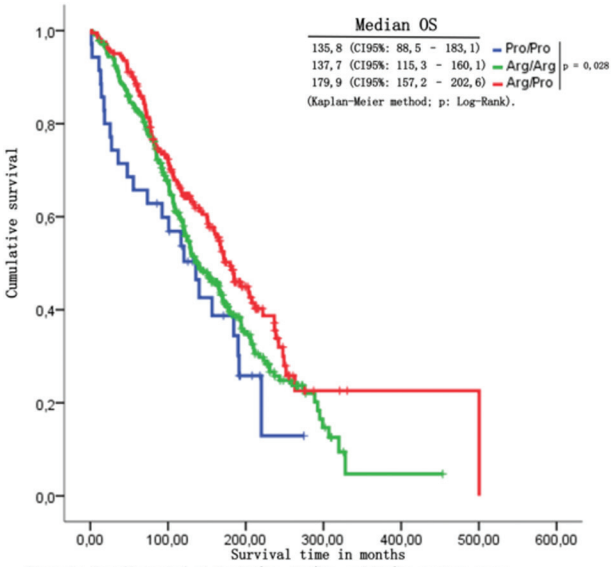


Figure 1a: Overall survival of the Arg/Arg, Arg/Pro, and Pro/Pro genotype groups.

Summary/Conclusion: Thus, we conclude that the Pro/Pro genotype of TP53 codon 72 has a potential role in the progression and mortality of CLL patients, and maybe it could be related to RS. In contrast, the Arg/Pro genotype was associated with a lower risk of secondary neoplasms than the homozygous genotypes.

EP622 CRISPR/CAS9 AND MRNA-BASED GENE EDITING AND EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Background: Robust and efficient protocols for gene editing and expression are highly needed in order to facilitate study of gene function in primary tumour cells from patients with chronic lymphocytic leukemia (CLL). CLL cells are notoriously prone to apoptosis when cultured *in vitro* and are for being hard-to-manipulate. This makes it challenging to modulate their endogenous gene expression or to induce expression of exogenous genes. Conventional methods based on plasmid/siRNA transfection or viral transduction are not efficient in CLL cells.
Aims: Hence, the development of optimized methods adapted to CLL cells gives an opportunity of developing screening platforms to assess function of multiple genes in assays *in vitro*.
Methods: In this work we set up conditions for CRISPR/Cas9-based gene knockout and mRNA-driven gene overexpression in B cells freshly isolated from peripheral blood of CLL patients. We also developed a platform for high-throughput *in vitro* production of mRNA encoding multiple genes allowing to scale up eventual screening assays.
Results: We show, on one hand, that it is possible to set up electroporation conditions that only marginally affect CLL cell viability. At such conditions, electroporating CLL cells with ribonucleoprotein complexes containing recombinant Cas9 nuclease and synthetic guides one can achieve >70-80% of homozygous knockout of a given. On the other hand, electroporation with *in vitro* transcribed mRNA allows to achieve >90% of electroporation efficiency and finely modulate gene expression levels in CLL cells. Gene overexpression persists for up to 4 days and longer allowing to perform long-term *in vitro* assays.
Summary/Conclusion: CRISPR/Cas9- and mRNA-based platforms for gene editing and expression are readily applicable to minimally manipulated primary CLL cells.

EP623 THE SIGNS OF NEGATIVE SELECTION IN IGHV FRAMEWORK REGIONS ARE ASSOCIATED WITH WORSE OVERALL SURVIVAL OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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Background: The mutational status of the variable region of the immunoglobulin heavy chain (*IGHV*) genes remains the most significant prognostic factor in chronic lymphocytic leukemia (CLL) patients. Numerous studies confirmed an improved progression-free and overall survival (OS) for mutated (M) *IGHV* patients compared to unmutated (UM) patients. However, the groups of M and UM patients are also heterogeneous, and additional markers are used for a more accurate prognosis. There are some evidences that CLL is antigen-driven disease: gene-expression profile indicating activation of signaling pathways through the B-cell receptors (BCR), expression of similar BCRs (stereotyped cases), efficacy of drugs inhibiting BCR signaling, etc.
Aims: The aim of this work was to determine the prognostic value of the signs of antigen selection in *IGHV* sequences of CLL patients.
Methods: The study included 127 M *IGHV* CLL patients (88 men and 39 women aged 58.6±0.91 years). All patients gave written informed consent. The *IGHV* gene mutational status was assessed by a direct sequencing. BASELINe statistics was used to determine if antigen selection occurred (Uduman et al., 2011, 2014). Major stereotyped subsets were assigned using the ARResT/AssignSubsets tool. All analyzed sequences were presented in Genbank database. Mutations of *TP53* gene were analyzed in 88 patients by a direct sequencing and were revealed in three patients. OS was analyzed by Kaplan-Meier statistic.
Results: The distributions of replacement (R) and silent (S) mutations in the CDR (complementary determining region) and the FR (framework region) regions of M sequences were 75.7:24.3 and 61.1:38.9, correspondingly, and were in agreement with data of Rene et al. (2014). Using BASELINe statistics, we found that two sequences (1.6%) had signs of positive selection and 15 sequences (11.8%) had signs of negative selection in CDRs ($p<0.05$). The FR regions had signs of negative selection ($p<0.05$) in 37 (29.1%) cases. In other cases, the Σ statistic values were borderline ($p<0.1$) or insignificant ($p>0.1$). No associations of OS with signs of selection in CDRs were found. At the same time, OS was worse in CLL patients with signs of negative selection in FRs (group I, median of OS 111 months) compared to other M *IGHV* patients (group II, median of OS 202 months), p=0.027. Observed CLL patients of both groups were comparably by age (p=0.287), gender (p=0.488), Binet stage (p=0.37), *TP53* mutational status (p=0.781), and the expression of stereotyped BCRs (p=0.488). In comparison to group II, sequences of group I had higher numbers of S mutations in CDRs (1.94±0.23 vs 0.96±0.2; p=0.001) and in FRs (5.97±0.34 vs 2.73±0.19; p=0.001), slightly lower numbers of R mutations in FRs (4.7±0.39 vs 6.04±0.31; p=0.05), and significantly lower R to S ratio in FRs (41.1:58.8 vs 69.4:30.6; p=0.00001). Besides, the number of amino acid substitutions in codons 24-26, 80, 83, and 96 was significantly reduced (or absent) (p=0.00041, when comparing the total number). In multivariate analysis, which was carried out considering the recommendations of International CLL-IPI working group (2016), the following factors were predictive for OS of M CLL patients: clinical stage (Binet A vs Binet B-C), age (≤65 years vs >65 years), and negative selection in FRs (data of serum β2-microglobulin

concentration were missing; *TP53* mutations were detected in a small number of cases and had no prognostic value in our M *IGHV* group).
Summary/Conclusion: The obtained data suggest of possible impact of features of somatic hypermutation processes in CDRs and FRs of *IGHV* for CLL prognosis.

EP624 GENE EXPRESSION MODEL TO IDENTIFY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS WITH AN ULTRA-STABLE DISEASE. A CAMPUS CLL STUDY.

I. Del Giudice [1,*], S. Raponi [1], R. Soscia [1], A. Piciocchi [2], V. Arena [2], C. Ilari [1], L. Cafforio [1], N. Peragine [1], P. Mariglia [1], F. R. Mauro [1], R. Murru [3], M. Varettoni [4], A. Zucchetto [5], S. Molica [6], M. Gentile [7], A. Visentin [8], L. Trentin [8], G. M. Rigolin [9], A. Cuneo [9], R. Moia [10], G. Gaidano [10], A. Guarini [11], V. Gattei [5], R. Foà [1]

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Background: Chronic lymphocytic leukemia (CLL) shows an extremely heterogeneous clinical course. Among cases with a favorable immunogenetic profile (mutated immunoglobulin heavy chain variable region (IGHV) genes, absence of unfavorable FISH lesions), there are those with an ultra-stable (US) clinical course who do not progress for at least 10 years from diagnosis. In a previous study (Raponi et al, Ann Oncol 2018) we described the genetic landscape of US-CLL patients and suggested a predictive model, based on the expression of six genes, capable of identifying these cases at diagnosis.
Aims: To test the previously designed classifier model in an expanded multicenter cohort of cases, including US-CLL and patients that despite favorable immunogenetic features progressed and required treatment within 5 years from diagnosis (non-US-CLL), in the context of the Campus CLL group.
Methods: Sixty new patients (31 US-CLL and 29 non-US-CLL) were included. All showed a mutated IGHV status, normal FISH or del13q only. US-CLL showed a median follow-up of 15.3 years (range: 10-23), while non-US-CLL showed a median time to progression of 2 years (range: 0-4.9). Droplet digital PCR (ddPCR) was applied to quantify the expression of the 6 previously identified genes (*P2RX1, PLXND1, CPT1A, PRRC2C, GPM6A, SMCHD1*) (Raponi et al, Ann Oncol 2018). These 60 cases were pooled with the 79 of our previous study (total: 89 US-CLL and 50 non-US-CLL). The absolute expression values of each gene were used to refine the original decision tree model.
Results: The decision tree model was initially fit on a training dataset obtained by the resample with bootstrap of 139 patients (n=1390). The validation of the decision tree based model and self-consistency test were performed by k-fold cross validation (CV) method. The decision-tree is derived from the best predictive model in the R output, identifying 12 subgroups (nodes) and 5 associated factors (genes).
By applying the decision tree model to the original cohort of 139 patients and according to the absolute expression values of the 5 genes included in the final model (*GPM6A+P2RX1+PLXND1+PRRC2C+SMCHD1*), 127/139 (91.4%) were correctly classified and 12 (8.6%) were misclassified. In particular, all the 89 US-CLL were correctly predicted (sensitivity: 100%), as well as 38 out of 50 cases who developed a progressive disease were classified by the model as non-US-CLL (specificity: 76%). Overall, the positive and negative predictive values of the model were 88.1% and 100%, respectively.
Summary/Conclusion: Although for early stage and asymptomatic CLL patients 'watch and wait' remains the standard of care, early treatment intervention is a tempting investigational scenario in the era of novel drugs. Besides the impact on patients' counseling at diagnosis and subsequent monitoring, our approach could further refine the current prognostic algorithms of low-risk CLL (mutated IGHV and favorable FISH) by allowing to identify CLL patients who are very likely to remain stable for more than a decade and may never require treatment from those who may benefit from experimental early intervention.

EP625 SOMATIC HYPERMUTATION PROFILES IN STEREOTYPED IGHV4-34 RECEPTORS FROM SOUTH AMERICAN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

C. Stanganelli [1,*], D. Torres [2], C. Ortega [3], M. E. Márquez [3], V. Remedi [4], J. Cabrera [1], C. Mardaraz [5], C. Galvano [6], A. Krzywinski [6], C. Lang [7], L. Zanella [7], E. Agriello [7], R. Bezares [8], A. Pavlovsky [5], M. Pavlovsky [5], P. Oppezzo [3], I. Slavutsky [6]

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Background: Chronic lymphocytic leukemia (CLL) is the most common mature B-cell neoplasm in the West. IGHV (immunoglobulin heavy-chain variable region) mutational status displays strong prognostic value. About 40% of CLL patients carry quasi-identical B-cell receptor (BCR) immunoglobulins that can be assigned to distinct stereotyped subsets. IGHV4-34 is one of the most frequently used genes in CLL patients and mostly of them display an indolent outcome.
Aims: We here study the mutational profile of CLL patients expressing IGHV4-34 focusing on the different stereotypes that are present in this rearrangement and their correlation with prognostic factors and activation-induced cytidine deaminase (AID) expression, one of the hallmarks of disease progression in CLL.
Methods: A multi-institutional cohort of 1444 unselected CLL patients from Argentina (891), Brazil (358), Uruguay (116) and Venezuela (79) were analyzed. RT-PCR and bidirectional sequencing were done. Cytogenetics and molecular cytogenetics analysis were performed. IGHV sequences with <98% homology with respect to the germline counterpart were considered as mutated (M), whereas those with ≥98% homology were classified as unmutated (U). Silent (S) and replacement (R) mutations were analyzed per VH FR and VH CDR subregions. ARResT/AssignSubsets and ARResT/Teiresias were employed in order to identify major and minor/novel subsets, respectively. The study was approved by the local Ethics Committees of each Institution. All individuals provided their informed consent.
Results: We identified 144 (10%) IGHV4-34 expressing cases (78 males; mean age: 65.6 years; Rai stages: 0: 60.6%, I-II: 31.1%, III-IV: 8.2%); 119 M, 35 of them with stereotyped BCR. Subset #4 was the most frequent (71.4% of cases) followed by subsets #16 (17.1%), #29 (8.6%), and #201 (2.9%), with different distribution among countries. R mutations were more represented in VH FR2, VH CDR1 and VH CDR2 in subset #16 compared to subsets #4, #29, and non-stereotyped (NST) IGHV4-34 M-CLL with significant differences in VH FR2 between subset #16 and the NST IGHV4-34 M-CLL (p=0.0001). Asymmetric distribution in R/S mutations ratio among different VH subregions with higher ratio in VH CDR2 for subset #29 and, in VH CDR1 and VH FR2 for subset #16 was found. Analysis of somatic hypermutation profile showed significant differences in G28>D/E between subsets #4 and #16 (p<0.0001) and in P45>S for subsets #4, #16, and #29 vs NST M-IGHV4-34 (p=0.048). In addition, differences in E55>Q for subset #4 vs #16 (p=0.0376) or subset #16 vs NST (p=0.0001) or across subsets (p=0.0001) and, in S64>I for subset #29 vs NST (p=0.0001) were also observed. S64T was absent in subsets #4 and #16. High frequency of disruption of the glycosylation motif in VH CDR2 region was always present. All stereotyped IGHV4-34 cases showed normal karyotypes. Deletion 13q14 single was present in 42.8% of stereotyped cases with a different distribution among subsets. A shorter time to first treatment was found in NST vs stereotyped M-IGHV4-34 patients (p=0.034). AID overexpression was evaluated in 26 IGHV4-34 patients, 8 of them display expression, only 2 stereotyped. The remaining patients expressing AID were NST and 5/6 (83%) showed a U-IGHV status.
Summary/Conclusion: Our results add new information supporting the importance of recurrent amino acid changes at particular positions, contributing to refine the molecular characterization of our cohort and, reinforcing the role of the genetic background and environmental factors in CLL patients.

EP626 NGS APPROACH FOR IGHV REARRANGEMENT ANALYSIS IN CLL PATIENTS WITH OLIGOCLONAL DISEASE

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Background: Mutational status of the IGHV genes, IGHV gene family usage, and B-cell receptor stereotype are the key prognostic factors for CLL. However, the routinely used Sanger sequencing technique may fail for the cases with an expansion of more than one tumor B-cell clones, especially with rearranged genes of the same IGHV family (up to 4% CLL cases)
Aims: To evaluate the robustness of NGS technology for IGHV analysis in complicated CLL cases.
Methods: DNA samples from CLL patients (N=26) for whom we previously failed to obtain IGHV rearrangements data by Sanger sequencing included in the study. IGHV loci were PCR amplified as described in BIOMED-2 protocol and by Campbell et al. Sequencing libraries were prepared with Nextera XT kit (Illumina, USA) according to the manufacturer's recommendations and were analyzed with MiSeq Genome Analyzer (Illumina, USA). Sequencing data were processed via Mixcr software (Bolotin et al. https://github.com/milaboratory/mixcr). The mutational status and receptor stereotype were identified using IMGT and ARRest databases according to ERIC recommendations.
Results: In 20 cases two clonal rearrangements were identified; in 18 cases IGHV genes of the same family were used in both clones (IGHV3 for 14 patients and IGHV1 for 4). One patient had IGHV1-69 и IGHV7-4 genes rearrangements (these two families are usually amplified with the same primer). One more patient had IGHV1-69 and IGHV3-73. In 19 cases only one rearrangement was productive, and one patient had two productive IGHV rearrangements. Herewith the mutational status did not differ within the rearrangement pairs. Thus, we determined U-CLL for 16 patients and M-CLL for 4 patients. Besides, two patients with stereotyped receptor CLL#2 and one patient with CLL#1 were found in U-CLL group. Three patients were found with only one productive clonal rearrangement. The heterogeneity of Sanger sequencing in these cases was presumably related to an insufficient amount of tumor cells in the sample comparing with a high polyclonal background. Three patients had three clonal rearrangements. In two cases all rearrangements were productive (IGHV3 and IGHV4 families) and highly mutated. One of these patients had two malignancies - CLL and mantle cell lymphoma. Both these two cases were classified as M-CLL. The third case demonstrated the major productive rearrangement (91% clones) with unmutated IGHV3-53 gene and two small (<5%) unmutated clones with IGHV1-69 (productive) and IGHV3-74 (unproductive).
Summary/Conclusion: Using NGS approach we have shown that in the cases with two IGHV gene rearrangements from the same VH gene family, variants with IGHV3 family are the most common (77,7%). U-CLL variants were also prevalent. Though Sanger sequencing is still more suitable for routine IGHV gene analysis in CLL, a significant number of complicated cases might benefit from NGS technology, therefore, allow to obtain definite diagnosis and assign appropriate treatment.

EP627 SYSTEMATIC TRANSCRIPTOME ANALYSIS REVEALS DISTINCT COMPETING ENDOGENOUS RNA NETWORK IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Increasing studies have identified that non-coding RNAs play critical roles in the initiation and progression of tumors via participating in competitive endogenous RNA (ceRNA) networks. However, the roles and functions of the ceRNA network in chronic lymphocytic leukemia (CLL) remain poorly understood.
Aims: The present study aims to explore the transcriptomatic profile and construct the distinct ceRNA network in CLL.
Methods: The expression profile of RNAS of CLL patients, CLL cell lines (MEC-1 and EHEB) and healthy group were obtained by the illumina sequencing. R software was used for functional enrichment analysis. The data in the genome microarray map GSE22762 was used for survival analysis. The lncRNA/circRNA-miRNA-mRNA ceRNA networks were visualized by Cytoscape 3.7.2. Four DEmRNAs and the circRNA hsa_circ_0007675/hsa-miR-185-3p/TCF7L1 axis were verified by Quantitative real-time PCR.
Results: In the present study, 57 differentially expressed- (DE-)mRNAs, 1391 DElncRNAs, 335 DEmiRNAs and 10013 DEcircRNAs were identified comparing CLL patients with healthy donors. Meanwhile, 482 mRNAs, 6085 lncRNAs, 302 miRNAs and 1847 circRNAs were explored differently expressed between CLL cell lines and healthy donors. GO and KEGG analysis results showed that these differentially expressed genes (DEGs) are related to the occurrence and development of tumors.The survival analyses showed that 16 DEGs (INIP, IL3RA, CHD1, NLRP12, IL20RB, B3GALT4, SIT1, ACOT8, AGFGR, PCLAF, C19orf18, SELENOS, OR7A17, PCDH7, HNRNPC, PHGDH) were significantly differentially expressed.
The ceRNA network were constructed by Cytoscape software. In total, 11 mRNA nodes, 19 miRNA nodes, 105 lncRNA nodes were identified as differentially expressed profiles between CLL patients and control. Meanwhile, a total of 256 DEcircRNAs, 19 DEmiRNAs, and 11 DEmRNAs were employed to construct the ceRNA network between CLL patients and control. We verified four DEGs (TCF7L1, TRIM34, SLC30A10, HOXD4) and the circRNA hsa_circ_0007675/hsa-miR-185-3p/TCF7L1 axis. Compared with normal people, the expression of these four genes and hsa_circ_0007675 in patient specimens were significantly increased whereas the expression of hsa-miR-185-3p was downregulated ($p<0.05$).
Summary/Conclusion: In this study, we identified the expression profile of RNAs in CLL patients and CLL cell lines. Functional enrichment analysis and survival analysis revealed the potential functions of DEGs. The ceRNA network we established can help to further understand the pathogenesis of CLL and provide potential prognostic markers and novel therapeutic targets.

EP628 CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL): HIGH-RISK DATA FROM AN IRISH POPULATION.

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Background: CLL is the most common B-lymphoid malignancy in the Caucasian population, principally affecting the elderly and displaying marked genetic and clinical heterogeneity. Targeted treatments have proved successful in extending the life-expectancy of those with ultra-high risk CLL. The poor outcomes of this subgroup have been mostly attributed to *TP53* mutations. However, *SF3B1* and *NOTCH1* gene mutations are also significant driver mutations contributing to this ultra-high-risk group.
Flow cytometry has enabled the identification of further high-risk subgroups through the detection of surface pro-tumour microenvironment modulators - including CD49d, CD62L and ROR1. The most prognostically significant is CD49d which is associated with bulky lymphadenopathy and shortened overall and treatment-free survivals. Blocking these surface modulators has proved promising in inducing CLL apoptosis and clinical trials in this area are ongoing.
The National Cancer Registry of Ireland (NCRI) collects cancer incidence data from hospital in-patient enquiry (HIPE) data and laboratory reports. However, there is a potential for national incidence figures to underestimate real-world data.
Aims: We have performed an in-depth study of consecutive newly diagnosed CLL patients captured directly from the flow cytometry laboratory and compared our incidence figures to registry data from the NCRI. Including a second cohort of previously diagnosed CLL patients who required therapy during the study time period, we performed extended immunophenotyping (CD62L, CD49d and ROR1) and mutational analysis of *TP53* and *NOTCH1* genes in order to characterize disease biology in a representative Irish population.

Methods:
Two patient groups were recruited from three institutions (St. James's Hospital, University Hospital Limerick and the Midlands Regional Hospital) from October 2017 - September 2018. Group 1 included consecutive patients with newly diagnosed CLL and group 2 included previously-diagnosed patients who required treatment during the study time period. Ethics approval was granted and written informed consent was sought for biobanking, immunophenotypic and molecular analysis (extended flow panel, *TP35* and *NOTCH1* mutational status). If consent was not provided, the patients were included for epidemiological purposes only.
Results: 148 patients were included: 111 newly-diagnosed (1) and 38 known cases of known CLL pre-treatment (2). An incidence of 5 per 100,000 (females) and 11 per 100,000 (males) was established. The median age was 67.5 years with 58 patients (39%) aged ≥ 70 years. The male to female ratio was 2.2:1. Immunophenotyping and mutational analysis of groups 1 and 2 revealed: CD62L (1-63.5%; 2- 64%), CD49d (1- 27.1%; 2- 34.6%), ROR1 (1- 85.9%; 2- 88.5%), mutated *TP53* (1- 9.2%; 2- 11.8%) and mutated *NOTCH1* (1- 9.4%; 2 16.7%). The association between CD49d expression and lymphadenopathy was demonstrated. In cases where expression levels fell between 10-30%; CD62L had two (11.7%) and CD49d had nine (90%) cases of bimodal distribution patterns.

Table: Baseline characteristics.

Demographic, clinical and molecular Characteristics	All patients N=148		Group 1 N=111		Group 2 N=37	
Men	102	68.9%	76	68.5%	26	70.3%
Women	46	31.1%	35	31.5%	11	29.7%
Median age at diagnosis (Years)	67.5 (29-91)	-	69 (41-91)	-	60 (29-79)	
Binet stage A	97/148	65.6%	94/111	84.7%	3/37	8.1%
Binet stage B	28/148	18.9%	14/111	12.6%	14/37	37.8%
Binet stage C	23/148	15.5%	3/111	2.7%	20/37	54.1%
TP53 mutated	12/121	9.9%	8/87	9.2%	4/34	11.8%
NOTCH 1 mutated	13/115	11.3%	8/85	9.4%	5/30	16.7%
ROR1 ≥ 30%	96/111	86.5%	73/85	85.9%	23/26	88.5%
ROR1<30%	15/111	13.5%	12/85	14.1%	3/26	11.5%
CD62L ≥ 30%	70/110	63.6%	54/85	63.5%	16/25	64.0%
CD62L<30%	40/110	36.3%	31/85	36.4%	9/25	36.0%
CD49d ≥ 30%	32/111	28.8%	23/85	27.1%	9/26	34.6%
CD49d <30%	79/111	71.2%	62/85	72.9%	17/26	65.3%

Summary/Conclusion: We have established in-depth epidemiological and molecular analysis of an Irish patient cohort in an effort to redress the paucity of published Irish data. We have established that our CLL cohort and biobank benchmarks from a clinical and laboratory perspective to other international cohorts. A longitudinal study of the patient cohort will establish whether CD49d expression ≥10% is prognostically useful and whether cases of CD62L with bimodal patterns of expression have clinical relevance.

EP629 INFLUENCE OF INFLAMMATORY CYTOKINES ON S100A PROTEINS EXPRESSION IN CLL PATIENTS

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Background: S100A proteins possess a broad range of intra- and extracellular functions. The involvement of these proteins in inflammation-mediated responses is of particular interests, considering that inflammation represents one of the landmarks of malignancy. Processes such as inflammation and cellular stress trigger the release of S100A proteins to extracellular space, interacting with their receptors and activating numerous intracellular signaling pathways, for instance NF-κB and AP1. Through them, S100A proteins take part into regulation of some of the most essential cellular processes: cell differentiation, apoptosis, inflammation, proliferation, etc.
Aims: The aim of the study is to assess the role of inflammation in activation of S100A proteins via proliferation and inflammation related signaling pathways.
Methods: We observed 60 CLL patients' samples to isolate mononuclear cells (MNC) and CD19⁺ cells. MNC of CLL patients were treated with pro-inflammatory IL-6 and anti-inflammatory IL-10 cytokines, and inhibitors of JAK1/2, NF-κB and PI3K signaling pathways, to evaluate S100A4, S100A8, S100A9, S100A12 and NF-κB protein expression by immunoblotting. Also, we used immunocytochemistry to analyse the number of the S100As immunopositive MNC of CLL patients.
Results: S100A8 showed higher level of protein expression in MNC and CD19⁺ cells in comparison to healthy control. The number of immunopositive S100A4 ($p<0.05$) and S100A9 cells ($p<0.001$) was significantly decreased in CD19⁺ cells and MNC, respectively of CLL patients in comparison to healthy control. In addition, S100A4 and S100A9 proteins expression had statistically significant lower level of expression in MNC. Also, IL-6 stimulated expression of S100A8 and S100A4 in MNC of CLL, while the expression of latter one was prevented by NF-κB and JAK1/2 inhibitors. IL-10 reduced expression of S100A8 and S100A12 in MNC of CLL.
Summary/Conclusion: Pro-inflammatory IL-6 and anti-inflammatory IL-10 cytokines have opposite effect on inflammatory S100A8 protein in CLL, with a potential to be a prognostic marker.

EP630 RELEVANCE OF NRF2/KEAP1 AXIS IN CHRONIC LYMPHOCYTIC LEUKEMIA DEVELOPMENT

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Background: Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of long-lived resting clonal B lymphocytes in blood, bone marrow, and secondary lymphoid organs. Oxidative stress is known to be one of the mechanisms important in CLL development and progression. Specifically, NRF2/KEAP1 axis plays a crucial role in redox balance, inducing the expression of target genes, namely those related to antioxidant defenses.
Aims: The goal of this study was to clarify the relevance of NRF2/KEAP1 axis in CLL development, particularly through the evaluation of its target genes expression levels and their correlation with clinical and laboratory data, in order to identify potential new CLL diagnostic biomarkers.
Methods: We evaluated the expression levels of *NFE2L2*, *KEAP1*, *NFKB1*, *NQO1*, *HMOX1*, *GPX1*, *SQSTM1*, *TXNRD1*, *BCL2*, *GSTM1* and *HPRT* (endogenous control) genes in peripheral blood of 25 CLL patients and 30 healthy controls (CTL) using qPCR. Informed consent was obtained in accordance with the Helsinki Declarations. Mann-Whitney U and Kruskal-Wallis tests were used to assess the statistical significance between groups. Receiver operating characteristic (ROC) curves analysis was performed to analyze variables accuracy as diagnostic biomarkers. Patients were dichotomized according to the cut-off points obtained from the ROC curves constructed to predict death. All statistical analyses were two-sided and a $p<0.05$ was considered statistically significant.
Results: The 25 CLL patients studied were 13 males and 12 females with a median age of 73y, ranging between 48 and 83 years, and the 30 healthy controls, were 15 males and 15 females with a median age of 75 years, ranging between 54 and 99 years. At diagnosis, all CLL patients were Binet A (low risk). 24% of CLL patients presented low-risk cytogenetic abnormalities, 19% presented intermediate-risk, and 24% high-risk and 33% did not present any cytogenetic abnormalities. Our results showed, in CLL patients, an increase on gene expression levels of *NQO1* [CLL: m=0.161; interquartile range (IR)=0.283; CTL: m=0.023; IR=0.098; p=0.005] and *BCL2* [CLL: m=3,400; IR=6,353; CTL: m=0,434; IR=1,039; p<0,001) and a decrease of *NFKB1* (CLL: m=0,900; IR=0,690; p=0,014; CTL: m=1,752; IR=5,220; p=0,014) and *SQSTM1* (CLL: m=0,144; IR=0,395; CTL: m=0,880; IR=3,153; p<0,001), when compared to controls. None of the other evaluated genes showed significant differences between CLL patients and controls.

ROC analysis for these genes suggested that their expression levels might be possible diagnostic biomarkers for CLL *NQO1* (AUC:0,733; IC95%:0,593-0,873; cut-off>0,159; sensitivity=57%; specificity=85%; p=0,005); *BCL2* (AUC:0,882; IC95%:0,786-0,978; cut-off>0,532; sensitivity=91%; specificity=74%; p<0,001); *NFKB1* (AUC:0,695; IC95%:0,553-0,837; cut-off<1,030; sensitivity=64%; specificity=77%; p=0,014); *SQSTM1* (AUC:0,799; IC95%:0,676-0,921; cut-off<0,443; sensitivity=68%; specificity=87%; p<0,001)]. No correlation was found between gene expression levels and CLL patients' survival, as well as with other clinical and laboratory data.

Summary/Conclusion: The decrease of *NFKB1* and *SQSTM1* gene expression levels observed in our study confirms the importance of oxidative stress in CLL, and the increase of *BCL2* and *NQO1* reflect the ability of tumor cells to resist cell death. Furthermore, as these genes are target of the NRF2/KEAP1 axis, our study suggests the relevance of the NRF2/KEAP1 axis for CLL development, being the levels of *NFKB1*, *SQSTM1*, *BCL2* and *NQO1* genes potential new diagnostic biomarkers.

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Chronic lymphocytic leukemia and related disorders - Clinical

EP631 OTHER MALIGNANCIES IN THE HISTORY OF CHRONIC LYMPHOCYTIC LEUKEMIA – A RETROSPECTIVE, MULTICENTER COHORT STUDY BY ERIC, THE EUROPEAN RESEARCH INITIATIVE ON CLL, IN HARMONY

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Background: Other malignancies occurring in patients with CLL are a well-known, but insufficiently investigated area, highlighting the need for further research.

Aims: To leverage the understanding of other malignancies in CLL, particularly regarding potential links to chemoimmunotherapy (CIT) and/or novel agents, as well as associations with relevant clinicobiological factors.

Methods: Data from consecutive sets of patients diagnosed with CLL between 2000-2016 were collected by affiliated members through ERIC and subjected to detailed statistical analysis. Collected variables included: demographics, stage at diagnosis, treatment, treatment response, death, cause of death, other malignancy (type, date of diagnosis, outcome), biomarker profiles.

Results: Overall, 13,808 patients from 64 centers were evaluated: 8,517 males, 5,291 females; median age: 66 (range, 27-92). At diagnosis, 74/16/10% of cases were classified as Binet stages A/B/C. Biomarker profiling (performed before frontline treatment): 1,055/6,310 cases (14.1%) with del(11q); 843/6,928 cases (10.8%) with *TP53* aberrations

[del(17p) and/or *TP53* mutation]; 3,127 (48%) and 3,390 (52%) cases with unmutated or mutated IGHV genes, respectively. With a median follow-up of 77 months (range, 49-199), 7,134/13,308 (53.6%) patients had received ≥1 line(s) of treatment (1: 59.3%, 2: 19.3%, 3: 11%, 4+: 10.4%). Therapies received (at any line) included only CIT/CIT+novel agents/only novel agents in 71.5/21.3/7.2% of cases, respectively. Frontline therapies were FCR (32.3% of cases), bendamustine+/-antiCD20 (10.7%), other CIT (mostly chlorambucil+antiCD20) (46.7%), BTKi+/-combinations (4.8%), idelalisib+/-combinations (0.5%), venetoclax+/-combinations (0.9%), various other regimens (4%). Within this series, 2,919/13,808 cases (21.1%) were reported with other malignancies besides CLL; cases with Richter's transformation (n=390/10,157, 3.8%) were not included in this count. CLL diagnosis preceded the other malignancy in 1,939 cases (14% of the cohort): of these, 317 and 1,622 cases developed other hematological or non-hematological malignant neoplasms, respectively. The great majority of the former concerned MDS/AML (31%) and other lymphoid malignancies (49%), excluding MGUS. The incidence of MDS/AML was significantly enriched in (i) patients with unmutated IGHV genes (p=0.05) or del(11q) (p=0.009); (ii) treated patients (p<0.001), particularly those receiving ≥3 treatment lines (p<0.01); and (iii) patients treated with FCR (p<0.001). FCR retained independence on multivariate analysis. Within the group of non-hematological malignant neoplasms, non-melanoma skin cancer (NMSC) accounted for 31% of cases; malignant neoplasms of the prostate, colon, breast, bronchus/lung and melanoma collectively accounted for 41.6% of cases. Several of these neoplasms were significantly more prevalent in untreated patients (p<0.01 for breast, prostate, colon), despite that the follow-up of treated vs untreated patients did not differ significantly. Only NMSC was significantly more prevalent (p=0.007) in treated patients.

Summary/Conclusion: We report strong associations between the development of other hematological malignancies, especially MDS/AML, and certain biological features as well as treatment for CLL, with a highly relevant risk for patients treated with CIT, particularly the FCR regimen. In contrast, the development of solid tumors appeared unaffected by treatment administration, prompting further investigation in specific patient subgroups that will be presented at the congress.

EP632 VENETOCLAX-OBINUTUZUMAB MODULATES CLONAL GROWTH: RESULTS OF A POPULATION-BASED MINIMAL RESIDUAL DISEASE MODEL FROM THE RANDOMIZED CLL14 STUDY

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Background: The CLL14 study has established fixed-duration treatment of the Bcl-2 inhibitor venetoclax and the CD20 antibody obinutuzumab (Ven-Obi) for patients (pts) with previously untreated chronic lymphocytic leukemia (CLL). High rates of undetectable minimal residual disease (uMRD) have been observed with one year of treatment.

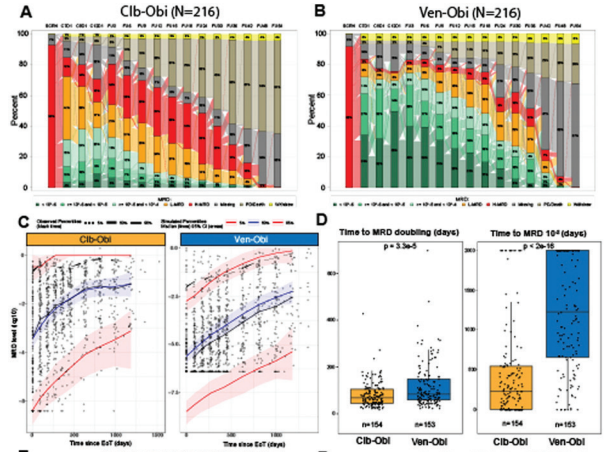
Aims: The aim of this report is to provide a population-based exploratory analysis of MRD growth dynamics after stopping Ven-Obi and chlorambucil-Obi (Clb) therapy and to compare growth trajectories between targeted treatment versus chemoimmunotherapy.

Methods: Pts were randomized 1:1 to receive 12 cycles of Ven with 6 cycles of Obi or 12 cycles of Clb with 6 cycles of Obi. MRD was analyzed by next-generation sequencing (Adaptive clonoSEQ Assay). Samples from peripheral blood (PB) are collected every 3-6 months. For the longitudinal analyses of MRD growth dynamics, a population-based logistic growth model with nonlinear mixed effects (NLME) approach was developed to estimate population and individual patient parameters. Cases with at least two measurable timepoints were included; data < LLOQ were incorporated by likelihood-based method. Prognostic markers were screened as covariates for impact on key model parameters based on statistical (Akaike information criterion) and graphical assessments. Statistical inference on MRD doubling time and time to reach 10^{-2} MRD level was derived for the stratified subgroups.

Results: Of 432 enrolled pts, 216 were assigned to receive Clb-Obi and 216 to Ven-Obi. At follow-up month 30, 7 (3.2%) pts in the Clb-Obi arm and 58 (26.9%) pts in the Ven-Obi arm had uMRD levels $<10^{-4}$ (Fig A,B). Based on the inclusion criteria for the population analysis, 154 pts from Clb-Obi arm and 153 pts from Ven-Obi arm were included. The model was well calibrated, and high concordance between observed and predicted values was confirmed (Fig C).

The median MRD level at EoT was significantly lower after Ven-Obi than after Clb-Obi ($10^{-6.00}$ vs $10^{-3.26}$, p<2e-16). Within the Ven-Obi arm, end of treatment MRD values did not differ between pts with low-risk and high-risk features, such as IGHV status ($10^{-5.79}$ for mutated IGHV vs $10^{-6.12}$ for unmutated IGHV) or *TP53* deletion/mutation ($10^{-5.38}$ for deletion/mutation vs $10^{-6.03}$ for non-deleted/mutated). The median MRD doubling time was significantly longer after Ven-Obi than Clb-Obi therapy (median days 84 versus 67 days, p = 3.3e-5)(Fig D). The median time from EoT to MRD level increase to 10^{-2} was also significantly longer after Ven-Obi therapy compared to Clb-Obi therapy (median 1225 days versus 227 days, p<2e-16)(Fig D).

Based on a covariate screening of 28 biological and clinical characteristics, the final model showed a significant impact on MRD growth dynamics by Ven-Obi treatment, high MRD levels at the start of treatment, high CLL-IPI, deletion11q, higher disease burden, response to treatment, and IGHV status (Fig E,F). Pts with *TP53* deletion/mutation also had higher growth, although statistical significance was not reached due to low number of pts. After adjusting all the covariates in the model, the effect of Ven-Obi treatment on MRD growth remained significant (Fig E,F).



Summary/Conclusion: This analysis establishes a robust, population-based model of MRD growth dynamics that allows description of growth trajectories and treatment effects after treatment cessation. In addition to more effective MRD eradication with Ven-Obi, our results demonstrate that MRD growth is modulated more efficiently by BCL2-targeting treatment in contrast to genotoxic chemoimmunotherapy.

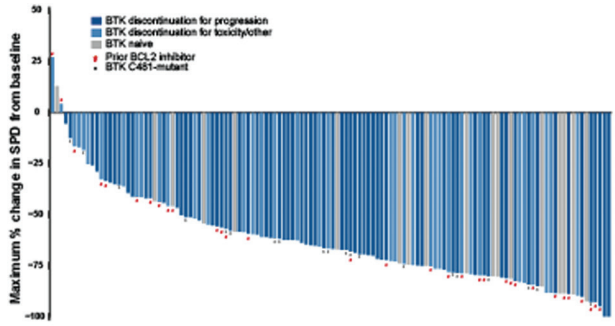
EP633 PIRTOBRUTINIB (LOXO-305), A NEXT GENERATION, HIGHLY SELECTIVE, NON-COVALENT BTK INHIBITOR IN PREVIOUSLY TREATED CLL/SLL: RESULTS FROM THE PHASE 1/2 BRUIN STUDY

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Background: Despite the marked efficacy of covalent BTK inhibitors (BTKi) in CLL/SLL, the development of resistance and discontinuation for adverse events can lead to treatment failure. Moreover, pharmacological liabilities of these agents such as low oral bioavailability or short half-life can lead to suboptimal BTK target coverage and ultimately result in acquired resistance in some patients (pts). To address these limitations, pirtobrutinib (LOXO-305), a highly selective, non-covalent BTKi that inhibits both WT and C481-mutated BTK with equal low nM potency was developed.
Aims: To evaluate safety and efficacy of pirtobrutinib in previously treated CLL/SLL.
Methods: BRUIN is a multicenter phase 1/2 trial (NCT03740529) enrolling pts with advanced B-cell malignancies who have received ≥2 prior therapies. Oral pirtobrutinib was dose escalated in a standard 3 + 3 design in 28-day cycles. The primary endpoint was MTD/RP2D identification. Efficacy evaluable pts included all dosed pts who underwent their first response evaluation or discontinued therapy. Safety was assessed in all pts (n=323). Response was assessed according to the iwCLL 2018 criteria, including PR with lymphocytosis (PR-L).
Results: As of 27 September 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, and 66 other B-cell lymphomas) were treated on 7 dose levels (25-300mg QD). Among the 170 CLL/SLL pts, the median age was 69 (range 36-84) years. Median number of prior lines of therapies was 3 (range 1-11), 86% of CLL/SLL pts had received a prior BTKi, and 67% an anti-CD20 antibody, chemotherapy, and BTKi; 21% had received a PI3K inhibitor and 34% venetoclax. At enrollment, high risk features such as 17p deletion were present in 25% (20/81), TP53 mutation in 30% (27/91), and unmutated IGHV in 88% (71/81). Pirtobrutinib demonstrated high oral exposures, with doses ≥100mg QD exceeding the BTK IC90 for the entirety of the dosing interval. No DLTs occurred. Consistent with pirtobrutinib's selectivity, the only treatment-emergent adverse events regardless of attribution or grade seen in ≥10% of pts (n=323) were fatigue (20%), diarrhea (17%) and contusion (13%). Responses were observed at the first dose level of 25mg QD. A RP2D of 200mg QD was selected for future studies. At the efficacy cutoff date, 150 CLL/SLL pts remained on therapy and 139 were efficacy evaluable (121 BTKi-treated). Median follow-up was 6 months (range 0.6-17.8+) for efficacy evaluable pts. The ORR was 63% with 69 PRs, 19 PR-Ls, 45 SDs, 1 PD, and 5 discontinued prior to first response assessment (Figure). An additional 37 pts were ongoing and awaiting initial radiologic assessment. Responses deepened over time; among pts with at least 10 months of follow-up (n=29), the ORR was 86%. ORR was not influenced by the reason for prior BTKi discontinuation (i.e. progression vs intolerance), or other classes of prior therapy received (including a covalent BTK and a BCL2 inhibitor). Of the 88 responding pts, all except 5 remain on therapy (4 progressed, and 1 achieved a PR and electively discontinued). The longest followed responding pt continues on treatment for 17.8+ months.



Data cutoff date of 27 September 2020. Data for 13 CLL/SLL patients are not shown in the waterfall plot due to 4 having no target lesions identified at baseline, 5 with no/incomplete post-baseline lesion measurements, and 4 discontinued prior to first post-baseline disease assessment.

Summary/Conclusion: Pirtobrutinib demonstrated promising efficacy in CLL/SLL pts following multiple prior lines of therapy including a covalent BTKi and a BCL2 inhibitor. Importantly, the activity of pirtobrutinib was not restricted to pts with BTK C481 mutations. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index.

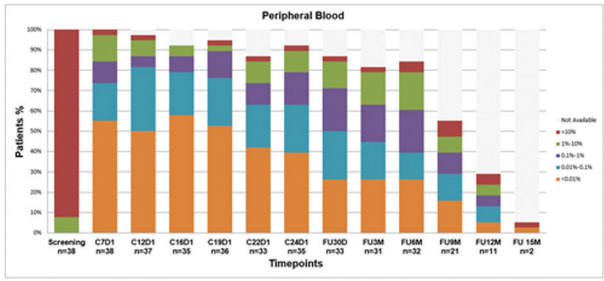
EP634 MINIMAL RESIDUAL DISEASE-DRIVEN TREATMENT INTENSIFICATION WITH SEQUENTIAL ADDITION OF IBRUTINIB (IBR) TO VENETOCLAX (VEN) IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): THE IMPROVE STUDY

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Background: Undetectable MRD (uMRD) has become an achievable endpoint for patients (pts) with CLL, in particular using the BCL2 inhibitor VEN allowing treatment discontinuation in a MRD-driven approach. uMRD can be reached in a proportion of pts with VEN mono, and in larger fraction in combination with the BTK inhibitor IBR. It remains to be established who can achieve best responses with single agent or combination strategies.
Aims: This phase 2 multicenter MRD-driven Italian study aims at discontinuing treatment upon reaching uMRD in pts with relapsed/refractory CLL treated with VEN mono or through the addition of IBR in pts who did not achieve uMRD with the single agent.
Methods: VEN mono (up to 400 mg/day as per label) was administered for 12 months. MRD in peripheral blood (PB) and bone marrow (BM) was evaluated using the ERIC 6-color flow panel. Pts with uMRD in both PB and BM at C12D1 discontinued VEN at C12D28. Pts with detectable MRD in PB and/or BM added IBR 420 mg/day from C13D1 and continued both drugs up to C24D28, uMRD, progression or toxicity (whichever first). After C24D28, pts with detectable MRD and still in response continued IBR alone. The primary endpoint was uMRD4 (<1 CLL cell in 10^4 leukocytes) in both PB and BM.
Results: 38 pts (recruited from Nov 2017 to Jul 2018) started VEN. Median number of prior therapies was 1 (range 1-4), 61% were previously treated with FC+/-R; 8/33 (24%) carried del(17p); 10/30 (33%) *TP53* mutations, and 24/30 (80%) unmutated IGHV. One pt discontinued treatment due to myelodysplasia (unrelated to VEN) and 1 pt

progressed on VEN mono before C12D1, 1 evaluation was missed due to COVID-19. As of 31 Jan 2021, overall response rate with VEN mono was 36/38 (95%), 19 CR and 17 PR. As per protocol, 17 pts (45%) with uMRD4 in PB and BM at C12D1 discontinued VEN at C12D28. 19 (55%) responsive cases with detectable MRD at C12D1 added IBR to VEN from C13D1. By combining IBR and VEN for a median of 7 months (range 3-10) 5/10 pts in PR improved their response to CR, 16/19 (84%) achieved uMRD4 in both PB and BM (Fig. 1), thus stopping both therapies. The remaining 3/19 continued IBR. After a median follow up of 30 months, median PFS has not been yet reached; 3 pts progressed without treatment need, 1 pt restarted VEN mono as per protocol, 2 pts developed Richter transformation. 11/33 pts (33%) who discontinued treatment in uMRD, after a median observation of 30 months remain uMRD (6 treated with VEN only). No cases of clinical and/or laboratory tumor lysis syndrome were reported in 39 pts (1 excluded from the efficacy analysis because of atypical phenotype). Adverse events were mild, with no discontinuations or dose reductions; with prolonged follow-up no new relevant toxicities occurred.



Summary/Conclusion: Our updated results demonstrated that a sequential MRD-guided approach is feasible and leads to an overall uMRD in 33/38 pts (87%) with either VEN mono or in combination with IBR. Interestingly, 84% of pts who did not achieve uMRD after VEN alone obtained uMRD after the addition of IBR and the remaining 3 patients who did not obtain uMRD even after the combination, could be selected for continuous IBR. Median PFS is not yet reached after 30 months of follow-up. This MRD-driven sequential approach allows to reach identical depth of response in each patient enrolled in the study using a personalized intensification avoiding unnecessary drug exposure, ultimately identifying the few pts that may benefit from continuous IBR. Time to clinical progression, response to VEN retreatment, and characteristics of pts with persistent MRD remain to be established.

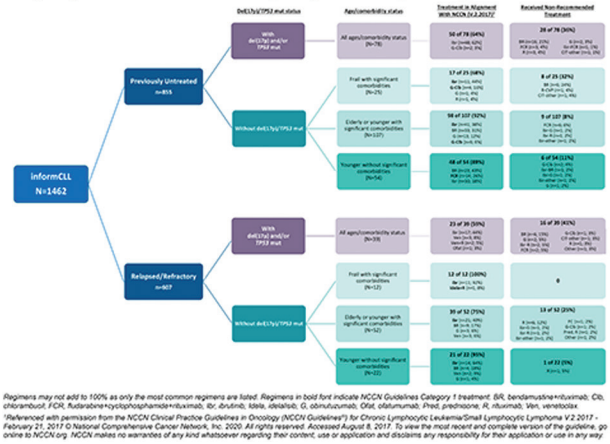
EP635 REAL-WORLD APPLICATION OF NATIONAL COMPREHENSIVE CANCER NETWORK CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®) FOR CLL/SLL FROM THE INFORMCLL REGISTRY

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Background: NCCN Guidelines® provide recommendations on evolving standards of care to inform treatment (tx) decisions.
Aims: To understand the application of guidelines in routine clinical practice, we assessed how tx regimens in the informCLL registry (Mato *ASH* 2020) aligned with National Comprehensive Cancer Network (NCCN®)-recommended regimens for CLL/SLL.
Methods: informCLL enrolled patients (pts) ≥18 years (y) receiving approved CLL tx (10/2015–6/2019) and who provided informed consent. Pts were categorized by del(17p)/*TP53* mutation (mut) status, line of therapy, and age/comorbidity. Comorbidities were assessed using Charlson Comorbidity Index (CCI); significant comorbidities (SC) were defined as CCI ≥3 (Mato *Blood Adv* 2020). For pts without del(17p)/*TP53* mut, age/comorbidity groups were: (1) frail with SC (≥65 y + CCI ≥3), (2) elderly (≥65 y + CCI <3) or younger with SC (<65 y + CCI ≥3), (3) younger without SC (<65 y + CCI <3). For this analysis, NCCN Guidelines for CLL/SLL V.2.2017 were used given 74% enrollment in ≥2017.
Results: Of 1462 pts enrolled (previously untreated [1L], 58%; relapsed/refractory [R/R], 42%), community-based practices enrolled 93%. Median age was 71 y (range 34–95); median CCI was 1.0 (range 0–11) and 16% had CCI ≥3. 27% of pts (n=389) had del(17p)/*TP53* mut data available. Alignment with NCCN-recommended regimens was 59–64% for pts with del(17p)/*TP53* mut and 68–100% for pts without del(17p)/*TP53* mut. Most pts with del(17p)/*TP53* mut (1L, n=78; R/R, n=39) had Category (Cat) 2A ibrutinib (ibr) as recommended (1L, 62%; R/R, 44%), but a quarter had non-recommended chemoimmunotherapy (CIT) with bendamustine+rituximab (BR) or fludarabine+cyclophosphamide+R (FCR) (1L, 24%; R/R, 21%). In pts without del(17p)/*TP53* mut who were frail with SC (1L, n=25; R/R, n=12), 60% of 1L pts had Cat 1 ibr or obinutuzumab+chlorambucil, but 24% received BR, which was not recommended; all R/R pts had Cat 1 ibr or idelalisib+R. In pts without del(17p)/*TP53* mut who were elderly/younger with SC (1L, n=107; R/R, n=52), 69% of 1L and 58% R/R pts had Cat 1 ibr or Cat 2A BR. Of pts without del(17p)/*TP53* mut who were younger without SC (1L, n=54; R/R, n=22), 87% of 1L and 82% R/R pts had Cat 1 or 2A with CIT (BR or FCR), or ibr. Despite guideline recommendations for prognostic testing, a majority of pts (73%, n=1073) had no data available for del(17p)/*TP53* mut status. For these pts the most common tx regimens were ibr (44%), CIT (32%), and anti-CD20 monotherapy (14%).

Figure. Alignment with NCCN Guidelines for CLL/SLL in previously untreated and relapsed/refractory patients in informCLL



Regimens may not add to 100% as only the most common regimens are listed. Regimens in bold font indicate NCCN Guidelines Category 1 treatment. BR, bendamustine+rituximab; Clb, chlorambucil; FCR, fludarabine+cyclophosphamide+rituximab; Ibr, ibrutinib; Idela, idelalisib; O, obinutuzumab; Ofat, ofatumumab; Pred, prednisone; R, rituximab; Ven, venetoclax.

†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2017 - February 21, 2017 © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 8, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Summary/Conclusion: A third of pts with del(17p)/*TP53* mut, a high-risk population with poor outcomes after CIT, did not receive NCCN-recommended regimens. Most pts without del(17p)/*TP53* mut received recommended tx across age/comorbidity groups. A majority of pts in the registry lacked del(17p)/*TP53* mut data and therefore may have received suboptimal tx. These results underscore a need for awareness of NCCN Guidelines recommendations to better inform tx decisions, especially in the community setting. *References:* Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2017 - February 21, 2017 © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 8, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

EP636 IBRUTINIB TREATMENT IN THE FIRST-LINE SETTING FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: UP TO 7 YEARS OF FOLLOW-UP IN THE RESONATE-2 STUDY

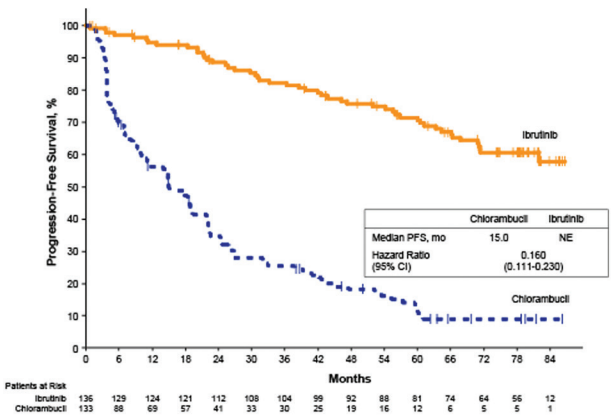
P. Ghia [1,*], C. Owen [2], T. Robak [3], A. Tedeschi [4], O. Bairey [5], J. Burger [6], P. Hillmen [7], S. Coutre [8], S. Devereux [9], S. Grosicki [10], H. McCarthy [11], J. Li [12], D. Simpson [13], F. Offner [14], C. Moreno [15], S. Dai [16], A. Szoke [16], J. P. Dean [16], T. J. Kipps [17], P. Barr [18]

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Background: Ibrutinib, a once-daily Bruton's tyrosine kinase inhibitor, is approved in the European Union and other regions for the treatment of adult patients with chronic lymphocytic leukemia (CLL); it is the only targeted therapy associated with both a significant progression-free survival (PFS) and overall survival (OS) benefit in multiple randomized phase 3 studies compared with established chemotherapy/chemoimmunotherapy regimens in patients with previously untreated CLL/small lymphocytic lymphoma (SLL).
Aims: To report extended long-term follow-up data for first-line ibrutinib vs chlorambucil in older patients with CLL/SLL from the RESONATE-2 study.
Methods: The phase 3 RESONATE-2 study enrolled patients with previously untreated CLL/SLL who were aged ≥65 years and without del(17p) (N=269). Patients were randomly assigned in a 1:1 fashion to receive once-daily single-agent ibrutinib (420 mg) until disease progression or unacceptable toxicity (n=136) or chlorambucil (0.5–0.8 mg/kg) for up to 12 cycles (n=133). Long-term outcomes included PFS, OS, overall response rate (ORR), and safety. Responses were assessed by the investigator per 2008 iwCLL criteria.
Results: Overall, significant PFS benefit was sustained for patients treated with ibrutinib vs chlorambucil (hazard ratio [HR] 0.160 [95% confidence interval (CI) 0.111–0.230]) after up to 7 years of follow-up (median 74.9 months; range 0.1–86.8 months) (Figure). In addition to the overall population, PFS benefit with ibrutinib was observed in the subgroup of patients with high-risk genomic features, including unmutated IGHV (HR 0.109 [95% CI 0.063–0.189]) and del(11q) (HR 0.033 [95% CI 0.010–0.107]). At 6.5 years, 61% of patients treated with ibrutinib vs 9% of patients treated with chlorambucil remained progression-free. Ibrutinib treatment resulted in an OS rate of 78% at 6.5 years. The ORR for ibrutinib-treated patients was 92%, and the complete response (CR/CRi) rate rose to 34% at the current follow-up. For adverse events (AEs) of interest, ongoing rates remained low for grade ≥3 hypertension (year 5–6: 5%, n=4; year 6–7: 4%, n=3) and grade ≥3 atrial fibrillation (year 5–6: 1%, n=1; year 6–7: 1%, n=1); there were no grade ≥3 major hemorrhage events in years 5–7. Grade ≥3 AEs leading to dose reductions were observed in 1% (n=1) of patients in year 5–6 and 1% (n=1) of patients in year 6–7. For patients who had dose reductions due to any grade AEs (n=31 across years 0–8), 22/31 (71%) had resolution or improvement of the AE. Progressive disease was the primary reason for discontinuations in year 5–6 (5%, n=4) and year 6–7 (6%, n=4). AEs of any grade leading to discontinuations were observed in 3% (n=2) of patients in year 5–6 and none in year 6–7. With up to 7 years of follow-up, 47% of patients remain on single-agent ibrutinib.

Figure. Investigator-Assessed Progression-Free Survival.



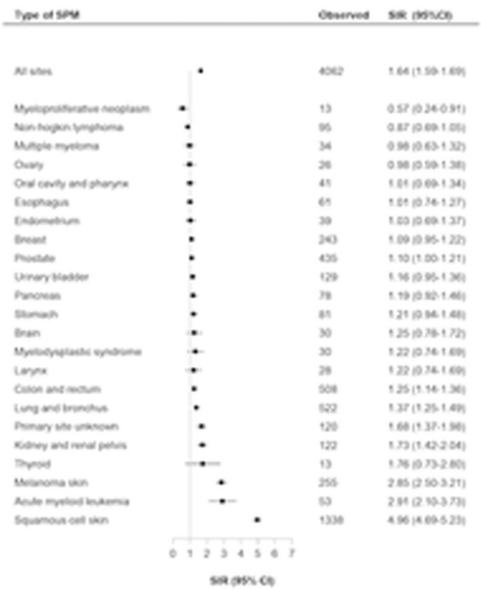
Summary/Conclusion: With extended long-term follow-up from RESONATE-2, first-line treatment with ibrutinib demonstrated sustained PFS and OS benefit for patients with CLL/SLL, including patients with high-risk genomic features. Deepening of responses continued over time. Low rates of grade ≥3 AEs of interest were observed at up to 7 years of follow-up. Discontinuations and dose reductions due to AEs were rare, and most AEs leading to dose reduction resolved or improved. No new safety signals were observed, and ibrutinib continues to be well tolerated.

EP637 SECOND PRIMARY MALIGNANCIES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A NATIONWIDE, POPULATION-BASED STUDY IN THE NETHERLANDS

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Background: The longevity of patients with chronic lymphocytic leukemia (CLL) improved progressively over the past decades due to efficacious therapies in the upfront and relapsed/refractory setting. The downside of this improved longevity is the development of second primary malignancies (SPMs), which, in turn, may attribute to morbidity and excess mortality in CLL patients. Therefore, awareness of the magnitude of SPMs in CLL is essential for health-related planning and surveillance activities.
Aims: In this nationwide, population-based study, we assessed the risk of SPM development in CLL patients diagnosed in the Netherlands compared with the general Dutch population.
Methods: We selected all CLL patients diagnosed in the Netherlands between 1989-2018 from the Netherlands Cancer Registry. To counteract surveillance bias, an SPM was defined as a malignancy occurring at least six months after CLL diagnosis. Of note, transformations were regarded as the same entity as the primary tumor and basal cell carcinomas were excluded from the analysis since they were not registrated nationwide throughout the entire study period. CLL patients were followed from the date of diagnosis to SPM development, death, or end of follow-up (December 31, 2018, whichever occurred first). Standardized incidence ratios (SIRs)—with associated 95% confidence intervals (CIs)—were calculated using the exact Poisson method as the ratio of the observed malignancies in the CLL population and the expected malignancies in an age-, sex-, and period-matched group from the general population.
Results: A total of 23,622 CLL patients (61% males; median age 69 years) were included in this analysis, of whom 4,062 (17%) subsequently developed an SPM after a median follow-up time of 4 years (IQR:1-8 years). Overall, the risk of SPMs in CLL patients was 64% higher than in the general population (SIR 1.64; 95% CI: 1.59-1.69; Figure 1). The increased risk was observed both for solid (SIR 1.72; 95%CI 1.66-1.77) and hematological malignancies (SIR 1.24; 95%CI 1.11-1.37) with no sex-related differences. However, patients aged 18-60 were more at risk for the development of an SPM (SIR 1.88; 95%CI 1.76-2.01) as compared to patients aged above 60 years (SIR 1.58; 95%CI 1.52-1.63). The overall risk of solid SPMs was significantly heightened for the following sites (in order of increasing risk): skin (squamous cell and melanoma), kidney and renal, primary site unknown, lung, colon and rectum and prostate. As for hematological malignancies, the risk of developing acute myeloid leukemia (AML) was significantly increased compared to the general population. Conversely, myeloproliferative neoplasms were less frequently observed than in the general population (Figure 1).



Summary/Conclusion: In this nationwide, population-based study, we demonstrated that CLL patients have an increased risk of developing various SPMs compared to the general population. SPMs in CLL may originate from shared pathophysiological factors, environmental exposures, host characteristics, or some combination of the three. In addition, CLL-related therapy could have attributed to the development of an SPM, particularly in AML. Collectively, our study findings can be used in the communication between patient and physician about appropriate surveillance activities and interventions to counteract the increased morbidity and excess mortality associated with SPMs. The current study serves as a benchmark to assess how the spectrum of SPMs may alter in a contemporary era with chemo-free treatment options.

EP638 TG-1701, A SELECTIVE BRUTON TYROSINE KINASE (BTK) INHIBITOR, AS MONOTHERAPY AND IN COMBINATION WITH UBLITUXIMAB AND UMBRALISIB (U2) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND LYMPHOMA

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Background: TG-1701 is a selective, covalent BTK inhibitor administered once daily (QD). Both the "U2" combination (anti-CD20 mAb ublituximab + the PI3Kδ-CK1ε inhibitor umbralisib) and BTK inhibition are highly active in treatment-naïve (TN) and relapsed/refractory (R/R) CLL, each having previously demonstrated superiority over standard chemoimmunotherapy. Herein we report the results of the dose escalation of TG-1701 monotherapy and TG-1701+U2.

Aims: The primary objectives of the study are to characterize the safety profile and define the recommended Ph 2 doses for the drugs alone and in combination.

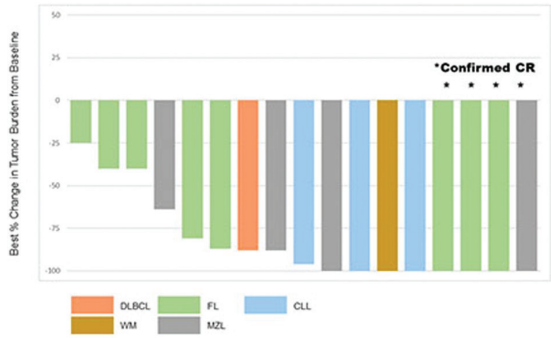
Methods: Patients with R/R CLL, MCL and Waldenström's (WM) were enrolled in an ongoing Ph 1 study initially evaluating dose escalation (DE) of oral TG-1701 QD continuously administered in 28-day cycles (100, 200, 300, and 400 mg). After characterizing the safety profile of TG-1701 monotherapy, we implemented a parallel DE arm of TG-1701+U2. Select dose levels of TG-1701 monotherapy were expanded. All patients were treated until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw.

Results: As of 03 February 2021, 123 patients were treated with TG-1701 as follows: 25 in the monotherapy DE arm, 61 in the 200 mg disease-specific cohorts (20 CLL [5 TN], 21 MCL [4 TN], 20 WM [8 TN]), 20 in the 300 mg CLL cohort (4 TN), and 17 in the 1701+U2 DE arm. The median # of prior therapies was 1 (range, 1 - 10). All patients were BTKi-naïve. All 123 patients were evaluable for safety. TG-1701 was well tolerated and the maximum tolerated dose (MTD) for monotherapy was not reached at 400 mg (demonstrating near 100% saturation of the BTK at all dose levels studied). Treatment emergent adverse events (TEAE) of clinical interest included atrial fibrillation (AF 4.0% of patients, G ≥3 in 1 case), G ≥3 hypertension (2.4%), and bleeding events (18.7%, all G1-2). No cases of ventricular tachyarrhythmia were reported. TEAEs leading to TG-1701 dose reduction occurred in 6.5% of patients. TEAEs leading to treatment discontinuation occurred in 1.6% of patients (AF, COVID-19). At the data cut-off, 119 patients were evaluable for response, including 40 in DE (Table). The median duration of response has not been reached among responders overall. The median follow-up (mFU range) was 15.9 mos (1.3 - 28.6+) in DE and 8.5 mos (1.4 -15.6+) in disease-specific cohorts. No complete responses (CR) were confirmed on TG-1701 monotherapy. The objective response rate (ORR) for 1701+U2 was 82.3% with a 23.5% CR rate. Best change from baseline in tumor burden in patients in the 1701+U2 combination arm is presented in the figure below.

Table. Response per investigator review by treatment group

	DE arm (N = 23)	200 mg CLL (N = 20)	200 mg MCL (N = 20)	200 mg WM (N = 20)	300 mg CLL (N = 19)	1701+U2 DE arm (N = 17)
ORR, %	56.5	95.0	60.0	95.0	100	82.3
CR, %	0	0	0	0	0	23.5
Very good PR, %	4.3			0		5.9
PR, %	47.8	95.0	60.0	70.0	100	52.9
Minor response, %	4.3			25.0		0
mFU mos	17.5	11.6	8.2	9.7	5.8	14.3

Best change from baseline in tumor burden in patients in the combination arm



Summary/Conclusion: TG-1701 exhibits an encouraging safety and efficacy profile. The combination of 1701+U2 has been well tolerated and dose escalation continues. The combination shows enhanced depth of response over TG-1701 monotherapy. Recruitment to this study (NCT03671590) continues.

EP639 ZANUBRUTINIB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA: 34-MONTH FOLLOW-UP RESULTS

W. Xu [1,*], S. Yang [2], K. Zhou [3], L. Pan [4], Z. Li [5], J. Zhou [6], S. Gao [7], D. Zhou [8], J. Hu [9], R. Feng [10], H. Huang [11], T. Wang [5], M. Ji [12], H. Guo [12], J. Huang [12], W. Novotny [12], S. Feng [12], J. Li [1]

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Background: Zanubrutinib is a highly selective, potent, and irreversible Bruton's tyrosine kinase (BTK) inhibitor approved in China for the treatment of adult patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The previous publication of this study reported that zanubrutinib is highly active in R/R CLL/SLL, with a well-tolerated safety profile (*J Hematol Oncol.* 2020;13:48). We present here the long-term results of this study.
Aims: To evaluate the efficacy, safety, and tolerability of zanubrutinib in patients with R/R CLL/SLL.
Methods: In this single-arm, multicenter, phase 2 study (NCT03206918), patients with R/R CLL/SLL received oral zanubrutinib (160 mg twice a day) continuously until progressive disease (PD) or unacceptable toxicity. Efficacy endpoints including overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) were assessed by an independent review committee (IRC) per International Workshop on CLL guidelines (*Blood*. 2008;111:5446) or the Lugano Classification (*J Clin Oncol*. 2014;32:3059) for CLL and SLL, respectively.
Results: Ninety-one patients (82 with CLL; 9 with SLL) were enrolled from 11 sites in China. Median age was 61 years (range, 35-87). Most patients had ≥1 poor prognostic variable, including unmutated immunoglobulin heavy chain variable region gene *(IGHV*; 56.0%), del(17p) or TP53 mutation (24.2%), and del(11q) (22%).
With a median 33.9-mo follow-up period (range, 0.8-41.4), 31 patients (34.1%) discontinued treatment primarily due to progressive disease (PD) in 15 patients and adverse events (AEs), regardless of relation to study drug, in 14 patients. Most patients (66%) were still on zanubrutinib treatment. The efficacy data are presented in the **Table**. The overall response rate was generally consistent across all subgroups analyzed, including those with unfavorable prognostic factors. Patients with del(17p) and/or TP53 mutation and del(11q) achieved high response rates of 91% (95% CI, 70.8%>98.9%) and 100% (95% CI, 83.2%>100%), respectively.
The most commonly reported treatment-emergent adverse events (TEAEs) are listed in the **Table**. Most AEs regarding to lab abnormalities were with low CTCAE severity (grade 1-2) and without clinical consequences. Second primary malignancies were reported in 5 patients (2 gastric adenocarcinoma; 1 each of colon cancer, breast cancer, and rectal cancer). Only 1 patient reported atrial fibrillation (grade 2). TEAEs leading to death were reported in 6 patients (2 pneumonia; 1 each for cardiopulmonary failure, brain herniation, and multiple organ dysfunction syndrome; 1 with cardiac failure, pneumonia, and respiratory failure). TEAEs leading to dose modification were reported in 42 (46.2%) patients. Commonly reported TEAEs leading to treatment discontinuation included pneumonia (n=4) and hepatitis B (n=2).

Table.

Efficacy, n (%)	**N=91**	
CR	6 (6.6)	
PR	63 (69.2)	
PR-L	11 (12.1)	
SD	3 (3.3)	
PD	3 (3.3)	
Not evaluable[a]	2 (2.2)	
Discontinued before first assessment, n (%)	3 (3.3)	
Overall response rate (95% CI) (%)	87.9 (79.4, 93.8)	
Estimated progression/death event free rate at		
24 months (95% CI) (%)	80.5 (70.5, 87.4)	
36 months (95% CI) (%)	68.1 (56.6, 77.4)	
DOR event free rate at		
24 months (95% CI) (%)	83.4 (73.2, 90.0)	
36 months (95% CI) (%)	69.9 (57.0, 79.6)	
Common nonhematologic AEs (>30% any grade), n (%)	**Any Grade**	**Grade ≥3**
Upper respiratory tract infection	51 (56.0)	11 (12.1)
Hematuria	39 (42.9)	0
Pneumonia	34 (37.4)	22 (24.2)
Purpura	31 (34.1)	0
Hypokalemia	28 (30.8)	7 (7.7)
Common hematologic AEs,[b] n (%)		
Neutropenia	71 (78.0)	46(50.5)
Thrombocytopenia	48 (52.7)	15 (16.5)
Anemia	36 (39.6)	10 (11.0)

AE, adverse event; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
[a] 'Not evaluable' were due to missing anatomy imaging of 2 patients.
[b] Incidence of neutropenia, thrombocytopenia, and anemia were summarized based on group term.

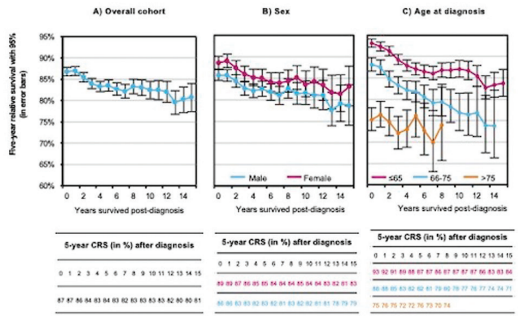
Summary/Conclusion: Results with longer follow-up continue to show a high response rate. Deep and durable responses were achieved in all patient subgroups including patients with high-risk cytogenetics. Data support the tolerability of long-term zanubrutinib treatment in R/R CLL/SLL, with no new safety signals identified.

EP640 CONDITIONAL RELATIVE SURVIVAL AMONG PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A NATIONWIDE, POPULATION-BASED STUDY IN THE NETHERLANDS

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Background: Therapeutic advances in chronic lymphocytic leukemia (CLL) across various therapy lines over the past decades significantly improved the outcomes of CLL patients at the population level. The greater longevity of CLL patients requires measures that capture the prognosis for long-term CLL survivors because survival estimates measured from diagnosis are no longer relevant. Conditional survival is an appropriate measure in this respect because it considers the survival likelihood of patients who have already survived several years post-diagnosis. At present, studies on conditional relative survival (CRS) in CLL have hitherto been lacking.
Aims: This nationwide, population-based study examined up-to-date estimates of 5-year relative survival (RS) at diagnosis and for each additional year survived up to 15 years post-diagnosis among CLL patients in the Netherlands.
Methods: We selected all CLL patients diagnosed in the Netherlands between 1989 and 2018—with survival follow-up through 2019—from the Netherlands Cancer Registry. We used RS to approximate the disease-specific survival. RS was calculated as the ratio of the observed patients' overall survival over the expected survival of an age-, sex- and period-matched group from the general population. We estimated RS using the hybrid approach to provide up-to-date survival estimates for patients diagnosed between 1989 and 2018 who were alive during the follow-up interval of 2008-2019. The survival estimates produced herein can be interpreted as the predicted survival probabilities of patients during 2008-2019. Five-year RS was stratified by sex and age at diagnosis (18-65, 66-75, and >75 years) and calculated up to fifteen years post-diagnosis. Differences in survival estimates were considered significant when the 95% confidence intervals (CIs) did not overlap
Results: A total of 22,840 CLL patients (61% males; median age, 69 years) were diagnosed in the Netherlands during 1989-2018, of whom 16,439 (72%) were at risk under the hybrid approach. Overall, 5-year RS was 87% (95% CI, 86%>88%) at diagnosis and gradually decreased over time, reaching 81% (95% CI, 77%>84%) at 15 years post-diagnosis (Figure 1A). This pattern was observed irrespective of sex, with no obvious sex differential in survival over time (Figure 1B). There was, however, an apparent age differential in 5-year RS at diagnosis, with corresponding estimates (95% CI) of 93% (92%>94%), 88% (87%>90%), and 75% (73%>79%) for patients across the three age groups, respectively (Figure 1C). Five-year RS decreased with each additional year survival post-diagnosis irrespective of age. As a result, the prognostic effect of age mainly persisted during the follow-up period.



Summary/Conclusion: CLL patients continue to experience considerable excess mortality in contemporary clinical practice—as compared to equivalent groups from the general population—despite surviving up to 15 years post-diagnosis. This finding might be explained by the indolent and largely incurable nature of CLL. As such, further progress is warranted to decrease excess mortality in CLL. Furthermore, our data underscore that excess mortality is more significant in elderly patients, especially among over 75-year-olds. Therefore, age above 75 might be considered in prognostic models such as the CLL-IPI to enhance prognostication. Collectively, CRS statistics may offer CLL patients and their physicians information to engage in dialogue about personal health-related planning and surveillance activities.

EP641 SYSTOLIC FUNCTION OF THE LEFT VENTRICULAR MYOCARDIAL IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA RECEIVING IBRUTINIB.

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Background: The effect of anticancer drugs on the systolic function of the left ventricular (LV) myocardium determines the prognosis and survival of patients (pts). The systolic function of the LV myocardium in pts with chronic lymphocytic leukemia (CLL) treated with ibrutinib (Ib) has not been sufficiently studied.
Aims: Evaluate LV myocardial systolic function in pts with CLL receiving Ib.
Methods: We examined 227 pts with CLL in dynamics, receiving Ib, at the age of 66.0 (32.0-91.0) years, among which 144 men at the age of 66.0 (32.0-91.0) years and 83 women at the age 65.0 (39.0-83.0) years. We examined 116 pts before the start of Ib therapy and after 3-30 months, median 15.0 (10.0-21.0) months of Ib treatment. Other111 pts at the time of the first examination had already received Ib for 9.0 (6.0-14.0) months, they were also examined in dynamics: the interval between visits 1 and 2 was from 3 to 32 months, the median was 15.0 (10.0-23.5) months. All pts underwent echocardiography (Echo) with tissue Doppler at 2 follow-up visits. Indicators of LV systolic function were compared as dependent and independent values.
Results: In a longitudinal comparison, patients at visit 2 (n = 125) showed a decrease in the ejection fraction (EF) from 68.3 (63.4-72.7)% to 66.9 (62.4-70.9)% Simpson (p = 0.024). We separately analyzed changes in systolic function in pts with baseline EF greater than / equal to 60% (n = 112). In this pts group, there was also a decrease in EF from 69.5 (58.4-82.5)% to 67.2 (51.7-84.5)% according to Simpson (p = 0.004), which indicates a clear trend towards decrease in systolic function of the LV myocardium. When comparing Echo parameters as independent values in pts treated with Ib (n = 111) with pts before Ib treatment, an increase in the indexed end diastolic volume (iEDV) and the indexed end sistolic volume (iESV) was noted. Thus, in the pts group receiving Ib, iEDV was 55.1 (47.3-64.7) ml versus 49.8 (44.1-59.4) ml in patients before Ib treatment (p = 0.01), iESV in pts receiving Ib 17.7 (13.5-22.8) ml versus 15.8 (12.1-20.1) ml in pts before starting Ib treatment (p = 0.04). Probably, the tendency to dilatation of the LV chamber leads to a gradual decrease in LV systolic function and, under certain conditions, to a sharp decrease in EF. Thus, we encountered a sharp drop in EF in a 74-year-old patient who was added obinutuzumab to Ib. A previously stable patient after 4 injections of obinutuzumab developed heart failure with severe dyspnea at the level of functional class 3, a sharp decrease in EF from 58.1% to 35.2%, dilatation of the LV cavity - the end-diastolic volume increased from 119.7 ml to 165. 0 ml. Thus, it should be borne in mind that the combination of Ib with anticancer drugs affecting cardiomyocytes can lead to a sharp drop in EF with the development of severe heart failure.
Summary/Conclusion: In patients with CLL receiving ibrutinib, there is a tendency towards a decrease in systolic LV myocardial function. An increase in the LV cavity in patients with CLL, taking Ib, may be one of the reasons for a decrease in systolic LV myocardial function.The use of Ib with other antineoplastic drugs that affect the systolic function of the myocardium can lead to a sharp drop in the LV ejection fraction and the development of severe heart failure. Probably, in patients taking Ib, the vulnerability of myocardial systolic function and sensitivity to the effects of various agents on cardiomyocytes is formed.

EP642 PRELIMINARY RESULTS OF THE PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED B-CELL MALIGNANCIES INTOLERANT TO IBRUTINIB AND/OR ACALABRUTINIB

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Background: Many patients with B-cell malignancies require continuous treatment with Bruton tyrosine kinase inhibitors (BTKi). Adverse events are a common reason for ibrutinib or acalabrutinib discontinuation. Early data from BGB-3111-215 showed zanubrutinib was well tolerated in patients with B-cell malignancies who were intolerant to either ibrutinib or acalabrutinib. Here we report preliminary results of the BGB-3111-215 trial, with a median follow-up of 4.2 months.
Aims: To assess the safety of zanubrutinib and recurrence of adverse events that led to prior BTKi intolerance.
Methods: Patients meeting protocol criteria for intolerance to ibrutinib, acalabrutinib, or both (without documented progressive disease) were given zanubrutinib monotherapy (160 mg twice daily or 320 mg once daily). Recurrence of adverse events that led to intolerance of prior BTKi and additional safety measures were assessed based on the Common Terminology Criteria for Adverse Events v5.0. Investigators determined responses using disease status at study entry as baseline and established disease criteria.
Results: As of November 1, 2020 (data cutoff), 44 patients (n=34 chronic lymphocytic leukemia/small lymphocytic lymphoma, n=6 Waldenström macroglobulinemia, n=2 mantle cell lymphoma, n=2 marginal zone lymphoma) were enrolled, received ≥1 dose of zanubrutinib, and analyzed for safety. The median age was 70.5 y (range, 49-91); median duration of treatment was 4.2 months (range, 0.1-12.6). The median number of prior regimens was 2 (range, 1-12). Regarding prior BTKi, 39 patients received ibrutinib only, 4 received ibrutinib and acalabrutinib, and 1 received acalabrutinib only. The median number of ibrutinib- or acalabrutinib-intolerant adverse events per patient was 2 (range, 1-5). 83% of ibrutinib and 78% of acalabrutinib intolerant events did not recur on zanubrutinib; **Table**. At data cutoff, 43 patients remained on treatment; 1 withdrew consent due to zanubrutinib-unrelated grade 3 syncope. Overall, 34 patients (77.3%) reported any adverse event; most commonly reported adverse events were myalgia (n=9; 20.5%), contusion (n=8; 18.2%), dizziness (n=7; 15.9%), fatigue (n=7; 15.9%), and cough (n=5; 11.4%). Grade ≥3 adverse events were reported in 6 patients (13.6%), serious adverse events in 1 patient (2.3%, febrile neutropenia and salmonella infection), adverse events requiring dose interruptions in 6 patients (13.6%), and adverse events leading to dose reduction in 2 patients (4.5%). No adverse events led to zanubrutinib discontinuation. No deaths were reported. All efficacy evaluable patients (26/26 [100%]) maintained (10 [38.5%]) or achieved deepening (16 [61.5%]) of their response.

Recurrence and Severity Change of Adverse Events Leading to Ibrutinib or Acalabrutinib Intolerance

	Adverse events leading to ibrutinib and acalabrutinib intolerance, N	Recurrence on zanubrutinib, n (%)		Severity change of recurrence on zanubrutinib, n (%)	
		No	Yes	Recurred at lower severity	Recurred at same severity
Ibrutinib	87	72 (82.8)	15 (17.2)	13 (86.7)	2 (13.3)
Acalabrutinib	9	7 (77.8)	2 (22.2)	1 (50.0)	1 (50.0)

Note: Multiple events of the same preferred term for a patient are counted once for the event per the worst grade experienced before and after enrollment.

Summary/Conclusion: Zanubrutinib provided an additional treatment option after intolerance to other BTKi, demonstrating tolerability and sustained or improved efficacy. Updated results will be presented.

EP643 A PHASE 1A/B DOSE ESCALATION STUDY OF THE MUTATION AGNOSTIC BTK/FLT3 INHIBITOR LUXEPTINIB (CG-806) IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL MALIGNANCIES

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Background: Luxeptinib (CG-806) is a potent, non-covalent oral inhibitor designed to target BTK and FLT3. It suppresses BCR signaling pathways (through inhibition of LYN, SYK, BTK, AKT, ERK) in cell lines and primary CLL cells, kills malignant B-cells insensitive to ibrutinib or venetoclax at low nM concentrations, and shows enhanced activity in combination with venetoclax. Luxeptinib is currently being evaluated in a Phase 1a/b trial in patients with relapsed or refractory B-cell malignancies (NCT03893682).
Aims: Primary objectives are to assess the safety and tolerability of Luxeptinib and determine the recommended Phase 2 dose for future clinical trials in patients with R/R CLL/SLL or NHL. Key secondary objectives include elucidation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, and evidence of antitumor activity.
Methods: Luxeptinib is administered continuously as oral capsules BID in 28-day cycles, in ascending cohorts of 3 patients. Treatment emergent adverse events (TEAEs) and tumor responses are evaluated per disease specific guidelines.
Results: As of December 4, 2020, a total of 16 patients (age 65.8 ± 7.9 years, 9 CLL/SLL, 3 follicular lymphoma, 1 Richter's transformation lymphoma, 1 Waldenstrom's macroglobulinemia, 1 mantle cell lymphoma, 1 diffuse large B cell lymphoma) with a median of 3 prior systemic regimens (range of 1 - 12) have been treated with luxeptinib at doses of 150 mg (n=1), 300 mg (n=1), 450 mg (n=6), 600 mg (n=4) and 750 mg (n=4). The most common drug-related or possibly drug-related TEAEs included nausea in 6 (37.5%), vomiting in 5 (31.3%), diarrhea and neutropenia in 4 (25%) each, and fatigue in 3 (12.5%) patients. Drug related grade ≥ 3 TEAEs included neutropenia (n=3, 18.8%, no fevers were reported), thrombocytopenia, diarrhea, hypertension, and headache (n=1, 6.3% each). One patient, who had developed grade 2 hypertension during screening and prior to dosing on C1D1, experienced grade 4 hypertension after Luxeptinib treatment at 750 mg BID for 5 days. While this was considered a DLT per protocol, CG-806 plasma levels in this patient were lower than those observed in patients at this and lower dose levels. No drug-related hypertension has been observed in any other patient treated to date. The steady-state (C_{min}) plasma levels of luxeptinib in patients treated with ≥ 600 mg BID were generally in the 1-2µM range and were sustained over multiple cycles. PD analysis demonstrated that C_{min} of Luxeptinib in the plasma of patients treated with doses of 300 mg or higher significantly reduced levels of phosphorylated BTK, SYK, ERK and FLT3 in EOL-1 reporter cells in a plasma inhibitor activity assay, demonstrating multi-target engagement. All 3 CLL patients with elevated lymphocyte counts pre-treatment experienced on-target lymphocytosis upon initiation of luxeptinib therapy.
Summary/Conclusion: Luxeptinib has a favorable safety profile in patients treated with 150 mg to 600 mg BID over multiple cycles. A single DLT (grade 4 hypertension in one patient with pre-existing hypertension) led to expansion of the 750 mg dose level to 6 patients. Pharmacodynamic studies documented inhibition of SYK, BTK and ERK in the BCR signaling pathway. Enrollment of patients with R/R CLL/SLL and NHL at dose level 5 (750 mg) is ongoing and updated clinical data will be presented at the meeting.

EP644 TEN-YEAR FOLLOW-UP OF 415 CLL PATIENTS TREATED WITH FLUDARABINE CYCLOPHOSPHAMIDE-BASED CHEMOIMMUNOTHERAPY IN THE FRONTLINE ARCTIC AND ADMIRE TRIALS, A COMPREHENSIVE ASSESSMENT OF PROGNOSTIC FACTORS

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Background: ADMIRE and ARCTIC were phase II randomised controlled trials recruiting between July 2009-September 2012 comparing fludarabine, cyclophosphamide and rituximab (FCR) with or without mitoxantrone (FCMR) or the addition of mitoxantrone with low dose of rituximab (FCM-miniR).
Aims: To assess how pre-specified prognostic factors, minimal residual disease (MRD), toxicity and number of treatment cycles affect progression free survival (PFS) and overall survival (OS) in the combined ADMIRE/ARCTIC cohort.
Methods: ARCTIC/ADMIRE provided long-term data on 415 previously untreated CLL patients. Kaplan-Meier survival estimates, and Cox proportional hazards models assessed PFS and OS according to potential prognostic factors, toxicities and treatment cycles received. Penalised multivariable Cox regression identified the prognostic factors predictive of PFS and OS. Multiple imputation by chained equations was used to account for missing data.
Results: Median duration of follow-up is 84 months. There is no significant difference in the hazard ratios for PFS or OS between FCR and FCM-R and between FCR and FCM-miniR. Overall PFS is 65 months (95% confidence interval (CI) 56,72) and OS is 108 months (CI 101,not reached).
Univariable Cox regression analysis of PFS by pre-treatment prognostic factors revealed unmutated IGHV genes (UM-IGHV), 17p/11q deletion, TP53 mutations, CLL-IPI, %CD38+ cells, decreasing CD20 mean fluorescence intensity (MFI), %CD49d+ cells, CCR6 (MFI and %+ cells) and LAIR1 MFI to be associated with shortened PFS. A baseline multivariable penalised Cox regression analysis of PFS found UM-IGHV, CCR6, 17p/11q deletion, TP53 mutations, CD49d and SF3B1 mutations remained prognostic for PFS.
Similar univariable analysis of OS found increasing age, positive direct Coombs test, UM-IGHV, deletion 17p, TP53 mutations, CLL-IPI and %CD49d+ cells, and decreasing CCR6 MFI and LAIR1 MFI to be associated with shortened OS. Multivariable penalised Cox regression by pre-treatment factors found age, %CD49d+ cells, d17p, TP53 mutations and direct Coombs test remained prognostic for OS. Mutations in ATM, BIRC3, NOTCH1 and SF3B1 are not associated with shortened OS.
Detectable marrow MRD ($>10^{-4}$) 3 months after therapy completion is associated with inferior PFS and OS on univariable analysis. Incorporation of MRD into a prognostic multivariable model revealed that UM-IGHV, MRD, d17p/TP53 mutations and %CD49d+ cells are predictive of PFS. In the same model for OS age, MRD, %CD49d+ cells, d17p/TP53 mutations and direct coombs test are predictive of OS (Table 1).
Grade 3/4 infection-related toxicities are associated with inferior PFS and OS however the occurrence of other toxicities are not associated with inferior outcomes. Hypogammaglobulinemia is not associated with the probability of grade 3/4 infection or shortened PFS/OS. Participants who received 3 cycles or less of the prescribed 6 cycles for reasons other than progressive disease had inferior PFS and OS and more likely to have other poor prognostic features.

Table 1 | Multivariable penalised Cox regression model results for PFS and OS

	Progression-free survival			Overall survival		
	Coefficient (standard error)	Hazard ratio (95% CI)	Frequency variable selected from 42 imputed datasets^	Coefficient (standard error)	Hazard ratio (95% CI)	Frequency variable selected from 42 imputed datasets^
VH mutation status Unmutated vs. Mutated	0.328 (0.13)	1.39 (1.08 to 1.79)	42	N/A*		
3 month post-treatment marrow MRD status Positive vs. Negative	1.03 (0.12)	2.81 (2.22 to 3.56)	42	0.39 (0.18)	1.48 (1.04 to 2.1)	42
Standardised CD49d (% of positive cells)	0.0302 (0.0416)	1.03 (0.95 to 1.12)	31	0.0737 (0.0686)	1.08 (0.941 to 1.23)	36
Deletion 17p &/or mutated TP53 Yes vs. No	0.0862 (0.1)	1.09 (0.896 to 1.33)	20	0.098 (0.146)	1.1 (0.828 to 1.47)	24
Age at randomisation >65 years vs. ≤65 years	N/A*			0.129 (0.15)	1.14 (0.847 to 1.53)	42
Direct Coombs test Positive vs. Negative	N/A*			0.0496 (0.147)	1.05 (0.788 to 1.4)	24

* Variables marked as N/A were penalised and therefore not selected as prognostic for either PFS or OS in the multivariable penalised Cox model.
Other variables included in the model but selected in 5 or fewer imputed datasets in both the PFS and OS models are not presented.
^ Multiple imputation by chained equations (MICE) was used to account for missing data, with 42 imputed datasets generated. A penalised Cox regression model was run for each imputed dataset. Variables frequently selected from the imputed datasets by the penalised Cox model are considered to be more predictive of the outcome than those not selected or selected infrequently. Each variable selected contributes to predicting the outcome in combination with the other selected variables, even if it is not significantly associated with the outcome itself.

Summary/Conclusion: A multivariable analysis of prognostic factors and MRD reveals the key prognostic factors for shortened OS to be age, MRD, d17p/TP53 mutation and CD49d. Mutations in ATM, BIRC3, NOTCH1 and SF3B1 were not predictive of shortened OS and many other factors routinely assessed for CLL prognostication have little value. Patients discontinuing therapy early or who experience significant infection-related toxicity have inferior outcomes and should be considered high risk for early progression.

EP645 OUTCOME OF 100 TP53-DISRUPTED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED FRONT-LINE WITH IBRUTINIB. A REAL-LIFE CAMPUS CLL STUDY.

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Background: Disruption of the TP53 gene, including 17p13 deletion (17p-) and/or *TP53* gene mutation (TP53m), is a negative prognostic biomarker in chronic lymphocytic leukemia (CLL) associated with genome complexity, early relapse and shorter survival after chemo-immunotherapy. Although the first-in class BTK inhibitor ibrutinib has proven to be highly active in CLL with unfavorable features, data on treatment-naive (TN) patients with TP53 abnormalities derive from almost 90 patients included in 5 clinical trials.

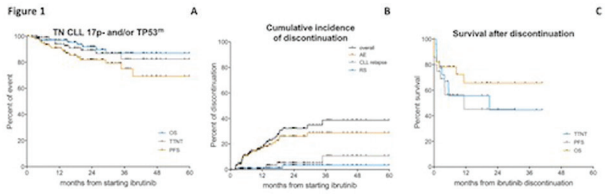
Aims: The aim of this study is to describe the efficacy and discontinuation rate of ibrutinib in TN CLL patients with TP53 disruption in the real-life setting.

Methods: Medical charts of CLL patients followed in 14 centers belonging to the Italian Campus CLL network were retrospectively reviewed to identify CLL with 17p- (cut-off 10%) and/or TP53m treated front-line with ibrutinib. The primary endpoint was the rate of discontinuation. Secondary endpoints were progression-free survival (PFS), time-to-next treatment (TTNT), overall survival (OS). Survival after ibrutinib discontinuation was also assessed. CLL diagnosis and response assessment were carried out according to the iwCLL 2018 guidelines. Adverse events were classified according to the CTCAE v5.0 grading. Statistical analyses were performed with Prism 7.

Results: One hundred TN CLL patients were recruited in this study. Fifty-one patients were male, the median age at the start of ibrutinib was 71 years (range 37-87), including 35 octogenarians, the median CIRS was 4 (range 0-13), 42 had a creatinine clearance <60ml/min. According to Rai's classification, 27 were in stage III and 18 in stage IV. □2-microglobulin was increased in 28 patients. Seventy-seven patients were IGHV unmutated, 33 displayed only 17p-, 22 only TP53m and 45 both 17p- and TP53m.

The overall response rate was 84%, including 10% of complete remissions (confirmed by bone marrow biopsy). After a median follow-up of 24 months, 13 patients relapsed, 10 required further therapy, 2 developed a Richter syndrome (RS) transformation and 8 died (4 infections, 1 melanoma, 1 RS, 1 sudden death). The median PFS, TTNT and OS have not been not reached. The 12, 24 and 36-month PFS was 91%, 82% and 75%, respectively. The 12, 24 and 36-month TTNT was 94%, 89% and 82%. The 12, 24 and 36-month OS was 96%, 92% and 87% (Fig. 1A). We observed that PFS was shorter in patients older than 75 years (2-yy PFS 69% vs 89%, p=0.04) and who did not respond (85% vs 66%, p=0.03).

Twenty-eight patients discontinued treatment, 20 due to adverse events (8 infections, 5 atrial fibrillations, 4 others and 3 deaths), 6 due to CLL progressions and 2 RS. After 12 and 24 months of treatment, the cumulative incidence of discontinuation for the whole cohort was 18% and 32%. In particular, it was 17% and 26% due to adverse events, 1% and 5% due to CLL relapse, 1% and 3% for RS (Fig. 1B). Patients who discontinued ibrutinib due to adverse events had a shorter PFS and OS (both p<0.0001). After a median observation of 14 months after ibrutinib discontinuation, the estimated median PFS and TTNT were 11 and 20 months, respectively (Fig. 1C). Overall, 22 infective events (9 grade □3), 8 atrial fibrillations, 8 minors but no major occurred.



Summary/Conclusion: We report the largest real-life study of ibrutinib in TN CLL patients with TP53 abnormalities, confirming the efficacy of ibrutinib in this subset of patients. Although ibrutinib discontinuation is not uncommon, only a few patients needed further treatment. Patients who stopped ibrutinib due to adverse had a shorter survival.

EP646 REAL-WORLD EFFICACY AND SAFETY OF VENETOCLAX IN CHRONIC LYMPHOCYTIC LEUKAEMIA – FIRST DATA FROM THE VERONE STUDY, IN PATIENTS WITH VENETOCLAX MONOTHERAPY

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Background: The efficacy and tolerability of venetoclax (V), a first-in-class selective oral B-cell lymphoma 2 (BCL-2) inhibitor, were shown in previous clinical trials for patients with chronic lymphocytic leukaemia (CLL). However, real-world data having assessed V in non-selected CLL patients are limited.

Aims: This French observational, prospective ongoing study aims to describe the effectiveness and tolerability of V in a real-life setting, and the V use in routine clinical practice.

Methods: This prospective non-interventional study is conducted in adult patients starting V for CLL (NCT03415035). This first analysis was performed in patients treated with V monotherapy, 16 months after the first inclusion in the study. The Overall Response Rate (ORR), and the Progression-Free Survival (PFS) were estimated at 1 year after V start in patients with at least one follow-up visit (evaluable population).

Results: From March 2018 to June 2020, 158 patients, included in 60 centres, started V monotherapy for CLL and were retained in the safety population, 153 met all the selection criteria (analysed population), and at date 62 entered the evaluable population. In the analysed population (n=153), baseline patient and CLL characteristics were as follows: mean age, 72.1±10.3 years; male, 69.3%; ECOG ≥2, 17.9%; ≥1 comorbidity, 86.9%; median CLL duration, 8.3 years (range: 0.1 - 29.4); prior CLL therapy, 96.7% (median number in pre-treated patients: 2, range 1 – 9; 1/2/≥3 prior treatment lines, 19,6%/31,8%/48,6%; including chemo-immuno-therapy 83.7%, B-cell receptor inhibitors 73.9%; Del(17p), 15.0%; *TP53* mutation, 12.4%.Prior to the first V intake, preventive measures were taken in most patients (hospitalisation 86.1%, hydration

86.7%, antihyperuricemic prophylaxis 72.8%, laboratory assessments 62.7%). The median duration of the ramp-up period was 5.0 weeks (range 1.0 – 23.9), and 72.8% reached the recommended daily dose of 400 mg at the moment of the analysis. In the 62 patients of the evaluable population, the 1-year ORR was 85.5% [95% CI 76.7% - 94.3%]. Considering the median follow-up of patients of 13.1 months, the 1-year estimate for PFS was 80.2% [95% CI 68.8% - 88.6%]. Overall, 81.0% of the 158 patients of the safety population experienced adverse events [AEs, mainly as neutropenia (43.0%) and diarrhoea (23.4%)], 58.2% ≥grade 3 AEs, 45.6% serious AEs (SAEs), and 19.6% V-related SAEs. Three patients experienced 4 fatal V-related AEs (deterioration of the general status, ascites, hepatic failure, and unknown cause at home). Over the ramp-up period, 16 patients (10.1%) experienced tumour lysis syndrome (assessed as serious in 3 patients, 1.9%; leading to treatment discontinuation in 4 patients, 2.5%).

Summary/Conclusion: Our first real-world data show that V monotherapy is effective in non-selected pre-treated CLL patients, with similar outcomes as compared to clinical trials. Early safety data are reassuring with few tumour lysis syndromes leading to treatment discontinuation during the ramp-up period. Further results are expected next year.

EP647 POTENTIAL CAPABILITIES OF MRNA ROR1 AND MIR-155 FOR MRD ASSESSMENT IN CLL

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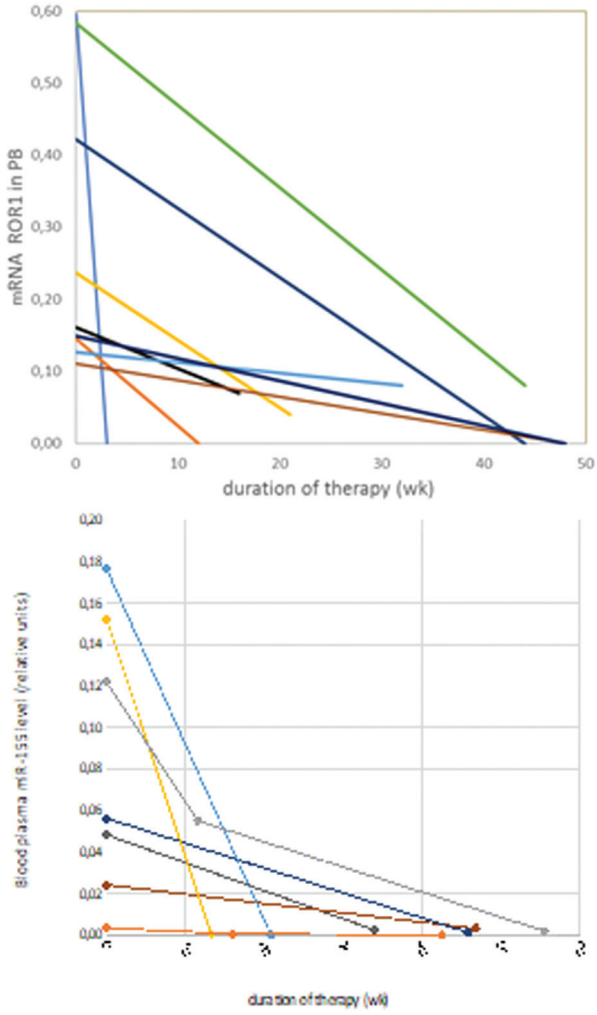
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Background: The most used methods for assessing minimal residual disease (MRD) in CLL are based on flow cytometry or RQ-PCR with allele-specific oligonucleotide primers. Recently, the assessment of MRD by the level of specific extracellular DNA using the most sensitive ddPCR technologies, as well as NGS approaches, has been proposed. Blood mRNA and microRNA molecules can also be studied as probable informative biomarkers of MRD in CLL (Giudice I.D., et.al., 2019). The use of plasma nucleic acids promises to be more effective in assessing MRD because they can detect the presence of B-CLL cells in different compartments, including lymph nodes and bone marrow. A new flow cytometric method for assessing MRD status has been proposed based on analysis of the tumor-associated antigen ROR1 (CD160-ROR1 FCA) (Farren T.W., et. al., 2020). ROR1, a receptor transmembrane tyrosine kinase, is highly expressed by cells during embryonic development but is not found in adult tissues. Expression of antigen ROR1 has been found in patients with B-CLL cells and independent of anatomical niches, clinical B-CLL heterogeneity, or B-cell activation. Another knowledge onco-associated RNA in CLL is mir-155 (Stolyar M.A., et. al., 2020; Cui B., et. al., 2014).

Aims: To investigate the usefulness of the combination of two ROR1 mRNA and miR-155 for evaluating the effectiveness of CLL therapy.

Methods: This study included blood samples from 37 B-CLL patients and 9 of it were observed before and during therapy of fludarabine, cyclophosphamide, rituximab combination. The control group consisted of 51 healthy donors. The expression level of ROR1 mRNA and miR-155 was determined by RT-PCR using Formula Gena Ltd kits. The results were statistically evaluated using the R- package.

Results: We did not find expression of mRNA ROR1 in venous blood and miR-155 in plasma of healthy donors. Overexpression of ROR1 (Me=0.16) was observed in 70% of our CLL patients before treatment. miR-155 level in this group was Me=0.05 relative units. Both RNAs were weakly dependent on the blood cells count or disease stage. Initially, increased ROR1 expression decreased in all patients during therapy (Figure). In most patients, the level of circulating miRNA-155 in the blood plasma also decreased (Figure). RNA dynamics correlated with clinical improvement. Further enhancement the analytical sensitivity of PCR for selected RNAs may be useful in developing new approaches to assessing MRD in CLL. It is important to note that for these tests there is no need for preliminary sequencing of allele-specific regions of immunoglobulin genes, as well as in expensive devices for NGS.



Dynamics of mRNA ROR1 and miR155 in venous blood samples after initiation of CLL therapy

Summary/Conclusion: The dynamics of mRNA ROR1 and miR-155 levels could be explored in the future as biomarkers of residual disease in CLL

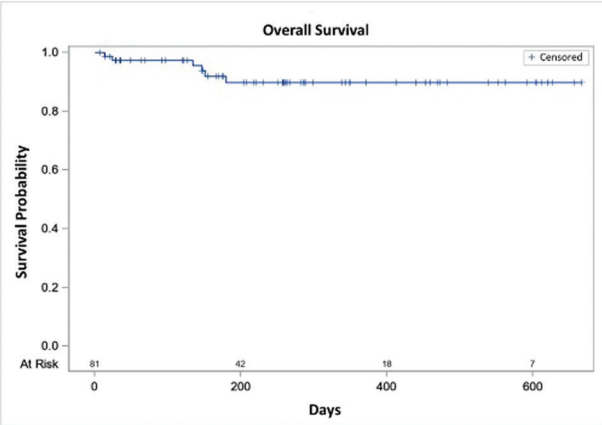
EP648 SAFETY AND EFFECTIVENESS OF VENETOCLAX IN COMBINATION WITH RITUXIMAB IN ELDERLY PATIENTS WITH RELAPSED/REFRACTORY CLL TREATED UNDER REAL-LIFE CONDITIONS – DATA FROM THE OBSERVATIONAL STUDY VERVE

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Background: In clinical trials, treatment of chronic lymphocytic leukaemia (CLL) with venetoclax (Ven) has shown promising efficacy and good tolerability. However, patients treated in clinical trial often represent a selected group not representative for patients treated in daily practice. Prospective real-world data on Ven usage are limited.
Aims: We conduct a prospective non-interventional observational study assessing effectiveness, safety, and quality of life in relapsed/refractory patients (RR) treated with Ven in Austria, Germany, and Switzerland. The population enrolled is representative for patients treated with Ven according to local label. This report focuses on patients treated with Ven in combination with rituximab (R).
Methods: Adult patients with CLL requiring therapy treated with Ven+R according to local label are eligible for the study. Patients' visits are scheduled at the physician's discretion and according to clinical practice. Study documentation is possible at baseline, weekly during ramp-up, monthly until the end of 6 months and 3-monthly afterwards up to a maximum of 3 years. Response assessment according to IwCLL criteria can be documented at the end of ramp-up, after 3, 12, and 24 months.
Results: On November 15th, 2020, 87 patients receiving Ven+R were enrolled, 81 had received at least one dose of Ven (= safety population), and for 65 treatment response had been documented at least once (=effectiveness population). Median age was 73 years, 75% of patients were male, 63% had at least one comorbidity, most commonly cardiovascular (46%), 59% received comedication. Patients were pre-treated with a median of 1 (range 1-10) line of therapy, e.g. chemo-immuno-therapy (CIT; 76%) or B-cell receptor inhibitors (33%). Del(17p), *TP53* mutation, and presence of unmutated *IGHV* had been diagnosed in 26%, 26%, and 41%, respectively (excl. missing data: 33%, 34%, 73%).
With a median observation time of 254 (range 1-667) days, 81% of patients experienced at least one AE, 46% experienced CTCAE grade 3/4 AEs, SAEs were reported in 30%. Grade 5 AEs were reported in two patients, tumour lysis syndrome (TLS) in 10 patients (12%). The median for progression-free survival (PFS) and overall survival (OS) has not been reached, the 12-month estimates were 88,1% (PFS) and 89,8% (OS). 6 cases of death were reported as not treatment related. At 12 months, an estimated 84,7% of patients remain on therapy. The reported best overall response at 12 months was 78,7% (CR+CRi 36,1%; PR: 42.6%). Remissions appeared to deepen with longer treatment duration.



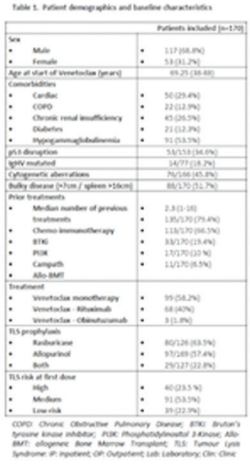
Summary/Conclusion: Under real-world conditions, Ven+R is used in elderly patients. The treatment was well tolerated. Most patients receive Ven+R in second line of therapy after initial CIT. Patients present with high-risk features, e.g. del(17p); yet, the response rate was high. Despite the advanced age of the enrolled patient population, PFS and OS estimates are like those observed in the Ven+R pivotal phase III trial MURANO.

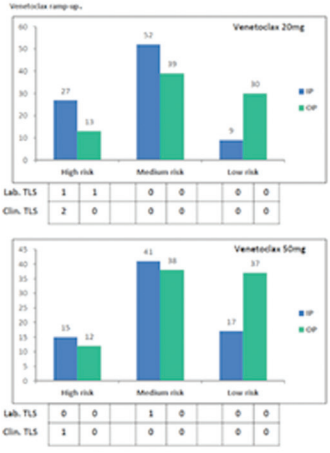
EP649 COMPARISON OF VENETOCLAX INPATIENT AND OUTPATIENT RAMP-UP STRATEGIES FOR CLL. UK MULTICENTRE RESTROSPECTIVE STUDY

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Background: Recommendations for venetoclax initiation in Chronic Lymphocytic Leukaemia (CLL) include inpatient admission during ramp-up dosing for patients at High-risk of Tumour Lysis Syndrome(TLS). Outpatient-based monitoring for high-risk TLS risk subgroup has been implemented in some centres. It is of interest to evaluate patterns of TLS monitoring and safety of this practice in the real world setting.
Aims: The primary objective is to evaluate TLS incidence CLL patients treated with venetoclax outpatient ramp-up in routine clinical practice. Secondary objectives are identifying the dose and time-point in which TLS occurs, management of TLS, TLS outcomes and impact on treatment delivery.
Methods: We performed aUK multi-centre, retrospective observational study, analysing consecutive adult CLL patients treated with venetoclax monotherapy or in combination with anti-CD20 monoclonal antibody (May/2016 to December/2020). Patients treated within clinical trials were excluded. Key outcomes were: Development of biochemical or clinical TLS after each venetoclax dose escalation, frequency of TLS between outpatient and inpatient ramp-up strategy, treatment delay/discontinuation after TLS events, frequency of rasburicase use for TLS treatment and TLS-related morbidity and mortality. Response rate using iwCLL criteria was collected.
Results: 170 patients from 11 UK centres were included. Patient's characteristics are shown in Table 1. 17p deletion and/or TP53 mutation was present in 34.5% (n=53), 51.7% had bulky disease (>7cm). 66.5% were previously Bruton Tyrosine Kinase inhibitor (BTKi) exposed. 99 patients (58.2%) had venetoclax monotherapy. All patients received TLS prophylaxis during the first steps of escalation, 63.2% with rasburicase. 23.5% (n=40) of patients had high TLS risk at initial ramp up. 127 high-TLS-risk dose escalations occurred, 52% (N=66) as inpatient. Overall, 7 TLS events were observed (3 clinical, 4 biochemical), 6/7 in the high-risk group (4.7% of high-risk escalations). 2/7 were outpatients at TLS onset and were admitted, 4/7 received emergency rasburicase and 1/7 required haemodialysis. There were no deaths or treatment discontinuations related to TLS, 6/7 patients had the next dose delayed. Most TLS events occurred at 20 and 50mg dose level and at the 6h post-dose timepoint (Fig. 2). 46 episodes of single laboratory abnormality were observed. Raised serum phosphate the most frequent (67.4%), 15.2% required admission and 17.4% patients had subsequent dose delayed for that reason. Complete and partial response rates were 45.9% and 39.1% respectively. All patients who experienced TLS episodes achieved some grade of response (CR or PR). CR rate in patients with isolated hyperphosphatemia was 80%.





Summary/Conclusion: Our real-word observational study revealed thathigh-risk patients could be managed as outpatients without a significant increase in TLS events or admission compared to impatient escalation. As previously described, TLS occurred predominantly at initial ramp up stages and early timepoints. We observed higher than expected proportion of inpatient ramp up medium and low risk patients. Despite low numbers, no deaths or discontinuations due to TLS were observed. Single laboratory abnormalities were frequently observed, mainly hyperphosphatemia, but only rarely translated into dose delays or TLS. Higher CR rates were positively associated with TLS and isolated hyperphosphatemia.

EP650 MOLTO, A MULTICENTER, OPEN LABEL, UNCONTROLLED, PHASE II CLINICAL TRIAL ON SAFETY AND EFFICACY OF VENETOCLAX, ATEZOLIZUMAB AND OBINUTUZUMAB IN RICHTER TRANSFORMATION OF CLL: SAFETY INTERIM ANALYSIS

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Background: Diffuse large B-cell (DLBCL) transformation from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Richter Syndrome (RS), has poor prognosis. Venetoclax, Bcl-2 inhibitor, has shown activity in DLBCL-RS. Atezolizumab is a humanized monoclonal antibody (MoAb) targeting PD-L1 on tumor-infiltrating immune cells/tumor cells and prevents PD-1 receptor-B7.1 interaction. Obinutuzumab, antiCD-20 MoAb, presents greater antibody-dependent (AD) cellular cytotoxicity, AD cellular phagocytosis and direct cell death compared to rituximab. Preliminary data showed safety and activity of atezolizumab+/-obinutuzumab in heavily pretreated DLBCL.
Aims: MOLTO is a multicenter international phase II study (EUDRACT 2018-005028-40) evaluating safety and efficacy of venetoclax, atezolizumab, obinutuzumab combination in 28 RS.
Methods: Treatment consists of 35 cycles with obinutuzumab (1000 mg C1-8), atezolizumab (1200 mg C1-18) and venetoclax (400 mg/d C1-35), in untreated DLBCL-RS from CLL/SLL. Initial safety run phase consists of 9 pts receiving at least 3 courses. Enrollment would have been stopped in case of ≥3 non-infective/non-hematologic therapy-related G≥4 adverse events (AEs). Remaining pts received same treatment schedule of initial safety cohort.
Results: Enrollment started from October 2019. As none of the 9 pts of the safety run phase developed an infective and/or non-hematological G ≥4 AE, enrollment went on and, as of February 2021, a total of 14 pts received at least 1 cycle of therapy. In table 1 are shown pts characteristics. Overall, 110 cycles have been administered. Five serious AE (SAEs) were recorded in 4 pts: 1 fever of unknown origin (FUO) and 1 case of autoimmune encephalitis, both G3, resolved and not leading to treatment discontinuation, and 1 G5 pneumonia. The remaining 2 SAEs were related to hospitalization due to disease progression (PD). Twelve/14 pts (85.7%) developed at least 1 AE of any grade. Severe (G 3-5) hematological toxicity was recorded in 7 pts, while 5 pts (including 3 developing SAEs) experienced severe non-hematological toxicity. The most common hematological toxicity was thrombocytopenia: 20 episodes/110 courses (18.2%), 9 being G≥3. Other G≥3 hematologic toxicities included: 10% neutropenia and 0.9% anemia. Two severe non-hematological toxicities were recorded: 1 hyperamylasemia and 1 hypercalcemia. Seven pts (50%) experienced a grade 2 FUO and only 1 major infection was observed. Two were the AE of special interest: 1 autoimmune myositis and 1 autoimmune encephalitis both successfully managed with steroids. No G≥3 infusion related reactions (IRR) occurred and all G1/2 have been considered associated to obinutuzumab. Venetoclax ramp-up was successfully completed in all pts, in 2 cases accelerated dose-escalation (Koening et al. 2020) was performed due to rapidly PD. No laboratory or clinical tumor lysis syndrome (TLS) was recorded. Overall, 9 pts are still on treatment with a median time on study of 4.4 (range 1 - 16.7) m, only 1/5 pts discontinued treatment due to toxicity.

Table 1. Patients' characteristics

	Number (%)
Age Median (range)	69.5 yrs (range: 51-81)
Pts with age ≥65 years	11 (78.6)
Male/Female	6/8
N° of pts pretreated for CLL	9 (64.3)
Median number of prior CLL Tx (range)	1 (0-3)
N° of pts pretreated with BTKi	5 (35.7)
N° of pts pretreated with CIT	5 (35.7)
Bulky disease (≥ 5 cm)	11 (78.6)
Presence of del17p and/or *TP53mut*	6 (42.9)
Ann Arbor Stage	
I	1 (7.1)
II	2 (14.3)
III	6 (42.9)
IV	5 (35.7)

Summary/Conclusion: The combination venetoclax, obinutuzumab and atezolizumab was well tolerated even in elderly pts. In the absence of significative warning, Independent Data Monitoring Committee allowed the accomplishment of safety run phase. Obinutuzumab-atezolizumab combination did not result in an enhanced rate or severity of IRR. In this highly proliferating disease, venetoclax did not lead to TLS even when applying accelerated ramp-up. Accrual is ongoing, and updated results will be presented at the meeting.

EP651 TREATMENT OF CLL RELAPSED/REFRACTORY PATIENTS IN COVID-19 PANDEMIC: A REAL-LIFE EXPERIENCE WITH VENETOCLAX-RITUXIMAB COMBINATION IN SOUTHERN ITALY.

S. Molica [1,*], P. Sportoletti [2], B. Martino [3], C. Patti [4], G. Mineo [5], D. Mannina [6], V. Leone [7], M. Musso [8], S. Siragusa [9], G. Palumbo [10], V. Minardi [11], P. Scalzulli [12], G. Tarantini [13], A. Maggi [14], I. Angeletti [15], A. Greco [16], L. Levato [17], M. Rossi [18], M. Gentile [19], C. Stelitano [20], C. Califano [21], C. Selleri [22], A. Rocino [23], A. M. Risitano [24], F. Chiurazzi [25], G. Farina [26], A. M. Giordano [27], A. L. Chiarenza [28], P. Musto [29], N. Di Renzo [30], F. Pane [31], F. Di Raimondo [28]

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Background: Given the multifactorial immune defect characterizing chronic lymphocytic leukemia (CLL), it appears conceivable that these patients have risk factors that increase their likelihood of complications and death from COVID-19.
Aims: To evaluate incidence and severity of COVID-19 cases in a well-defined cohort of patients with CLL receiving venetoclax-based combinations.
Methods: We administered a survey to a cohort of CLL treating hematologists from hematological centers in southern Italy. Participants were asked: a) to indicate whether they had offered a test for detection of COVID-19 infection (mainly nasopharyngeal swabs) only to CLL patients who reported symptoms or universally; b) to provide information on the incidence of COVID-19 infection and its severity; c) to specify reasons of possible treatment modifications. The survey was restricted to relapsed-refractory (R/R) CLL patients treated from Feb 1st to Dec 31th 2020 with time-limited venetoclax/rituximab (VR) combination as recommended by MURANO protocol (venetoclax for up to 2 years plus rituximab for the first 6 months), within their clinical practice.
Results: A specific questionnaire was sent to 30 CLL hematologists, but only 26 responded to all questions. We considered suitable for the present analysis the 24 questionnaires compiled by hematologists who declared to have treated at least one patient with VR combination in the observation period. Of those, 20.8% worked in academic hospitals. Overall, the survey allowed to collect data on 124 patients who were treated with VR combination. The median number of patients treated in each center was 5 (range,1-15).COVID-19 surveillance tests consisted of viral RNA reverse transcriptase PCR (RT-PCR) on nasopharyngeal swabs. Generally, a policy of universal SARS-CoV-2 testing to be performed on patients at different time-points of therapy was used. Most patients (83/124, 66.9%) were tested before beginning the ramp-up with venetoclax; moreover 66/124 (53.2%) were regularly tested before each rituximab infusion (Fig 1).Reasons for potential change of the schedule of treatment were also investigated. The survey revealed that adherence to treatment was relatively high (70.8%). Only 29.1% physicians modified the therapeutic program mainly because of grade 3 neutropenia. Changes consisted of transient interruption of venetoclax, reduction of doses, and delay of rituximab infusion.Only 2/124 patients (1.6%) had a symptomatic RT-PCR proven diagnosis of COVID-19 infection and required hospitalization. Both patients needed oxygen therapy and admission into an intensive care unit. Of those, 1 patient who was receiving VR combination at the time of COVID infection, eventually died. The second patient developed COVID-19 infection while receiving venetoclax monotherapy (after the VR combination period). He recovered from COVID-19 infection and after 21 days of treatment interruption, he was able to restart venetoclax.
Summary/Conclusion: Results of the present survey provide information, thus far lacking, on the use in real-world clinical practice of VR combination during the COVID19 pandemic in 2020. Current literature on the prevalence of COVID-19 infection in CLL, has some limitations (i.e., small size sample, heterogeneity of treatment, restriction to only the first pandemic wave); this survey, performed on a large number of CLL patients treated with VR combination only seems to provide additional information on safe management of CLL treatment during the COVID19 pandemic.

EP652 LEUKEMIA CUTIS IN CHRONIC LYMPHOCYTIC LEUKEMIA: A RETROSPECTIVE STUDY OF THE FRENCH INNOVATIVE LEUKEMIA ORGANIZATION (FILO)

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Background: Cutaneous infiltration by leukemic cells with clinically identifiable skin lesions, also called leukemia cutis (LC), has seldom been reported in chronic lymphocytic leukemia (CLL). There is no available data on the genetic background of LC-CLL.
Aims: In this study we retrospectively analyzed the clinical, histopathological, and molecular features of 46 CLL patients with specific LC from centers of the FILO.
Methods: We collected clinical and biological data including cytogenetic aberrations assessed by FISH, karyotype, IGHV mutational status and amplicon-based next-generation sequencing of 13 CLL-associated mutated genes from peripheral CLL cells.
Results: We identified 46 cases of skin biopsy-proven LC-CLL. All patients had proven CLL prior to LC. Median time between skin manifestations and CLL was 5.4 years (1-18 years). Skin lesions were either diffuse (n=16), localized (n=13) or regional (n=9). Head and neck were the most common site (22 cases) with a high incidence of earlobe lesions (10/46 cases), while lesions on arms and legs, trunk and extremities were found in 17, 13, and 14 cases respectively. The most common skin manifestations were papulonodular (24/46 cases) and non-infiltrated erythematous lesions (n= 9). Plaques, vesicles, mosquito bite-like, rhinophyma-like, ulcerations or necrotic lesions were uncommon. Some infiltrates appeared at the sites of previous scars following herpes, mosquito bite or a plant wound in 4 patients.
A majority of cases were IGHV mutated (n=21/37, 57%). The IGHV4-34 gene ranked among the most frequent IGHV genes (8/37, 21.6%) as compared to usually 10% of CLL. Conventional karyotype was performed in 25 patients. It was normal in 8 cases (32%) and complex (>3 abnormalities) in 6 cases (25%). An intriguing finding was the unexpected high frequency of t(14;18) translocation in 6/25 patients (25%), while it usually occurs in < 5% of CLL. Among the 34 cases tested by FISH: trisomy 12 was frequent (10/34; 29%), while 13q, 11q and 17p deletions were found in 23%, 12% and 9% respectively. Molecular testing was performed in 38 patients: 13 patients harbored only one mutation (34%) while 11 patients had 2 to 5 mutations. The most frequently mutated genes were *NOTCH1/FBXW7* (34%), *TP53* (21%), *SF3B1* (13%) and *BIRC3* (13%).
Follow-up data were obtained for 34 patients. Skin lesions tended to occur in stage A and before any treatment: 20 patients (60%) had skin lesions before the first line of treatment while 14 (40%) had received at least 1 line of treatment before any skin manifestations. Six patients developed skin lesions later in the course of the disease. Thirty-one patients were treated: 13 patients received a fludarabine or bendamustine-based regimen, 5 chlorambucil based, 5 Ibrutinib, 4 polychemotherapy, 1 obinutuzumab, 2 venetoclax and 1 idelalisib. Treatment was initiated because of the presence of skin lesions in 15 patients. Systemic treatment led to a complete skin response in 74% (23/31) of patients. The 8 patients who did not experience a complete skin response (among which the 5 patients treated with chlorambucil) achieved a partial response of the systemic CLL disease as well.
Summary/Conclusion: In this large CLL-LC cohort, we did not find a specific clinical or biological profile associated with LC, nor any difference related to morphology or site of skin lesions. t(14;18) is enriched

and we are currently investigating its significance in this atypical clinical presentation of CLL. Our results suggest that CLL patients with cutaneous lesions are not associated with poor prognosis features and they respond well to CLL systemic treatment.

EP653 MANAGEMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND ARTERIAL HYPERTENSION WHO ARE ON IBRUTINIB THERAPY.

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Background: One of the possible cardiotoxic effects of ibrutinib (Ib) is the induction of arterial hypertension (AH). In addition, some patients (pts) who are assigned Ib already have hypertension. Poorly managed hypertension may have a direct impact on the prognosis and survival of pts with CLL receiving Ib.
Aims: To assess the manageability of hypertension and the effectiveness of antihypertensive therapy in pts with chronic lymphocytic leukemia (CLL), receiving Ib.
Methods: We conducted a prospective study for 56 months with the inclusion of 217 pts with CLL receiving AH-inducing Ib. In 116 (53.5%) pts AH was diagnosed before Ib therapy, in 24 (11.1%) pts AH occurred during Ib treatment. Out of 140 pts with AH: grade 1 - 15 pts (10.7%), grade 2 - 41 pts (29.3%), grade 3 - 84 pts (60%). Among pts with CLL and AH there were 86 men aged 67.0 (60.0-72.0) years and 59 women aged 67.0 (59.0-74.0) years.
As part of a comparative analysis, a 24-hour blood pressure monitor (24h-BPM) was carried out in dynamics against the background of antihypertensive therapy in three groups of pts: with CLL and AH receiving Ib (n=140) and pts with AH without cancer receiving AH treatment on an outpatient basis (n=159) and in a hospital (n=100). Pts did not have significant differences in age and sex composition. All pts received antihypertensive therapy, while the pts group with CLL and hypertension was under our distant controlled treatment. Combined antihypertensive therapy was required in 40.8% of patients with CLL and AH: a combination of 2 drugs - 54.9%, of 3 drugs - 33.3%, of 4 drugs - 9.8%. Pts in the comparison groups received antihypertensive therapy prescribed by the doctors of the hospital and polyclinics. Comparison of blood pressure (BP) indicators in dynamics according to 24h-BPM data in pts with CLL and AH receiving Ib was carried out, as well as comparison in the three indicated groups.
Results: During the observation period in pts with CLL and AH receiving Ib, we managed to achieve an effective decrease in blood pressure on our antihypertensive therapy: according to the control 24h-BPM, the 24-hour average systolic blood pressure (24-SBP) significantly decreased (p=0.009), 24-hour average diastolic blood pressure (24-DBP) (p=0.014), hypertensive time index (HTI) of SBP (p=0.006) and DBP (p=0.009) in waking period and in sleep period HTI of SBP (p=0.046) and DBP (p=0.008). When compared in 3 groups: pts with CLL and AH receiving Ib showed a more significant decrease in 24-SBP, 24-DBP (p=0.001) and HTI during wakefulness and sleep (p <0.0001) compared with pts in the population. Target blood pressure in the pts group with CLL and AH was achieved significantly more often than in the population (p <0.0001). In pts with CLL and AH on the background of antihypertensive therapy, significantly less pts with an unfavorable daily night picker profile (p=0.0003). Pts with CLL and AH, who received angiotensin-converting enzyme (ACE) inhibitors, had better overall survival, which was not observed with other antihypertensive drugs (p=0.001).
Summary/Conclusion: Despite the possible induction of hypertension by Ib, in pts with CLL treated with Ib, it is possible to achieve an effective reduction in blood pressure on antihypertensive therapy. To control AH 40.8% pts with CLL and AH, combination therapy with a predominance of two-component therapy is required. Pts with CLL and AH taking ACE inhibitors have higher overall survival rates compared to pts with CLL who did not receive this group of drugs.

EP654 EFFECTIVENESS AND SAFETY OF IBRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND MANTLE CELL LYMPHOMA (MCL) IN BELGIAN ROUTINE CLINICAL PRACTICE WITH A 3-YEAR FOLLOW-UP

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Background: The Belgian ibrutinib Real-World (RW) Data (BiRD) study is a multicenter, observational study of adults with a confirmed diagnosis of CLL, MCL, or Waldenström's macroglobulinemia (WM) eligible for reimbursed ibrutinib treatment at treatment initiation or participating in a Medical Need Program and switched to reimbursed treatment in Belgium. RW studies provide valuable insights into ibrutinib effectiveness and safety in routine clinical practice. Here we present updated results from the third interim analyses (IA) with a median follow-up of 34.3 months for the CLL cohort and 35.8 months for the MCL cohort.
Aims: To assess ibrutinib outcomes (primary: progression-free survival [PFS] and overall response rate [ORR]; secondary: included overall survival [OS] and safety) in RW patients (pts) with previously untreated or relapsed or refractory (R/R) CLL and R/R MCL in Belgium.
Methods: Data were collected both prospectively (pro) and retrospectively (ret). Total population results were adjusted for left truncation.
Results: Effectiveness results are presented in the Table.
In the CLL cohort, 221 pts (pro n=71; ret n=150) were included in the effectiveness population; 64.3% were male, median age at ibrutinib initiation was 72 (range, 38-90) years, median time from diagnosis to ibrutinib initiation was 5.8 years, 27.4% were previously untreated 59.1%, had del17p and/or *TP53* mutation, and 72.5% had no *IGHV* mutation. The median PFS for CLL was 38.3 months (51.5/not reached [NR] months in the pro/ret cohorts). ORR was 90.0% (complete response [CR] 16.7%, partial response [PR] 51.6%, PR with lymphocytosis 21.7%). Median OS was NR. Of the 226 pts in the CLL safety population, 96.9% had ≥1 treatment-emergent adverse event (TEAE) and 52.2% had ≥1 serious TEAE. TEAEs led to dose reduction, interruption, or discontinuation in 21.2%, 31.9%, and 26.5% of pts, respectively. TEAEs of interest in pts with CLL reported as % (% difference from second IA, after an additional 15.3 months of follow-up) were: major bleeding 4.9% (-0.4%); infection 66.4% (9.3%); hypertension 17.3% (5.1%); atrial fibrillation (AF) 10.6% (3.2%); arthralgia/myalgia 16.8% (4.1%); diarrhea 21.7% (3.2%). Median treatment duration for pts with CLL was 25.5 months (19.6/28.6 months pro/ret), and 135/226 pts (58.7%) remain on treatment.
In the MCL cohort, 76 pts (pro n=20; ret n=56) were included in the effectiveness population; 76.3% were male, median age at ibrutinib initiation was 74 (range, 47-88) years, and median time from diagnosis to ibrutinib initiation was 2.8 years. The median PFS for MCL was 18.6 months (21.5/26.8 months in the pro/ret cohorts). ORR was 93.4% (CR 39.5%, PR 53.9%). Median OS was 32.2 months. Of the 76 pts in the MCL safety population, all had ≥1 TEAE and 67.1% had ≥1 serious TEAE. TEAEs led to dose reduction, interruption, or discontinuation in 31.6%, 43.4%, and 26.3% of pts, respectively. TEAEs of interest in pts with MCL reported as % (% difference from second IA, after an additional 15.2 months of follow-up) were: major bleeding 7.9% (1.3%); infection 64.5% (6.6%); hypertension 6.6% (0%); AF 21.1% (4.0%); arthralgia/myalgia 11.8% (0%); diarrhea 35.5% (5.2%). Median treatment duration for pts with MCL was 24.7 months (22.8/25.3 months pro/ret), and 26/76 pts (34.2%) remain on treatment.

Table. Effectiveness results

	CLL			MCL		
	Pro	Ret	Total[a]	Pro	Ret	Total[a]
N	71	150	221	20	56	76
Overall median PFS, months (Q1-Q3)	51.5 (29.1-NR)	NR (15.7-NR)	38.3 (12.2-66.4)	21.5 (6.1-40.5)	26.8 (17.3-61.4)	18.6 (8.2-46.2)
36-month PFS rate, % (95% CI)	55.6 (38.5-69.7)	65.0 (55.5-73.0)	53.8 –[b]	29.7 (6.8-54.6)	40.7 (27.2-53.7)	31.4 –[b]
PFS: Mutated *IGHV*, months (Q1-Q3)	NE	49.9 (37.3-49.9)	49.9 (21.3-49.9)	NE	NE	NE
PFS: Unmutated *IGHV*, months (Q1-Q3)	NE	53.5 (31.6-NR)	53.5 (31.6-NR)	NE	NE	NE
PFS: Del17p and/or *TP53* mutation, months (Q1-Q3)	NE	49.7 (27.3-NR)	41.5 (21.3-NR)	NE	NE	NE
PFS: No del17p and *TP53* mutation, months (Q1-Q3)	NE	49.9 (31.3-NR)	49.9 (17.8-NR)	NE	NE	NE
POD24,[c] months (Q1-Q3)	NE	NE	NE	NE	NE	18.5 (7.2-27.1)
POD>24,[d] months (Q1-Q3)	NE	NE	NE	NE	NE	21.5 (16.8-NR)
Median OS, months (Q1-Q3)	NR (20.7-NR)	NR (38.3-NR)	NR (21.3-NR)	NR (16.6-NR)	43.2 (29.1-NR)	32.2 (13.1-NR)
36-month OS rate, % (95% CI)	60.6 (45.8-72.6)	76.3 (67.8-82.9)	62.9 –[b]	53.3 (29.4-72.4)	62.0 (47.4-73.6)	47.5 –[b]

CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; pro, prospective; ret, retrospective. [a]Total population adjusted for left truncation. [b]95% CI not calculated as analysis adjusted for left truncation. [c]PFS ≤24 months under the most recent prior line for MCL (n=19). [d]PFS >24 months under the most recent prior line for MCL (n=15).

Summary/Conclusion: Results over a median follow-up of 35+ months from the BiRD study confirm the sustained effectiveness of ibrutinib in both CLL and MCL. TEAEs were manageable in elderly patients with no new safety signals.

Chronic myeloid leukemia - Biology & Translational Research

EP655 NEUTROPHIL EXTRACELLULAR TRAPS ARE INCREASED IN CHRONIC MYELOID LEUKEMIA AND ARE DIFFERENTIALLY AFFECTED BY TYROSINE KINASE INHIBITORS

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Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) driven by the BCR-ABL1 fusion gene. Atherothrombotic complications are increasingly reported with the use of certain tyrosine kinase inhibitors (TKI's). The mechanism underlying these complications is not fully understood but may involve off-target effects that promote vascular toxicity. In response to various stimuli, neutrophils can expel extracellular strands of decondensed DNA in complex with histones and additional proteins called neutrophil extracellular traps (NETs). These structures have the ability to ensnare and kill microbes but are also implicated in the pathogenesis of thrombosis.
Aims: Study NET formation in CML and evaluate a possible contribution of BCR-ABL1 and of TKI's to NET formation.
Methods: Neutrophils were isolated from CML patients (n=9) and from age and gender matched controls (n=9) by Percoll gradient. NETosis was evaluated by measuring the levels of accepted NETosis markers. NET formation was assessed by the NETosis Assay Kit (Cayman chemical) as well as by immunofluorescence (IF). Expression of citrullinated histon H3 (H3cit), an established marker of NETosis and of PAD4, an initiator of this process, was determined by Western blot and IF. CD11b expression and reactive oxygen species (ROS) production were analyzed by FACS and ELISA, respectively. Assessments were performed in resting and in PMA/ionomycin stimulated neutrophils and after *ex vivo* treatment with clinically relevant concentrations of imatinib (5.3 µM), ponatinib (0.17 µM) and dasatinib (0.22 µM). To validate our findings and further study the effect of BCR-ABL1 and TKIs on NETosis, we prepared BCR-ABL1 retroviral transduced HoxB8-immortalized mouse hematopoietic progenitors which differentiate into neutrophils *in vitro*.
Results: Neutrophils from patients with CML had a significant increase in NETs formation as assessed by morphology and by an increase in DNA-associated neutrophil elastase compared to normal neutrophils, at baseline ($p \leq 0.05$, $p \leq 0.03$, respectively) and after PMA stimulation ($p \leq 0.005$, $p \leq 0.002$, respectively). In accordance, H3cit and PAD4 expression (staining and WB) and ROS generation were also higher in CML samples compared to controls ($p \leq 0.04$). Ponatinib treatment of neutrophils from CML patients significantly augmented DNA-associated neutrophil elastase levels as compared to DMSO, imatinib and dasatinib treated neutrophils ($p \leq 0.05$ for all comparisons). Ponatinib treatment also led to increased ROS levels in CML neutrophils as compared to DMSO and imatinib ($p \leq 0.05$). Differentiated BCR-ABL1-transduced HoxB8 neutrophils stimulated with ionomycin demonstrated increased H3cit & PAD4 expression. These processes were significantly reduced by Cl-amidine, a PAD4 inhibitor. Ponatinib and nilotinib increased H3cit expression in HoxB8-BCR-ABL1 cells after stimulation with ionomycin. However, no significant difference was found in ROS generation of ionomycin stimulated HoxB8 neutrophils transduced with empty vector or with BCR-ABL1. Also, no difference was observed in ROS levels of HoxB8-BCR-ABL1 cells treated with the different TKIs.
Summary/Conclusion: Our findings support the hypothesis that CML is associated with increased NET formation which is further augmented by ponatinib, suggesting a possible role for NETs in promoting vascular toxicity in CML. In the BCR-ABL1/HOXB8 model, NETs formation is PAD4 dependent. Further studies are needed to assess the possible role of increased NETs formation in CML on the CVS associated with BCR-ABL1 and TKIs exposure.

EP656 PROFILES OF NK CELL SUBSETS ARE ASSOCIATED WITH SUCCESSFUL TYROSINE KINASE INHIBITOR DISCONTINUATION IN CHRONIC MYELOID LEUKEMIA AND CHANGE FOLLOWING INTERFERON TREATMENT

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Background: Recent studies have shown that approximately 50% of chronic myeloid leukemia (CML) patients receiving tyrosine kinase inhibitor (TKI) with a sustained deep molecular response (DMR) can acquire treatment free survival (TFR), meaning without molecular relapse (MR), and that prior interferon (IFN) treatment and relatively high natural killer (NK) cell levels at and after TKI discontinuation are associated with TFR. Moreover, we recently reported that post-TKI discontinuation IFN treatment could prevent MR.
Aims: To clarify the possible mechanism of TFR in CML patients, here we evaluated whether NK cells are associated with MR in patients with CML, and investigated the effects of post-TKI discontinuation IFN treatment on lymphocyte subsets.
Methods: Part of patients with CML in our previous study of INF-α post TKI discontinuation following a DMR were included in this patient population. After immunophenotyping, the associations between lymphocyte and NK cell subsets and MR after TKI discontinuation were analyzed in the subset of patients who did not receive IFN-α and the effects of IFN-α on these same cell subsets were evaluated in those who did.
Results: Thirty-four patients measuring blood lymphocyte subclasses were included in this study. The median follow-up time was 32 (13-67) months. After TKI treatment discontinuation, 12 patients with $0.0032\% < BCR\text{-}ABL1^{IS} \leq 0.1\%$ received IFN-α treatment, three (25%) of which experienced protocol-defined molecular relapse ($BCR\text{-}ABL1^{IS} > 0.1\%$); 22 patients did not receive IFN-α treatment, 9 of whom (37.5%) eventually experienced MR. In the 22 patients who did not receive IFN therapy, there were no significant differences in Tregs or NK cells at TKI discontinuation between the nonrelapsed and relapsed patients. At one month after TKI discontinuation, the nonrelapsed patients showed a significantly higher proportion and count of NK cells than the relapsed patients (median counts and ranges of 529/mm^3, 346-827 and 279/mm^3, 45-645), respectively) (p=0.016). In particular, the proportion and count of CD56dim NK cells were significantly higher in the nonrelapsed patients (median: 29.92% (range: 7.42%>48.59%) and median: 467/mm^3 (range: 200-955), respectively) than in the relapsed patients (median: 16.01% (range: 2.09%>31.46%) and median: 362/mm^3 (range: 58-438), respectively) (p=0.017 and p=0.079, respectively). In contrast, at one month after TKI discontinuation, the nonrelapsed patients showed significantly lower proportions and counts of CD4+ T cells and CD4+CD25+CD127low/- Tregs than the relapsed patients. In the 12 patients who received IFN-α treatment, the level of CD56bright NK cells was increased significantly after both 3 and 6 months of IFN-α treatment.
Summary/Conclusion: NK cells, especially cytotoxic CD56dim NK cells, are associated with MR after TKI discontinuation in CML patients.

Additionally, IFN-α treatment can gradually increase the level of CD56bright NK cells in CML patients.

EP657 TNF-MEDIATED CML CELL SURVIVAL RESISTS TKI TREATMENT AND THIS CAN BE TARGETED BY IKK2-INHIBITION

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Background: Treatment with tyrosine kinase inhibitors (TKIs) substantially improved the clinical outcome in CML. Although, the Bcr-Abl1-directed approach eliminates the majority of CML cells, TKIs often spare leukemic stem cells (LSCs). Interestingly, tumor necrosis factor (TNF) has been described to coordinate hematopoietic stem cell survival and a TKI persistent TNF signature in LSCs was identified. Elevated TNF plasma levels were observed in chronic phase (CP) and progressed CML and were significantly elevated in bone marrow and spleen in CML mouse models. Targeting the TNF-induced NFκB-signaling by overexpressing the inhibitory IκBα protein, impaired leukemogenesis in a retroviral model of Bcr-Abl1 driven disease.
Aims: Here, we aimed to complement TKI therapy by TNF pathway-directed treatment, to specifically target persisting CML cells in CP- and blast crisis (BC) CML.
Methods: Publicly available microarray data were analyzed for induction of TNF regulated pathways. 32D Bcr-Abl1, SCLtTA/Bcr-Abl1-BM, human K562 & KCL22 (imatinib-sensitive (S) and -resistant (R)) cells were evaluated using qRT-PCR, Western blot, annexin V & CFSE staining. CP-CML-CD34$^+$-cells and BC mononuclear cells (MNCs) were subjected to colony-forming unit (CFU) assays or annexin V + CFSE measurements upon treatment with the IKK2 small molecule inhibitor LY2409881 (LY) +/- nilotinib or DMSO as control, in the presence of TNF, IL1α or IL1β.
Results: Analysis of microarray data unveiled enrichment of TNF signaling molecules in the CD34$^+$CD38$^-$ compartment of CP-CML patient cells. 32D Bcr-Abl1 and primary murine SCLtTA Bcr-Abl1-BM cells exhibited enhanced TNF signaling compared to their Bcr-Abl1 negative counterparts. 32D Bcr-Abl1, KCL22 and K562 cells displayed no reduction in TNF signaling molecules upon TKI treatment, suggesting a Bcr-Abl1 kinase-independent persistence. The combination of nilotinib and LY reduced expression of IκBα and NFκB and abrogated their phosphorylation. This treatment reduced proliferation and induced apoptosis (fold change [fc]: 2.4; p<0.01) in KCL22 S cells. In primary CD34$^+$ CP-CML cells, we discovered diminished clonogenic potential compared to TKI alone (fc: 0.05; p<0.01). Replating revealed nilotinib to preserve cells with colony-forming ability, as previously reported. These LSCs were in turn targeted by IKK2 inhibition (fc: 0.17; p<0.01). Reduction of the clonogenic potential was accompanied by apoptosis induction upon combinatorial treatment compared to TKI alone (fc: 2.5; p<0.01), also in the non-dividing cell fraction (fc: 5.2; p<0.001). Gene set enrichment of microarray data comparing BC to CP patient cells displayed further upregulation of TNF signaling in BC-LSCs. Interestingly, IKK2 inhibition could bypass TKI resistance in KCL22 R cells by apoptosis induction (fc: 2.4; p<0.01). Also, in BC-CML MNCs, combined nilotinib and LY treatment significantly decreased self-renewal (fc: 0.1; p<0.01) and induced apoptosis (fc: 1.8; p<0.01). Furthermore, combinatorial treatment targeted persistent CML-CP LSCs in the presence of IL1α and IL1β (fc: 0.6 & 0.5; p<0.05), underlining the relevance of IKK2 inhibition as global approach to target the pro-leukemic inflammatory environment.
Summary/Conclusion: In conclusion, we demonstrate that elevated TNF signaling in CML patients persists during TKI treatment. By combining IKK2 inhibition with a Bcr-Abl1-directed TKI, we were able to target non-dividing CP-CML LSCs but also TKI resistant BC-CML cells. We suggest targeting of TNF-induced signaling as a promising approach to address TKI persistence and resistance in CP- and BC-CML.

EP658 AGE-RELATED DNA DAMAGE RESPONSE (DDR) IN HEMATOPOIETIC STEM CELLS FROM CHRONIC MYELOID LEUKAEMIA PATIENTS WHO ATTEMPTED TKI DISCONTINUATION.

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Background: Chronic Myeloid Leukemia (CML) is a myeloproliferative disease caused by the 9;22 chromosomal translocation which leads to the formation of the chimeric kinase BCR-ABL. The introduction of imatinib and other tyrosine kinase inhibitors (TKI) allowed excellent control of the disease in the majority of patients. In a number of patients, after a prolonged treatment, Ph+ cells become undetectable or below 10^{-4}, thus allowing a TKI discontinuation attempt. However, about half of CML patients experience a molecular relapse, which in 80% of cases occurs within 6 months from interruption, and need to resume treatment. There is currently no marker to predict the outcome of discontinuation.
Aims: Previous studies have shown that age can predict relapse after TKI discontinuation. We hypothesized that this may be linked to the DDR phenotype of leukemic stem cells (LSCs). We aimed to analyze the DDR status of LSCs, measured at diagnosis, in CML patients who attempted TKI discontinuation, and correlated it with treatment-free remission (TFR) duration.
Methods: CD26 has been proposed as a marker of CML LSCs. We sorted LSCs (CD45+CD34+CD38-CD26+) and normal HSCs (CD45+CD34+CD38-CD26-) from bone marrow samples obtained at diagnosis in 27 CP-CML patients who later discontinued TKI (imatinib, n=15; other TKIs, n=12). The analysis of DDR phenotype was performed by γH2AX immunofluorescence at confocal microscope. Clinical and molecular data were correlated with discontinuation outcome.
Results: CD26 staining correctly identified Ph+ cells within CD34+CD38- cells (Figure 1). We found that DDR in the CD34+CD38- population correlates with patients' age (p = 0.05) and that CD26+ LSCs present greater DDR compared to normal CD26- stem cells (117±48.9 vs 48.8±19.9; p<0.0001, Figure 1). A correlation was also found between DDR at diagnoses and the outcome of TKI discontinuation, which identifies patients in durable TFR as those with less DNA damage at onset (72.2±32.4 vs 107.6±18; p = 0.034). Another interesting finding of this study was the duration of molecular remission before the discontinuation: in fact, it was clear that the longer the duration of deep molecular remission, the lower the probability of relapse after the TKI discontinuation (p = 0.026).

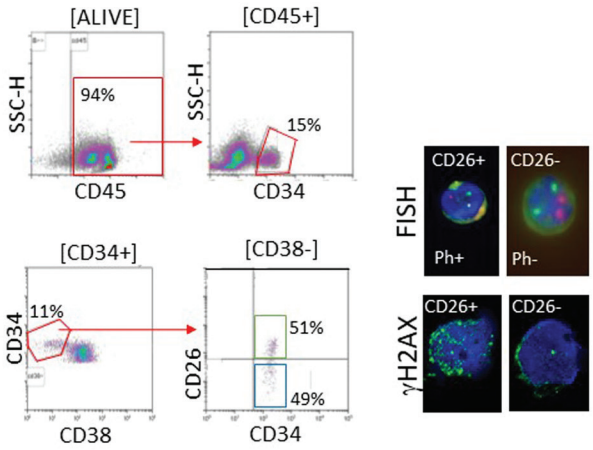


Figure 1. *Left*, FACS sorting protocol of CD45$^+$CD34$^+$CD38$^-$CD26$^+$ and CD45$^+$CD34$^+$CD38$^-$CD26$^-$ cells from a Ph$^+$CML patient sample. *Right*, representative images of BCR/ABL FISH and γH2AX analyses from isolated CD26$^+$ and CD26$^-$ cells are shown.

Summary/Conclusion: We identified DDR and duration of remission as potential biomarkers of relapse in CML patients after TKI discontinuation. Our data also indicate that CML LSCs possess a more pronounced DDR phenotype compared to normal HSCs. These results need to be validated in a larger cohort of patients.

EP659 ASSESSMENT OF LEUKEMIC STEM CELL CD26+ IN CHRONIC MYELOID LEUKEMIA PATIENTS WITH DEEP MOLECULAR RESPONSE.

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Background: Chronic Myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the reciprocal translocation t(9;22)(q34;q21) resulting in the *BCR-ABL1* fusion gene and the oncogenic protein P210 with constitutive tyrosine kinase activity. The study of this protein led to the development of tyrosine kinase inhibitors (TKI). It has been shown that patients with a deep and sustained molecular response could stop treatment. It is likely that relapse after TKI discontinuation is due to the persistence of Leukemic Stem Cell (LSC), which are transcriptionally quiescent. The expression of the enzyme dipeptidylpeptidase IV (CD26) is restricted to CD45+/CD34+/CD38- LSC in CML BCR/ABL1+, but is not found in other myeloid or lymphoid LSC. For this reason it is considered a novel specific biomarker of neoplastic cell in CML.
Aims: To detect the LSC (CD26+) in CML patients with different molecular responses (MR) and to assess if these cells remain in deep molecular response (DMR).
Methods: Peripheral blood samples from 174 CML patients (94 males and 80 females) were evaluated for detection of LSC by flow cytometry and quantitative PCR (qRT-PCR) for *BCR-ABL1* rearrangement. All individuals provided an informed consent, in accordance with our Institutional Ethics Committee. The analysis of both studies was carried out simultaneously on the same sample, during the follow up at different time points after diagnosis and under TKI treatment (Imatinib, Nilotinib, Dasatinib). Median age was 48 years old (range 18-82). The molecular responses in International Scale (IS) were: 6% (10/174) Null MR, 9% (15/174) Minimal MR, 16% (28/174) Minor MR, 27% (47/174) Major MR and 42% (74/174) DMR (BCR-ABL1 transcripts reduction ≥ 4 log, including $MR^{4.0}$, $RM^{4.5}$ and $RM^{5.0}$).
Flow cytometry studies were performed with 200 µl of whole blood stained with a panel of 8 antibodies: HLA-DR/CD45/CD38/CD26/CD34/CD117/CD123/CD3 using BD FACS Canto™ II flow cytometer. *BCR-ABL1* qRT-PCR was performed by Taqman method with the Molecular MD *One-Step* kit using a Rotor-Gene 6000 Q real-time thermal-cycler (QIAGEN).
Results: The immunophenotype and molecular response were analyzed in all 174 cases. It was observed that patients with good molecular response (≥3log BCR-ABL1 reduction) had a significantly lower percentage of cases with LSC compared to those who had <3log reduction (P<0.0074, RO: 2.7). The analysis of the 74 patients with DMR (40% (29/74) in $RM^{4.0}$, 55% (40/74) in $RM^{4.5}$ and 5% (4/74) in $RM^{5.0}$) showed that the LSC percentage was: 27% (8/29), 15% (6/41) and 0% (0/4) respectively. This suggests that the decrease in LSC could be related to deeper molecular responses.
Summary/Conclusion: Our results showed that CML patients with molecular response ≥3log BCR-ABL1 reduction were significantly associated with lower proportion of cases with persistence of LSC. When the LSC analysis was performed exclusively in cases with DMR, no significant differences were observed between $RM^{4.0}$, $RM^{4.5}$ and $RM^{5.0}$. However, we observed that the presence of LSC decreased as the depth of the molecular response increased.
Since the LSC is highly quiescent, it could be present even in cases with undetectable DMR. In our study LSC were not detected in 81% (60/74) of cases in DMR, while in the remaining 19% (14/74), CD26+ cells remain despite DMR. This new approach to the study of the LSC could be useful during the follow up of patients in DMR, especially if they would be included in clinical trials of treatment discontinuation.

EP660 EUTOS EXPERIENCE OF STANDARDISATION OF MOLECULAR MONITORING FOR CML (2016 – 2020). USE OF SECONDARY BCR-ABL1 REFERENCE MATERIALS FOR CONVERSION FACTOR VALIDATION AND ASSESSMENT OF MR4.5 DETECTION

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Background: Monitoring of *BCR-ABL1* mRNA levels using RT-qPCR assays standardised to the International Scale (IS) is essential for management of CML patients, especially when cessation of tyrosine kinase inhibitor therapy is intended. Before the development of secondary reference materials, laboratories used an expensive sample exchange process with reference laboratories for IS calibration. Secondary cell-based reference panels are now available that are traceable to and replicate the WHO primary reference material with an additional standard to include MR4.5.
Aims: To develop and evaluate the use of lyophilised cell line panels to derive and monitor stability of laboratory specific conversion factors (CFs) and the ability of laboratories to measure MR4.5.
Methods: From 2016 – 2020 samples were distributed annually to EUTOS references labs who agreed to participate (2016 n= 49, 2017 n=48, 2018 n=50, 2019 n=49). The samples were: three HL60/K562 cell line lysates at approximately 10%, 0.1% and 0.0032%BCR-ABL IS, a cDNA sample with known *ABL1* and *BCR-ABL1* copy number and secondary reference material panels composed of five vials of lyophilised cells (HL60/K562; LYO panel) supplied by Novartis (2016 -2019) or Thermo Fisher Scientific (Acrometrix™, 2020). IS values for both panels were assigned by reference to the WHO primary reference material for both *ABL1* and *GUSB*. All samples tested by RT-qPCR following normal lab protocols. Anonymised control gene transcript copy numbers over a 4 week audit period for 50 local routine samples were also collected.
Results: CFs were determined using the secondary reference lyophilised cell line panels using the method described at https://www.nibsc.org/documents/ifu/09-138.pdf. The validity of lab CFs was determined annually using: Optimal (+/- 1.2 fold): Previous panel CF / New panel CF = 0.83 – 1.2; Satisfactory (+/- 1.6 fold): Previous panel CF / New panel CF = 0.63 – 1.58; Unvalidated: Previous panel CF / New panel CF <0.63 or >1.58. The validity of CFs for all rounds are shown in the Table.

ABL1	**2016/2017 (n=43)**	**2017/2018 (n=45)**	**2018/2019 (n=42)**	**2019/2020 (n=39)**
Reference Panel	LYO	LYO	LYO	Acrometrix
% Optimal	32.6	60.0	53.8	48.7
% Satisfactory	34.9	22.2	28.2	43.6
% Unvalidated	32.6	17.8	17.9	7.7
GUSB	**2016/2017 (n=11)**	**2017/2018 (n=12)**	**2018/2019 (n=12)**	**2019/2020 (n=13)**
Reference Panel	LYO	LYO	LYO	Acrometrix
% Optimal	9.1	25.0	41.7	46.2
% Satisfactory	27.3	41.7	50.0	7.7
% Unvalidated	63.6	33.3	8.3	46.2

To assess whether labs could detect MR4.5 data were analysed in six categories: median number of *CG* transcripts reported for cell line lysates, detection of *BCR-ABL1* in DMR cell line samples and MR4.5 reference panel samples, *CG* and *BCR-ABL1* transcript number per ul cDNA, %*BCR-ABL1*/*CG* for cDNA sample and quality of *CG* audit data. The scores for each category were weighted, and combined scores calculated. In all rounds

>95% of labs were assessed as being able to detect MR4.5 in all or most samples.
Summary/Conclusion: The % of labs with CFs validated as optimal or satisfactory increased from 67.5% (2016) to 92.3% (2020) and 36.4 (2016) to 53.9% (2020) for *ABL1* and *GUSB* respectively. The percentage of laboratories able to detect MR4.5 in most samples was high across all years with a median of 98%. The EUTOS molecular standardisation study indicates that secondary reference panels can be used effectively to obtain and validate IS CFs over time, validate MR4.5 detection and monitor additional aspects of quality assurance.

EP661 ANALYSIS OF MRNA AND DNA LEVEL OF ATYPICAL BCR-ABL1 TRANSCRIPTS IN CML PATIENTS OUTLINED AN ELIGIBILITY FOR TKI STOPPING

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Background: Tyrosine kinase inhibitors (TKI) cessation in patients with chronic myeloid leukemia (CML) can be currently managed in clinical practice. However, only patients with major transcript types are eligible for TKI cessation according to European LeukemiaNet recommendation as BCR-ABL1 quantification for monitoring of measured residual disease (MRD) is standardized for e13a2/e14a2 transcripts only.
Aims: The collaborative EUTOS work aimed 1) to compare DNA and mRNA data measured by qPCR and ddPCR in CML patients with atypical BCR-ABL1 transcripts and 2) to evaluate DNA/mRNA pattern in the patients in deep molecular response (DMR) and their potential eligibility for TKI stopping.
Methods: Paired peripheral blood samples from 9 patients (e19a2=5; e13a3=2; e1a2=1; e6a2=1) with median follow-up 90 months (range 20-225 months) were measured by qPCR (n=223) and ddPCR (n=188). Four patients with e19a2, 1=e13a3 and 1=e6a2 responded to TKI with sustained DMR. Patient-specific genomic BCR-ABL1 fusions were characterized by NGS. The sensitivity of DNA and mRNA analysis varied between 10^{-4} – 10^{-5}. The deterministic model was applied to evaluate MRD pattern.
Results: The amount of mRNA and DNA BCR-ABL1$_{RelDG}$ (the quantity of BCR-ABL1 was determined in relation to the corresponding quantity in the diagnostic sample defined as 100%) highly correlated in samples collected from the start of TKI until achievement of DMR (defined as MRD at levels 10^{-4}-10^{-5}). Differences were found at DMR levels in 75/223 samples measured by qPCR and in 62/188 samples by ddPCR. Out of the 75 samples measured by qPCR, 60 samples were DNA quantifiable and mRNA POQR (positive outside of quantifiable range) or negative, 13 samples were DNA POQR and mRNA negative. Only 2 samples were quantifiable and POQR on mRNA and POQR and negative on DNA, respectively. By ddPCR, BCR-ABL1 was DNA quantifiable and mRNA POQR or negative in all 62 samples with discrepant levels.
A total of 203 samples were available for comparison of mRNA analysis by qPCR and ddPCR. Of these, 39 results were discordant at levels below 10^{-4}. Of these samples, 33 were quantifiable or POQR by ddPCR and were either POQR or negative by qPCR. Six samples were negative by ddPCR while positive by qPCR. DNA BCR-ABL1 levels were concordant by both techniques in 184 of 220 samples. Of the 36 discordant samples, 27 were BCR-ABL1 quantifiable by ddPCR, while POQR or negative by qPCR.
MRD pattern of the 6 patients in DMR was double negative in 1 patient with e19a2, DNA positive/RNA negative in 3 patients (e19a2, e13a3, e6a2) and double positive in 2 patients with e19a2.
Summary/Conclusion: The observed data on BCR-ABL1 atypical transcripts are highly similar to the published data with major BCR-ABL1. DNA and mRNA BCR-ABL1 quantity in CML patients with atypical transcripts were highly concordant at levels above 10^{-4}. The discrepancy was found at DMR levels, where majority of samples were DNA quantifiable or POQR, while POQR or negative on mRNA. ddPCR showed higher precision in DNA and mRNA detection/quantification compared to qPCR at DMR levels. According to the previously proposed traffic light stratification model of probability of treatment free remission (TFR) after TKI stop, 1 patient has high probability of TFR, 3 patients have intermediate probability and 2 patients have low probability of TFR.
We assume that TKI stopping protocols may be safe also for CML patients with atypical BCR-ABL1 transcripts, especially if precision of MRD monitoring is enhanced by using ddPCR and optionally by DNA analysis.
Support: EUTOS2018, MZCR 00023736

EP662 ANALYSIS OF MYELOID MUTATIONS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA AND THEIR ASSOCIATION WITH ADVERSE EVENTS AND RELAPSE AFTER DISCONTINUATION.

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Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the *BCR-ABL1* fusion gene and is treated using tyrosine kinase inhibitors (TKI). The development of new technologies such as next-generation sequencing (NGS) has led to major advances in the understanding of CML pathogenesis. Molecular studies are beginning to reveal genetic profiles associated with adverse events among patients with CML, including thrombotic events, resistance and/or intolerance to TKI and risk of progression. Moreover, the majority of studies on TKI discontinuation show that approximately half of patients maintain treatment-free remission (TFR), but the factors that determine this are yet to be elucidated.
Aims: Study the mutational profile of CML patients and its association with the development of adverse events and maintenance of TFR after TKI discontinuation.
Methods: We retrospectively analyzed 200 ng genomic DNA extracted from peripheral blood at diagnosis of 63 CML patients subsequently treated with TKI with a minimum follow-up of 3 years. NGS was performed with the MiSeq (Illumina) platform using the targeted panel Myeloid Solution™ (SOPHiA GENETICS). Only variants with VAF≥2%, MAF<1% and described as having a pathogenic or probably pathogenic effect were considered. Adverse events considered include thromboembolic or chronic ischemic events, progression to accelerated or blastic phase, and TKI resistance. With respect to TKI discontinuation, we considered relapse vs. no relapse, and late relapse (TFR maintained>6 months) vs early relapse (<6 months).
Results: Of the 63 patients, 32 (50.8%) were male; average age at diagnosis was 54 years. In 48 patients (76.2%) no mutation was detected; 15 (23.8%) presented ≥1 mutation, with an average allelic frequency (VAF) of 25.7%. The most frequently mutated genes were *ASXL1* (n=9) and *TET2* (n=3) (**Figure 1**). No association was found between the presence of mutation in the CHIP genes (*TET2*, *ASXL1*, *DNMT3A* or *JAK2*) and age.
Sixteen patients had a thrombotic event during follow-up (25.4%). No differences were found in the presence of CHIP mutations between patients with and without a thrombotic event (no event: 7/47, 14.9%; event: 4/16, 25%) or presence of any pathogenic mutation (no event: 10/47, 21.3%; event: 5/16, 31.3%).
Three patients (4.7%) developed TKI resistance; two of them carried pathogenic mutations. One patient presented two mutations in *ASXL1* (VAF 8-9%); the other in *WT1* (VAF 22%) and *KRAS* (VAF 24%), the latter patient was the only one in our series that advanced to blastic phase. Of the 24 patients who attempted TKI discontinuation, 17 (70.8%) maintained TFR for >6 months while 7 (29.2%) had early relapse. There was no difference between the patients who relapsed vs those who maintained TFR, or between early and late relapse in terms of myeloid mutations.

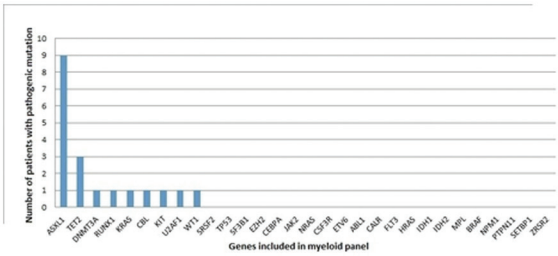


Figure 1. Pathogenic mutations detected in a series of 63 patients with CML.

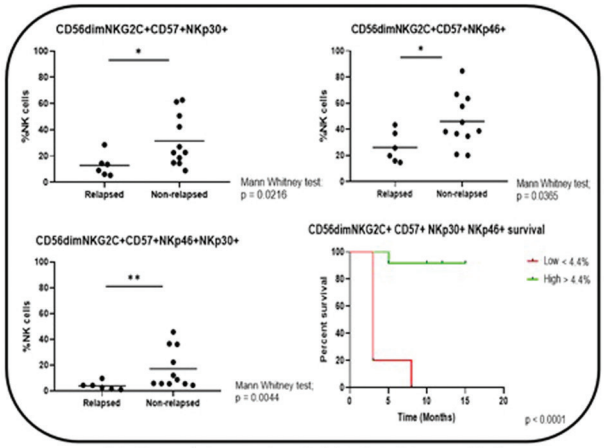
Summary/Conclusion: Less than a quarter of the CML patients analyzed presented pathogenic mutations. These results contrast with those observed in the BCR-ABL1-negative myeloproliferative neoplasms, of whom approximately 50% present mutations (besides the driver genes) and with a higher average VAF. Although patients with thrombotic events presented a higher incidence of myeloid mutations, these differences were not significant. Our results suggest that myeloid mutations are not predictive of TFR or relapse following TKI discontinuation. Larger series are needed to determine whether these mutations are associated with TKI resistance or blastic phase evolution.

EP663 COMPREHENSIVE IMMUNOPROFILE OF NK CELLS FROM CML PATIENTS IN TFR REVEALS A POSSIBLE ROLE OF MEMORY-LIKE NK CELLS

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Background: Long-term survival of patients with chronic myeloid leukemia (CML) has significantly improved since the introduction of BCR-ABL1 tyrosine kinase inhibitors (TKIs). Several clinical trials show that approximately half of patients who achieve a sustained deep molecular response during TKI treatment maintain molecular remission after stopping TKIs. There is currently no biomarker that reliably predicts treatment free remission (TFR) in CML, but growing evidence remarks the importance of the immune system, especially of Natural Killer (NK) cells in this scenario.
Aims: Our aim is to discover a biomarker for TFR prediction by analyzing the conventional and adaptive phenotype of NK cells at the time of discontinuation and their relation to successful TKI cessation, and to assess any phenotypic changes throughout the months without treatment.
Methods: Fifty chronic phase CML patients who participated in the Argentina Stop Trial were recruited from 7 Argentinian centers. Peripheral blood samples were collected before TKI stopping and then at months 3, 12 and at any time when $MR^{3.0}$ was lost. Freshly isolated mononuclear cells were immunophenotyped by staining with CD3, CD16, CD25, CD56, CD57, CD158, NKp30, NKp44, NKp46, NKG2A, NKG2C, NKG2D and PD-1 antibodies and subpopulations of NK cells were analyzed by flow cytometry (BD FACS Canto™II). Molecular recurrence-free survival was estimated by the Kaplan–Meier method. Mann Whitney test, Wilcoxon test or paired T test were performed to compare variables between groups, where $p<0.05$ was considered statistically significant. Quantitative variables were dichotomized according to ROC curves. Survival curves were compared with log rank test.
Results: Forty-six patients were analyzed with a median follow-up of 15 months (range 12-21) and with an estimated molecular recurrence-free survival of 67.4% at 12 months. At the time of discontinuation, non-relapsing patients had significantly higher frequencies of NK subpopulations with cytomegalovirus-related memory features ($CD56^{dim}CD57^{+}NKG2C^{+}$), but higher expression of cytotoxicity markers $NKp30^{high}$ ($p=0.0216$) or $NKp46^{high}$ ($p=0.0365$). Most important, a higher coexpression of NKp30 and NKp46 on $CD56^{dim}CD57^{+}NKG2C^{+}$ subpopulation (defined as memory-like NK, ML-NK) showed a significant difference in survival when relapsed vs non-relapsed patients were compared (0% vs 92% at 12 months, log rank test, $p<0.0001$) (Fig. 1). After TKI discontinuation, a significant and sustained increase or decrease over time could be seen for 4 NK cells subpopulations expressing CD57, NKG2D, PD-1 and NKp44, while NKp30, CD158, $CD57^{+}CD16^{+}CD158^{+}$, and ML-NK subpopulations did not significantly change over the course of 12 months.



Note: These analysis were performed only in patients that were positive for cytomegalovirus determination (CMV+) and showed a memory-like subpopulation of NK cells characterized by the expression of NKG2C receptor of 8% or higher.

Summary/Conclusion: Our study is the first, to our knowledge, to describe this adaptive-like subpopulations of NK cells with enhanced cytotoxicity-related phenotype which could have a protecting role in patients who do not relapse. Moreover, the ML-NK phenotype was retained more efficiently in TFR patients off-therapy, suggesting that the restored immune control observed at the time of discontinuation is not an entirely TKI-mediated effect, which could be used as a predictive biomarker. The clinical impact of NK cells in patients who have discontinued TKIs is still controversial. To fully understand their role, we are planning to carry out functional studies

EP664 TARGETING THE LEUKEMIC STEM CELL NICHE BY PI3K INHIBITORS IN CHRONIC MYELOID LEUKEMIA TO OVERCOME LEUKEMIC STEM CELL RESISTANCE

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Background: Recent data suggest that the disease-related microenvironment (stem cell niche) is critically involved in drug resistance of leukemic stem cells (LSC) in chronic myeloid leukemia (CML). Attacking the stem cell niche in CML may thus be an effective approach to overcome LSC resistance. We have recently shown that osteoblasts induce substantial LSC resistance against tyrosine kinase inhibitors (TKI) in CML. We also found that several BCR-ABL1 TKI, like ponatinib or nilotinib, exert growth-inhibitory effects on endothelial cells.
Aims: In the current study, we screened for drugs that are able to suppress the growth and viability of osteoblasts and endothelial cells in the CML context.
Methods: Proliferation was analyzed by measuring ^{3}H-thymidine uptake in niche-related cells and apoptosis was measured by AnnexinV/DAPI-staining.
Results: We found that PI3K/mTOR blocker BEZ235 and pan-PI3K inhibitor copanlisib suppress growth and viability of primary osteoblasts (BEZ235 IC_{50}: 0.05 µM, copanlisib IC_{50}: 0.05 µM), the osteoblastic cell line

Table 1. Rare BCR-ABL Variants in CML

Pt	Variant	Protein consequence	Type of mutation	KD Region	Previous TKI	TKI Post-study	Molecular response	BMR IS%
1	c.1322C>T	p.Pro441Leu	Missense	C-terminal	IM	DA	Not reached	120
2	c.1423_1424ins35	p.Cys475fs*11	Frame shift	C-terminal	IM	DA	MR2.0	0.15
3	c.1423_1424ins35	p.Cys475fs*11	Frame shift	C-terminal	NI	DA	MR2.0	0.16
4	c.1031_1215del	del;p.Arg362fs*21	Splice junction	C-loop	IM	DA	MR4.5	0.0032
5	c.1164C>T	p.Cys388	Synonymous	A-loop	NI	NI	MR3.0	0.055
6	c.967_995del	p.Leu323AlafsTer49	Frame shift	IBS	IM/DA	NI	MR3.0	0.02
7	c.923A>G	p.Glu308Gly	Novel missense	IBS	IM	NI	MR4.5	0.0028

IBS: Imatinib binding site; IM: Imatinib; DA: Dasatinib; NI: Nilotinib; BMR: Best molecular response.
At study entry, all the pts. were in chronic phase, only Pt. 1 evolved to blast crisis independently of the change in TKI. Pts. 2 and 3 exhibited the same 35bp insertion variant, and achieved non optimal responses, while in pts 4, 5, 6 and 7 good MR were obtained: Pts. 4 and 7 achieved deep molecular responses to 2nd generation TKI (MR4.5). A synonymous variant was described in Pt 5 and showed a good molecular evolution despite any TKI treatment changeIBS: Imatinib binding site; IM: Imatinib; DA: Dasatinib; NI: Nilotinib; BMR: Best molecular response.

CAL-72 (BEZ235 IC_{50}: 0.5 µM; copanlisib IC_{50}: 1 µM), primary umbilical vein-derived endothelial cells (BEZ235 IC_{50}: 0.5 µM; copanlisib IC_{50}: 0.5 µM), and the endothelial cell line HMEC-1 (BEZ235 IC_{50}: 1 µM; copanlisib IC_{50}: 1 µM). Moreover, we found that BEZ235 and copanlisib cooperate with nilotinib and ponatinib in suppressing growth and viability of osteoblasts and endothelial cells. Finally, BEZ235 and copanlisib were found to overcome osteoblast-induced resistance of K562 cells, KU812 cells, and primary $CD34^+/CD38^-$ CML LSC against nilotinib and ponatinib.
Summary/Conclusion: Together our data suggest that targeting niche cells by BEZ235 and copanlisib is an effective approach to overcome niche-induced TKI resistance in CML.

EP665 RARE MUTATIONS IN BCR-ABL THE KINASE DOMAIN IN CRONIC MYELOID LEUKEMIA PATIENTS.

R. Delamer [1,*], L. Ferrari [2], M. T. Cuello [1], P. Wernicke [2], M. J. Mela Osorio [2], M. Juni [2], G. Bendek [3], A. Bonacina [4], M. C. D'Acunto [5], C. Jozami [6], M. Perez [7], B. Moiraghi [8], M. J. Freitas [9], M. V. Ventriglia [10], N. Oliveira [9], R. Mariano [11], A. Varela [12], J. Gonzalez [13], M. E. Riva [14], V. Canonico [15], G. Barone [16], M. Catalan [17], M. Williams [18], L. Celebrin [19], M. V. Guerrero [16], M. S. Gomez [20], M. Stivel [15], D. Altuna [3], H. Bernard [21], J. Bordone [22], M. Ciccioli [16], A. Brodsky [23], M. G. Flores [13], G. Klein [24], M. Kruss [25], D. Moro [26], S. Ortiz [27], M. Pujol [28], M. A. Romero Maciel [29], M. Gil [30], B. Pertine [31], M. F. Figueroa [32], V. Montes de Oca [33], F. Baglione [34], M. E. Centurion [35], J. Martinez Rolón [36], F. Sackmann [36], I. Fernandez [36], M. A. Pavlovsky [36], C. Pavlovsky [36], I. Giere [1]

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Background: BCR-ABL kinase domain (KD) mutations are the most frequent mechanism of tyrosine kinase inhibitor (TKI) resistance in chronic myeloid leukemia (CML) patients (pts.). Detection of specific mutations influences the choice of the second or subsequent TKI lines. Intensive efforts are focused on characterizing their biological and clinical significance.
Aims: To characterize rare p210 BCR-ABL KD variants revealed in an argentine multicentric study.
Methods: This prospective study screened a cohort of CML TKI resistant pts, from 40 centers, from June 2011 to August 2020. Mutational analysis was performed by direct sequencing of BCR-ABL KD, NCBI sequence reference ID: NM_005157.5 (Branford *et al*, 2002). Molecular response was defined upon fusion transcript level measured by Real Time quantitative PCR (Gabert *et al*, 2003) and expressed in international scale as IS%BCR-ABL (Cross *et al*, 2012).
Results: Mutation screening was performed in 271 CML resistant pts. BCR-ABL DK mutations were detected in 26.2% (71/271) pts: single and compound mutations in 96% (68/71) and 4% (3/71), respectively. The most frequent mutations identified were T315I 35% (25/71) and F317L 11% (8/71). Only 10% (7/71) pts. unveiled rare variants with unknown TKI sensitivity and are described in Table 1. A novel BCR-ABL KD mutation was revealed.
At study entry, all the pts. were in chronic phase, only Pt. 1 evolved to blast crisis independently of the change in TKI. Pts. 2 and 3 exhibited the same 35bp insertion variant, and achieved non optimal responses, while in pts 4, 5, 6 and 7 good MR were obtained: Pts. 4 and 7 achieved deep molecular responses to 2nd generation TKI (MR4.5). A synonymous variant was described in Pt 5 and showed a good molecular evolution despite any TKI treatment changeIBS: Imatinib binding site; IM: Imatinib; DA: Dasatinib; NI: Nilotinib; BMR: Best molecular response.
Summary/Conclusion: Detected insertions and deletions variants conducting to truncated proteins, alternative splicing and changes in the Imatinib binding site (IBS) may affect TKI binding to BCR-ABL KD. Variants in the C-terminal region as the missense mutation (c.1322C>T) might confer worse prognosis. Even though the 35bp insertion (c.1423_1424ins35) conferred resistance to Imatinib (IM) and Nilotinib (NI), a sustained suboptimal response was achieved with Dasatinib (DA) therapy. The novel variant (p.Glu308Gly) affects a highly conserved IBS region, probably causing the IM resistance in our patient; however a deep response to NI was achieved. It is important to report single experiences in the treatment and follow up of pts. with uncommon mutations in order to be able to have more data regarding its clinical course. Our study highlights the need for BCR-ABL KD sequence analysis to characterize mutations in therapy resistant CML pts with the aim of guiding targeted treatment.

Chronic myeloid leukemia - Clinical

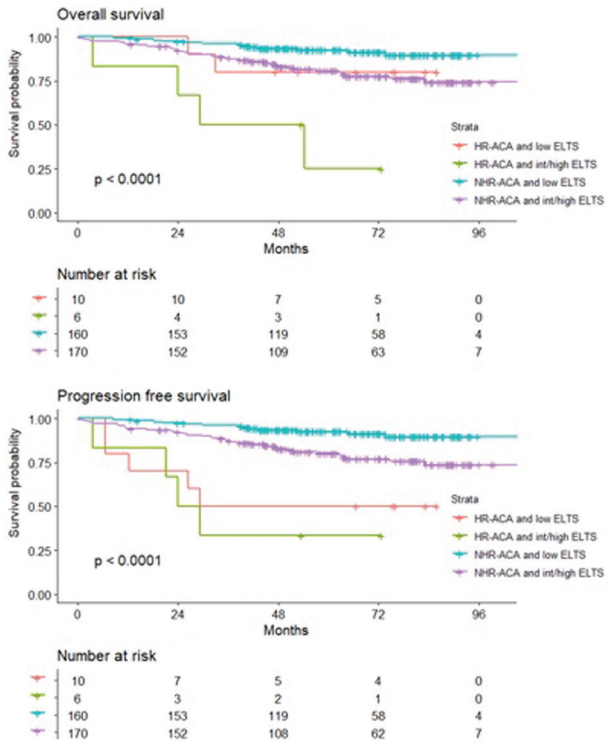
EP666 NEGATIVE PROGNOSTIC IMPACT OF HIGH-RISK ADDITIONAL CYTOGENETIC ABNORMALITIES IN ADDITION TO THE ELTS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Background: The negative prognostic impact of high-risk additional cytogenetic abnormalities (HR-ACAs) in chronic myeloid leukemia (CML) is well established. Also, the EUTOS long-term survival score ELTS may be used to identify patients at increased risk for CML-related death during TKI therapy. However, it has not been investigated if HR-ACAs and higher ELTS are related and if a better prognostic prediction may be achieved when combining HR-ACAs and the ELTS.
Aims: The objectives were to assess the relation of HR-ACA with the ELTS at diagnosis and to evaluate the impact of HR-ACA in addition to ELTS on survival in a real-world CML patient population.
Methods: This retrospective analysis was performed using data derived from a real-world population-based registry of 480 Dutch CML patients diagnosed between 2008 and April 2013 (The PHAROS CML Registry combined with HemoBase) with a follow-up until February 2016. HR-ACAs were defined according to the stratification of Hehlmann *et al.* (Leukemia 2020): +8, +Ph, +19, +21, +17 (or i[17q]), 3q26.2, 11q23, –7/7q– and complex karyotypes (≥3 ACAs) in Ph-positive cells. Loss of the Y chromosome and other ACAs were classified as low-risk ACAs. Overall and progression-free survival (OS and PFS) analyses were performed using the Kaplan Meier method and the log-rank method to test for equality. PFS in chronic phase CML was measured from diagnosis to death or progression to AP/BC; patients in AP/BC at diagnosis were excluded from this analysis.
Results: Cytogenetic assessments were available for 415 (86.4%) patients, of whom 20 (4.8%) had HR-ACAs. Trisomy 8 and an additional Ph-chromosome were the most prevalent HR-ACA. HR-ACA had a significant negative prognostic impact on both OS (HR 3.24; 95% CI, 1.61-6.49; p = 0.001) and PFS (HR 4.76; 95% CI, 2.44-9.35; p < 0.001). Low-risk ACA in Ph-positive cells or clonal cytogenetic aberrations in Ph-negative cells (CCA/Ph-) had no prognostic impact. No significant difference in Sokal-score or ELTS was found in patients with *versus* without HR-ACA (p = 0.573 and p = 0.831). HR-ACA was confirmed as an independent prognostic factor in a cox-regression multivariable analysis with the ELTS at diagnosis and type of first-line TKI as covariables. In our subgroup analysis, patients with both HR-ACAs and an intermediate to high ELTS at diagnosis had a markedly reduced OS compared to patients without HR-ACA or with a low ELTS (figure: plot 1). In the PFS analysis, both HR-ACA subgroups had a significantly reduced survival probability compared to patients without HR-ACA (figure: plot 2).



Summary/Conclusion: These results confirm the negative prognostic impact of HR-ACA on newly diagnosed CML patients and support its implementation as an independent risk-variable in a new prognostic model, including both the presence HR-ACA and the ELTS at diagnosis. Furthermore, they provide a first validation of the ACA risk stratification proposed by Hehlmann *et al.* since our survival analysis clearly distinguishes HR-ACAs from low-risk ACA or CCA/Ph-. Patients with HR-ACA at diagnosis or int/high ELTS, and especially when in combination, may benefit from a more aggressive treatment approach with upfront 2GTKI, a more stringent response monitoring and an early consideration of allogeneic stem cell transplantation in case of inadequate treatment responses.

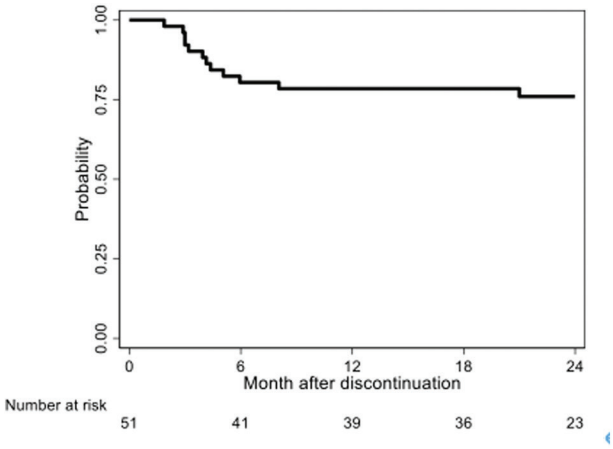
EP667 TREATMENT-FREE REMISSION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE FOLLOWING FRONTLINE NILOTINIB: RESULTS FROM JALSG N-STOP216

N. Takahashi [1,*], I. Matsumura [2], Y. Minami [3], T. Ono [4], T. Hata [5], S. Ohtake [6], Y. Atsuta [7], M. Kurata [7], K. Fujimaki [8], T. Nagao [9], C. Nakaseko [10], N. Iriyama [11], T. Miyamoto [12], N. Asou [13], H. Kiyoi [14], Y. Miyazaki [5]

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Background: Previously reported results from JALSG CML212 (UMIN000007909), a multicentrer open-labeled prospective randomized controlled phase 3 study on de novo chronic myeloid leukemia in chronic phase (CML-CP), showed that cumulative achievement rates of $MR^{4.5}$ (*BCR-ABL1* ≤0.0032% on the International Scale [$BCR\text{-}ABL1^{IS}$]) by 18 months were 33.0% (75/227) (95% CI:27.0–39.6%) in the nilotinib (NIL) arm and 30.8% (70/227) (95% CI: 24.9–37.3%) in the dasatinib arm, with no significant difference.
Aims: JALSG N-STOP216 (UMIN000024984), the next planned study, will evaluate patients with sustained $MR^{4.5}$, for at least 2 years on frontline NIL for estimating the rate of treatment-free remission (TFR), which is a new treatment goal in CML-CP.
Methods: BCR-ABL-positive CML-CP patients with ≥3 years of frontline NIL and sustained $MR^{4.5}$ for more than 2 years were enrolled in this trial. Patients restarted NIL after loss of major molecular response (MMR; $BCR\text{-}ABL1^{IS}$ ≤0.1%). The data cutoff was December 14, 2020, by which point all patients had completed 12 months of TFR, restarted NIL, or discontinued the study. All patients provided informed consent.
Results: A total of 54 patients were registered from 23 institutes and 51 patients were analyzed as FAS and PPS. Median age of the patients was 53 years (28–79 years). The proportions of Sokal low-, intermediate-, and high-risk groups were 41.2%, 35.3%, and 23.5%, respectively. The proportions of EUTOS low- and high-risk groups were 88.2% and 11.8%, respectively. The median duration of NIL treatment was 53 months (36–129 months), and the median duration of MR4.5 ($BCR\text{-}ABL1^{IS}$ ≤0.0032%) was 31 months (24–104 months). The median time to achieved MMR was 183 days (81–1567 days). At 12 months, 39/51 patients remained in TFR (76.5%; 95% CI:62.5%–87.2%) and 12 patients (23.5%) lost MMR. Of 11 patients who restarted NIL, 10 (90.9%) regained MMR in 6 months (1 discontinued study without MMR because of AE). At 12 months, 37/51 patients remained in MR4.0 ($BCR\text{-}ABL1^{IS}$ ≤0.01%) (72.6%; 95% CI:58.3%–84.1%); 14 patients (27.5%) lost MR4.0, and 31/51 patients remained in MR4.5 (60.8%; 95% CI:46.1%–74.2%); 20 patients (39.2%) lost MR4.5. No patient experienced disease progression. There was 1 death (pancreas cancer). At 24 months, the treatment-free survival (TFS) rate was 75.9% (95% CI:61.5%–85.6%; Fig.1). As estimated using the Kaplan–Meier method, TFS did not differ among Sokal risk groups (low, int, and high; p=0.5651), EUTOS risk groups (low and high; p=0.5389), duration of NIL (<4 years and ≥ 4 years; p=0.8910), duration of MR4.5 (<30 months and ≥ 30

months; p=0.5852), or time of MMR (<183 days and ≥ 183 days; p=0.1789).



Summary/Conclusion: JALSG N-STOP216 provides prospective TFR data in Japanese patients with CML-CP who achieved sustained MR$^{4.5}$ on frontline NIL. After stopping NIL, 76.5% of patients remained in TFR at 12 months later. The results suggest that a higher proportion of patients with CML-CP who achieved sustained MR$^{4.5}$ on frontline NIL will remain progression free without treatment compared with that in previous TFR trials.

EP668 TREATMENT-FREE REMISSION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE FOLLOWING FRONTLINE DASATINIB: RESULTS FROM JALSG D-STOP216

Y. Minami [1,*], I. Matsumura [2], N. Takahashi [3], S. Ohtake [4], Y. Atsuta [5], M. Kurata [5], S. Yano [6], N. Iriyama [7], Y. Ueda [8], Y. Ozawa [9], E. Sakaida [10], A. Mori [11], M. Yamamoto [12], T. Ono [13], K. Fujimaki [14], C. Nakaseko [15], T. Miyamoto [16], N. Asou [17], H. Kiyoi [18], Y. Miyazaki [19]

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Background: Previously reported results from JALSG CML212 (UMIN000007909), a multicenter open-labeled prospective randomized controlled phase 3 study on *de novo* chronic myeloid leukemia in chronic phase (CML-CP), showed that cumulative achievement rates of MR$^{4.5}$ (*BCR-ABL1* ≤0.0032% on the International Scale [*BCR-ABL1*^{IS}]) by 18 months were 33.0% (75/227) (95% CI:27.0–39.6%) in the nilotinib arm and 30.8% (70/227) (95% CI: 24.9–37.3%) in the dasatinib (DAS) arm, with no significant difference.
Aims: JALSG D-STOP216 (UMIN000024985), the next planned study, will evaluate patients with sustained MR$^{4.5}$, for at least 2 years on frontline DAS for estimating the rate of treatment-free remission (TFR), which is a new treatment goal in CML-CP.
Methods: BCR-ABL-positive CML-CP patients with ≥3 years of frontline DAS and sustained MR$^{4.5}$ for more than 2 years were enrolled in this trial. Patients restarted DAS after loss of major molecular response (MMR; *BCR-ABL1*^{IS} ≤0.1%). The data cutoff was December 14, 2020, by which point all patients had completed 12 months of TFR, restarted DAS, or discontinued the study. All patients provided informed consent.
Results: A total of 56 patients were registered from 25 institutes. Forty-nine of these patients were diagnosed with FAS and PPS[A1]. Median age of the patients was 52 years (24–80 years). Sokal low-, intermediate-, and high-risk group proportions were 40.8%, 44.9%, and 14.3%, respectively. EUTOS low- and high-risk group proportions were 91.8% and 8.2%, respectively. The median duration of DAS treatment was 51 months (36–129 months), and the median duration of MR$^{4.5}$ (*BCR-ABL1*^{IS} ≤0.0032%) was 30 months (24–64 months). The median time to achieve MMR was 178 days (83–1921 days). At 12 months, 29/49 patients remained in TFR (59.2%; 95% CI: 44.2%–73.0%), and 20 patients (40.8%) lost MMR. All the 22 patients (100%) who restarted DAS, regained MMR within 6 months. At 12 months, 27/49 patients remained in MR$^{4.0}$ (*BCR-ABL1*^{IS} ≤0.01%) (55.1%; 95% CI: 40.2%–69.3%), 22 patients (44.9%) lost MR$^{4.0}$, and among 25/49 patients that remained in MR$^{4.5}$ (51.0%; 95% CI: 36.3%–65.6%), 24 patients (49.0%) lost MR$^{4.5}$. No patients experienced disease progression or death for any reason. At 24 months, the treatment-free survival (TFS) rate was 59.2% (95% CI: 44.2%–71.4%; Fig.1). TFS did not differ among Sokal risk groups (low, int, and high; p=0.6300), EUTOS risk groups (low and high; p=0.4613), duration of DAS (<4 years and > ≥ 4 years; p=0.8522), duration of MR$^{4.5}$ (<30 and ≥ 30 months; p=0.8974), or time of MMR (<178 days and ≥ 178 days; p=0.1318).
Summary/Conclusion: JALSG D-STOP216 provides prospective TFR data in Japanese patients with CML-CP who achieved sustained MR$^{4.5}$ on frontline DAS. After stopping DAS, 59.2% of patients remained in TFR 12 months later. The results suggest that a higher proportion of patients with CML-CP who achieved sustained MR$^{4.5}$ on frontline DAS will remain progression free without treatment compared with that in previous TFR trials.

EP669 COMPARISON OF THE SOKAL AND EUTOS LONG-TERM SURVIVAL SCORES IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA RECEIVING TYROSINE KINASE INHIBITORS

X. Zhang [1,2,*], Y. Qin [1,2], Y. Lai [1,2], H. Shi [1,2], X. Huang [1,2], Q. Jiang [1,2]

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Background: There are limited studies comprehensively comparing the significance between Sokal and EUTOS long-term survival (ELTS) scores in patients with chronic-phase chronic myeloid leukemia (CML-CP) receiving tyrosine kinase inhibitor (TKI) therapy.
Aims: To compare the significance of the Sokal and ELTS scores in predicting the therapy responses and outcomes in CML-CP patients receiving front-line imatinib or the second generation (2G) TKI therapy.
Methods: Data from consecutive patients with newly-diagnosed CML-CP from January 2006 to August 2020 were reviewed. Propensity score matching (PSM) was performed to explore the impact of front-line TKI therapy choice in the CML-CP patients based on the Sokal or ELTS score.
Results: Data from 1559 CML-CP patients receiving front-line imatinib (n = 1331) or 2G TKI (n = 228) therapy were analyzed. In multivariate analyses, both the Sokal and ELTS scores could predict the probabilities of achieving complete cytogenetic response (CCyR) (ref. low-risk; Sokal: intermediate-risk, HR, 0.8 [0.7, 0.9], p = 0.005; high-risk, HR, 0.7 [0.6, 0.8], p < 0.001; ELTS: intermediate-risk, HR, 0.9 [0.7, 1.0], p = 0.080; high-risk, HR, 0.6 [0.5, 0.8], p < 0.001) and major molecular response (MMR) (ref. low-risk; Sokal: high-risk, HR, 0.8 [0.7, 1.0], p = 0.014; ELTS: intermediate-risk, HR, 0.8 [0.6, 0.9], p = 0.003; high-risk, HR, 0.6 [0.4, 0.8], p < 0.001) and failure-free survival (FFS) (ref. low-risk; Sokal: intermediate-risk, HR, 1.7 [1.3, 2.3], p = 0.001; high-risk, HR, 2.0 [1.5, 2.8], p < 0.001; ELTS: intermediate-risk, HR, 1.5 [1.2, 2.0], p = 0.003; high-risk, HR, 2.7 [1.9, 3.8], p < 0.001) and progression-free survival (PFS) (ref. low-risk; Sokal: intermediate-risk, HR, 2.1 [1.2, 3.5]; p = 0.006; ELTS: intermediate-risk, HR, 1.7 [1.0, 2.7]; p = 0.035; high-risk, HR, 3.9 [2.2, 6.7], p < 0.001) in all patients.

However, the ELTS score rather than the Sokal score was significantly-associated with the probabilities of achieving MR$^{4.5}$ (ref. low-risk; intermediate-risk, HR, 0.8 [0.6, 1.0], p = 0.046; high-risk, HR, 0.6 [0.4, 0.9], p = 0.026) and overall survival (OS) (ref. low-risk; intermediate-risk, HR, 1.8 [1.0, 3.2], p = 0.063; high-risk, HR, 5.0 [2.7, 9.1], p < 0.001). Similar findings were observed in those receiving front-line imatinib therapy. However, in those receiving front-line 2G TKI therapy, only the ELTS score could predict the probabilities of achieving CCyR, MMR, FFS and PFS, especially in the high-risk subgroup identified by the ELTS score who had lower probabilities of achieving CCyR (HR, 0.4 [0.2, 0.6], p < 0.001) and MMR (HR, 0.3 [0.1, 0.5], p < 0.001] and had inferior FFS (HR, 3.6 [1.8, 7.0], p < 0.001) and PFS (HR, 3.3 [1.2, 9.2], p = 0.022) than the low-risk subgroup. In the PSM analysis, although the intermediate-risk subgroup identified by both the Sokal (n = 267, 34.9%) and ELTS (n = 69, 31.5%) scores receiving front-line 2G-TKI therapy had higher 7-year probabilities of achieving CCyR (p < 0.001 and p < 0.001) and MMR (p = 0.003 and p < 0.001) and FFS (p = 0.012 and p = 0.004) than those receiving front-line imatinib therapy, the advantage for predicting the probability of PFS (p = 0.058) was only shown in those by the ELTS score.

Summary/Conclusion: Our findings provide evidence supporting the higher predictive performance of the ELTS score than the Sokal score in CML-CP patients receiving TKI therapy, especially front-line 2G TKI therapy. Patients identified as intermediate-risk by the ELTS score might benefit more from front-line 2G TKI therapy.

EP670 ASCIMINIB RESPONSES IN PONATINIB-PRETREATED PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Background: Resistance or intolerance to second-generation tyrosine-kinase inhibitors (2GTKIs) is a rough issue in chronic myeloid leukemia (CML) patients. Asciminib, not yet commercially available, inhibits ABL kinase activity by a mechanism distinct to that of currently used TKIs and maintains activity against many resistant forms of BCR-ABL1. Recent data from phase I-III trials showed high response rates with a good safety profile in patients failing to 2GTKIs. However, no studies have specifically addressed response rates with asciminib in ponatinib-pretreated (PPT) patients.

Aims: To present data on responses to asciminib in PPT and non-PPT patients in the setting of clinical practice.

Methods: We gathered retrospective clinical data from 31 patients treated with asciminib after failure of several lines of TKI treatment. Eleven patients received ponatinib at some point for a median time of 18 months. A total of 29 patients were included in the efficacy analysis (2 patients were excluded due to short follow-up). We defined failure as either resistance (BCR-ABL1[15] increase despite optimal TKI dosing) or intolerance (unacceptable toxicity leading to TKI termination). Asciminib use was provided by Novartis under a managed-access program (MAP). Data was collected from October 2018 to June 2020 in 25 institutions from the Spanish CML Group (GELMC).

Results: The median time on asciminib for the entire cohort was 9 months (7 in the PPT group and 13 in the non-PPT group). Median time on previous TKI for the entire cohort was 77 months (56 vs 105 for PPT and non-PPT patients, respectively). Median previous TKI lines before asciminib were 4, with no differences for PPT and non-PPT groups. Switch to asciminib was due to resistance in 5/11 (45%) vs 3/20 (15%) for the PPT and non-PPT, respectively, and due to intolerance in 6/11 (55%) and 17/20 (85%) for PPT and non-PPT groups. The median dose of ponatinib was 45 mg in resistant patients and 15 mg in intolerant patients.

Responses rates according to asciminib indication and previous exposure to ponatinib are shown in table 1. The probabilities of maintaining or improving responses were 100%, 56% and 22% for complete cytogenetic response (CCyR), major molecular response (MMR) and MR4.5 respectively in non-PPT group versus 27%, 18% and 0% in PPT group, respectively. Probability of improving baseline responses were 78%, 47% and 22% for CCyR, MMR and MR4.5 respectively in non-PPT group versus 33%, 10% and 0% respectively observed in PPT patients.

Concerning baseline mutational status, 12 (39%) of the 31 patients displayed BCR-ABL1 mutations (only 1 with T315I), with a heterogeneous pattern and no clear association with outcome: 7 patients in the non-PPT group (35%) and 5 patients in the PPT group (45%).

In terms of tolerability, 10/17 (59%) in the non-PPT-intolerant subgroup displayed side effects; whereas in the PPT-intolerant subgroup 3/6 patients (50%) displayed side effects: grade 1 rash, grade 3 pancreatitis, and grade 4 thrombocytopenia, accordingly.

At the end of follow-up, 27 (87%) continued receiving asciminib, 2 suffered from progression to blast phase and 2 patients showed loss of efficacy; notably, these 4 patients were in the PPT group, whereas all non-PPT continued on asciminib.

Best response to asciminib in non-PPT vs PPT patients

	Resistant (n=8)		Intolerant (n=21*)		Total (n=29*)	
	Non-PPT (n=3)	PPT(n=5)	Non-PPT (n=15*)	PPT (n=6)	Non-PPT (n=18*)	PPT (n=11)
CHR[a]	3/3 (100%)	5/5 (100%)	15/15 (100%)	6/6 (100%)	18/18 (100%)	11/11 (100%)
CCyR[a]	2/3 (66%)	1/5 (20%)	14/15 (93%)	2/6 (33%)	18/18 (100%)	3/11 (27%)
MMR[a]	0/3 (0%)	1/5 (20%)	10/15 (67%)	1/6 (17%)	10/18 (56%)	2/11 (18%)
MR4.5[a]	0/3 (0%)	0/5 (0%)	4/15 (27%)	0/6 (0%)	4/18 (22%)	0/11 (0%)
Patients without respective response at baseline						
CCyR[b]	2/3 (66%)	1/5 (20%)	5/6 (85%)	2/4 (50%)	7/9 (78%)	3/9(33%)
MMR[b]	0/3 (0%)	0/5 (0%)	7/12 (58%)	1/5 (20%)	7/15 (47%)	1/10(10%)
MR4.5[b]	0/3 (0%)	0/5 (0%)	4/15 (27%)	0/6 (0%)	4/18 (22%)	0/11 (0%)

Table 1. Responses to asciminib in non-ponatinib-pretreated patients and ponatinib-pretreated patients subgroups. *PPT*: ponatinib-pretreated patients. *CHR*: complete hematological response, *CCyR*: complete cytogenetic response, *MMR*: major molecular response, *MR4.5*: detectable disease with BCR-ABL1^{IS} < 0.0032%. *Two patients were excluded from response analysis due to short follow-up. [a]Patients with CHR, CCyR, MMR, or MR4.5 at baseline were evaluable for hematologic, cytogenetic, or molecular response and were considered responders if they maintained their response. [b]Evaluable patients without a CCyR, MMR, or MR4.5 at baseline.

Summary/Conclusion: Asciminib constitutes a valid treatment option for patients failing 2GTKIs. However, our data suggest that response rates after ponatinib failure are poor, with these patients remaining a high risk group in which alternative treatments are needed.

EP671 OUTCOMES BEFORE AND AFTER DOSE REDUCTION IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA RECEIVING BOSUTINIB OR IMATINIB

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Background: Bosutinib is approved for patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML), at a starting dose of 400 mg once daily (QD) in newly diagnosed patients in chronic phase (CP).
Aims: This analysis evaluated the impact dose reduction has on the outcomes of bosutinib and imatinib in patients with CP CML.
Methods: In the open-label BFORE trial, 536 patients with newly diagnosed CP CML were randomized to receive 400 mg QD bosutinib (N=268) or imatinib (N=268; 3 untreated). Dose could be reduced to 300 mg QD for toxicity. Following sponsor approval, dose reduction to bosutinib 200 mg QD was permitted for 4 weeks maximum; after this time, dose escalation or treatment discontinuation was required. Maintenance of response after dose reduction was defined as having a response >6 months after the first reduction. Database lock: June 12, 2020, 5 years after the last patient enrolled.
Results: In the bosutinib arm, dose reduction to 300 (without further reduction) or 200 mg QD was seen in 82 (31%) and 33 (12%) patients, and median time to dose reduction was 85 and 205 days. In the imatinib arm, 50 (19%) patients had a dose reduction to 300 mg QD, and median time to dose reduction was 92 days. Most common (≥2% of patients) treatment-emergent adverse events (TEAEs) leading to dose reduction were increased alanine aminotransferase (8%), thrombocytopenia (7%), diarrhea (7%), increased lipase (6%), increased aspartate aminotransferase (4%), nausea (4%), neutropenia (3%), rash (3%) and abdominal pain (2%) with bosutinib, and neutropenia (4%) with imatinib.
Of the patients who remained on 400 mg QD bosutinib (n=153) or imatinib (n=214), respectively, 120 (78%) and 139 (65%) achieved major molecular response (MMR). Among patients who had a bosutinib dose reduction to 300 mg QD, 51/82 (62%) had MMR >6 months after dose reduction: 14 (17%) maintained MMR before and after dose reduction and 37 (45%) achieved MMR for the first time after dose reduction. Seven (9%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. In the imatinib arm, 32/50 (64%) patients had MMR >6 months after dose reduction: 9 (18%) maintained MMR before and after dose reduction and 23 (46%) achieved MMR for the first time after dose reduction. One (2%) patient had MMR before dose reduction but discontinued treatment before the next >6 months assessment and 1 (2%) patient lost a previously attained MMR after dose reduction. Among patients who had a bosutinib dose reduction to 200 mg QD, 12/33 (36%) had MMR >6 months after dose reduction: 7 (21%) maintained MMR before and after dose reduction and 5 (15%) achieved MMR for the first time after dose reduction. Six (18%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. Similar trends were seen for complete cytogenetic response.
Summary/Conclusion: Management of TEAEs through bosutinib or imatinib dose reduction enabled patients to continue treatment, with a substantial number of patients achieving MMR for the first time after dose reduction.

EP672 SECOND-LINE BOSUTINIB FOR PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA: FINAL 10-YEAR RESULTS OF A PHASE 1/2 STUDY

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Background: Bosutinib is approved for patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML. In a phase 1/2 study, second-line bosutinib showed durable efficacy and manageable toxicity in patients with imatinib-resistant (IM-R) or imatinib-intolerant (IM-I) Ph+ CP CML.
Aims: The final efficacy and safety analysis of this phase 1/2 study and its extension study (NCT00261846 and NCT01903733) is presented.
Methods: Patients with Ph+ CP CML who received bosutinib starting at 500 mg/day after prior treatment with imatinib only were included. This analysis was based on ≥10 years of follow-up.
Results: 19% of patients were on treatment with bosutinib at year 10, and 13% were still receiving bosutinib at study completion after ≥10 years; 19% completed ≥10 years of follow-up. Median duration of treatment and follow-up were 26 and 54 months, respectively. Median (range) dose intensity was 436 (87–599) mg/day. The most common primary reasons for permanent treatment discontinuation were lack of efficacy (unsatisfactory response or disease progression; 27%) and adverse events (AEs; 26%). In patients with a valid baseline assessment, cumulative complete cytogenetic response (CCyR), major molecular response (MMR) and MR[4] rates were 50%, 42% and 37%, respectively (Table). Responses were durable, with estimated probabilities of maintaining CCyR, MMR and MR[4] >50% after ≥10 years (Table). At 10 years, cumulative incidence of on-treatment progression/death was 24% and Kaplan-Meier (K-M) overall survival 72% (Table). 55 deaths (IM-R: n=41; IM-I: n=14) occurred on study; causes of death were disease progression (n=30), AEs (n=16; none bosutinib-related), other (n=5) and unknown (n=4). Any grade treatment-emergent AEs (TEAEs) occurring in ≥40% of patients were diarrhea (86%), nausea (46%) and thrombocytopenia (42%). Pleural effusion, cardiac and vascular TEAEs occurred in 13%, 12% and 11% of patients, respectively. 28% of patients had AEs leading to permanent treatment discontinuation; the most common (≥2% of patients) were thrombocytopenia (6%), neutropenia (2%) and alanine aminotransferase increased (2%).

Outcome after ≥10 years[a]	IM-R N=195	IM-I N=89	Total N=284
Patients with CCyR, n/N	88/182	42/80	130/262
Cumulative CCyR rate, % (95% CI)	48 (41–56)	53 (41–64)	50 (43–46)
Probability of maintaining CCyR, % (95% CI)[b,c]	61 (49–73)	52 (32–73)	58 (48–69)
Patients with MMR, n/N	58/127	25/70	83/197
Cumulative MMR rate, % (95% CI)	46 (37–55)	36 (25–48)	42 (35–49)
Probability of maintaining MMR, % (95% CI)[b,c]	55 (39–70)	54 (15–93)	56 (41–71)
Patients with MR[4], n/N	50/127	23/70	73/197
Cumulative MR[4] rate, % (95% CI)	39 (31–48)	33 (22–45)	37 (30–44)
Probability of maintaining MR[4], % (95% CI)[b,c]	55 (38–73)	52 (8–96)	56 (39–72)
Cumulative incidence of on-treatment progression/death, % (95% CI)	29 (23–36)	14 (8–23)	24 (20–30)
Overall survival, % (95% CI)[b]	71 (63–79)	73 (60–87)	72 (64–79)

Molecular data not on International Scale and not available for patients in China, Russia, South Africa and India. CCyR imputed from MMR in extension study if valid cytogenetic assessment not available on a specific date.
[a]Outcomes reported after ≥10 years; few events (e.g., initial response, loss of response and death) occurred after year 10.
[b]K-M estimates.
[c]Among responders.

Summary/Conclusion: These 10-year data are consistent with prior results of durable efficacy and manageable toxicity with second-line bosutinib and support long-term bosutinib use in patients with CP CML after imatinib failure.

EP673 TREATMENT-FREE REMISSION IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH LOW-DOSE TKIS. A FEASIBLE OPTION ALSO IN THE REAL-LIFE SETTING?

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Background: Long-term use of TKIs may expose patients (pts) to significant adverse events (AEs) that may affect quality of life. In recent years, treatment-free remission (TFR) has become a new therapeutic goal and is considered feasible also by international expert guidelines. Most clinical trials have indeed demonstrated that this approach is safe in CML pts who have gained a sustained DMR during treatment at a standard dose. In the real-life practice, TKI dose reductions are often required to reduce AEs but their impact on the possibility of attempting a TFR is still a matter of debate.
Aims: To explore the attitude of Italian hematologists towards the prescription of TKIs at a reduced dose and its impact on TFR attempts in CML pts.
Methods: In September 2020 a questionnaire was sent to the 54 centers participating in the Campus CML. This interactive network connects Italian Hematology specialists active in the field of CML with the aim of sharing experiences and updates for the diagnosis and treatment of this disease, the identification and prevention of specific toxicities of the drugs used and also on possible future therapeutic approaches. The online survey consisted of questions regarding the use of reduced doses of TKIs in the clinical practice and the physicians' propensity to offer a TFR to these pts.
Results: The survey was completed by 45 centers (83%). All declared to have CML pts in treatment with low-dose TKIs (total number = 1.579). More in detail, this occurred in 22.4% of pts treated with imatinib, 24.2% with nilotinib, 34.0% with dasatinib, 70.3% with bosutinib and 74.5% with ponatinib. Dose reduction was due to AEs in most cases (70%), while only in the remaining pts TKIs were de-escalated after achieving molecular milestone. Most involved hematologists believed that reduced doses of TKIs should not influence TFR attempts; indeed, this approach was offered to 117 pts. The TKI most frequently used at reduced doses prior to a TFR attempt was imatinib (60 pts), followed by nilotinib (32 pts), dasatinib (22 pts) and, to a lesser extent, by ponatinib (2 pts) and bosutinib (1 patient). Before attempting TFR, 77 pts had received only one TKI, while 33 and 7 pts were, respectively, treated in second or later lines of therapy, with a median TKI duration of 121.8 months (range 16-221.9). At the time of TFR, all pts had already achieved a DMR, with a median treatment duration of 72 months. After a median follow-up from TKI discontinuation of 25 months (range 1.6-128.7), 88 pts (75.2%) were still in TFR. The median time to molecular recurrence (≥MMR) in the entire cohort was 3.9 months (range 1.6-29.6), and a MMR or a DMR was rapidly achieved in all cases after resuming TKI therapy (median time 5.8 months, range 1–25.8).
Summary/Conclusion: In this large series of real-life CML patient management in Italy, treatment with low-dose TKI represents an important reality and, as expected, bosutinib and ponatinib are the drugs more frequently used in this setting. While a third of Italian hematologists still has some uncertainties on the feasibility of attempting a TFR after using reduced doses of TKIs outside of clinical trials, TFR is most often considered a safe option also in the real-life practice in pts treated with TKIs at a reduced dose either because of AEs or due to an optimal response already achieved. Interestingly, only about 25% of our series experienced a molecular recurrence, less than reported in pts treated at a standard dose. Consequently, TFR was not impaired by low-dose TKI regimens. Updated results will be presented.

EP674 COVID-19 IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: DISEASE OUTCOMES AND FIRST VACCINATION DATA IN RUSSIAN FEDERATION

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Background: Due to the challenge of COVID-19 pandemic the prognosis for patients (pts) with hematologic (hem) tumors, including chronic myeloid leukemia (CML), was difficult to make. With the data accumulation and vaccination start in early 2021, a view of the problem begins to change.
Aims: We aimed to describe the disease course of COVID-19, treatment and first vaccination data in pts with CML in Russian Federation.
Methods: A total of 113 CML pts were analyzed: 106 pts with lab-confirmed or suspected COVID-19 and 7 pts vaccinated against COVID-19. Registration of COVID-19 cases was done prospectively during in person or remote consultations from March 2020 till February 2021. The pts were participants of CHRONOS19, a nationwide observational cohort study of adult (≥18 y) pts with wide spectrum of hem diseases (NCT04422470). We performed a sub-analysis for CML and COVID-19 cohort with the data of 3 hem clinics regarding diagnostics, disease course, treatment and outcomes. Additionally, we evaluated the tolerability and first vaccination results in 7 CML pts (Sputnik V in civil vaccination).
Results: Case registration corresponded to incidence in the country with clear 2 "waves": 1st one in March-August (n=35) and 2nd starting from September 2020 (n=71) (fig1). COVID-19 was clinically and/or lab diagnosed and treated according to current national recommendations. CML was newly diagnosed during COVID-19 in 8(8%) pts, while 86(81%) were on treatment and 12(11%) were in treatment-free remission (TFR). One case was in pregnant pt. CML phases were chronic(CP)/accelerated/blast crisis in 95(89,6%), 6(5,4%) and 5(5%) pts respectively. Median (Me) age of pts was 52 years (range 22-75), 58(55%) were male. No CML therapy during COVID-19 was in 34 (32%) pts (interrupted or not started), therapy was held in 67 (63%), no data in 5 (5%). Disease course of COVID-19 was asymptomatic, mild, moderate and severe in 5 (5%), 59 (56%), 29(27%) and 13(12%) pts respectively. No therapy for COVID-19 was in 30 (28%) pts, symptomatic therapy (fever relief, anti-cough, decongestants, vitamins etc) - in 73 (69%) pts, antiviral drugs and antibiotics were used in 28 (26%) and 44 (42%) pts respectively. Anticoagulants, corticosteroids and IL-6 inhibitors were introduced mainly during 2nd wave while hydroxychloroquine was abandoned (fig.1). Hospitalization was in 33(31%) pts, oxygenation was applied in 12 (11%) pts. The outcomes were as follows: 101(95%) pts alive (98 recovered, 3 not yet), 4 (3,7%) pts died (2 due to COVID, 2 to CML progression), 1(1,3%) –no data. No COVID reinfection was detected so far. No factors connected with moderate/severe vs asymptomatic/mild COVID-19 were found when analyzing gender, CML phase, TFR, comorbidities, 1st and 2nd wave, except age≥52 years (p=0,039). A trend of mild disease was in pts taking TKI vs without TKI (p=0,065).
Seven CP CML pts with Me age 63 years (range 50-70) were vaccinated against COVID-19 since December 2020: 2 had the 1st shot and 5 pts completed vaccination. All 7 pts tolerated the procedure well, with no adverse effects. One pt was checked for antibodies 21 days after the 2nd shot and revealed a high level of anti-SARS-CoV-2 IgG with coefficient of positivity 6,2 (reference range 0-0,9).

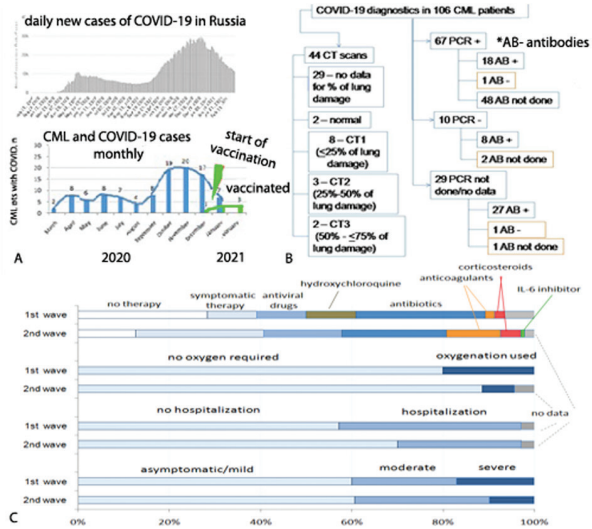


Figure 1. Incidence (A), diagnostics (B) and treatment (C) of COVID-19 in CML patients

Summary/Conclusion: The incidence, disease course and COVID-19 dependent mortality rates in CML pts seem to be similar to common population. Older age is a factor of moderate/severe disease course. The

TKI impact on COVID-19 course and post-vaccination immunity in CML pts need to be studied.

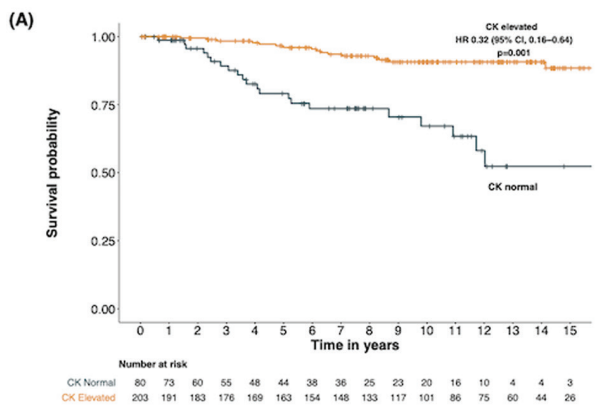
EP675 ASSOCIATION OF CREATINE KINASE ELEVATION WITH CLINICAL OUTCOMES IN CHRONIC MYELOID LEUKEMIA

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Background: Creatine kinase (CK) elevation is seen with tyrosine kinase inhibitor (TKI) treatment for Chronic Myeloid Leukemia (CML). Its correlation with musculoskeletal (MSK) symptoms and treatment outcomes in not well studied.
Aims: To measure the association CK elevation with overall (OS) and event-free survival (EFS) in patients with CML.
Methods: Retrospective, single-centre study on all newly diagnosed chronic phase CML patients from 2001 to 2017 seen and followed by senior author on study at Princess Margaret Cancer Centre, Toronto, Canada. Primary exposure was CK elevation after initiation of first line TKI, defined as two CK values above baseline within any 6 months period. Clinical variables were age, sex, cardiovascular risk factors (smoking, hypertension, diabetes mellitus, and hypercholesterolemia), sokal index and use of second line TKI. Primary outcome was OS, and secondary outcomes were EFS and cumulative incidence of CK elevation. The effect of covariates was measured as hazard ratio (HR, 95% CI) using cox proportional hazard models and compared with log rank test.
Results: Total 283 newly diagnosed CML patients were included. The median age was 49.8 years (18.0-82.0), 54.1% were male. The median follow-up was 8.8 years (IQR 4.4-12.7). The median baseline CK was 100 IU/L (10.0-1490). First line TKI were imatinib (78.1%), followed by dasatinib (11.0%), nilotinib (8.1%) and bosutinib (2.8%). 203 patients (72%) had CK elevation [76% (169/221) on imatinib, 54% (34/62) on second generation TKI (SG-TKI)]. The median time to CK elevation with imatinib was 1.0 years (IQR 0.8-1.3) compared to 1.2 years, (IQR 0.5-3.7) with SG-TKI. There was no difference in the cumulative incidence of CK elevation between imatinib (HR 0.92, 0.64-1.35) and SG-TKI. There was no difference in grade of CK elevation between different TKIs (anova, p=0.57). CK levels of patients with MSK symptoms were higher compared to those without (*t*-test, p=0.02). 3 patients on imatinib had rhabdomyolysis.
38 patients (13.4%) died during follow-up. Using CK elevation as time-dependent covariate, the Kaplan–Meier survival analysis showed that patients with CK elevation had a lower probability of death (7.8%, 16/203) compared to those with normal CK (27.5%, 22/80) (p<0.001). In multivariable Cox regression, the impact of CK elevation on OS remained unchanged: adjusted HRs for OS were 0.31 (0.16–0.60) for CK elevation; 3.39 (1.67–6.84) for intermediate sokal and 5.11 (1.95-13.4) for high sokal risk.
116 patients (41%) were considered for secondary outcome-EFS [98 discontinued treatment-46 suboptimal response or progression, 52-toxicity; 18 patients died without treatment related event]. Using CK elevation as time-dependent covariate, Kaplan–Meier survival function showed that patients with CK elevation had a lower probability of an event compared to those without CK elevation (p=0.003). In multivariable Cox regression, the impact of CK elevation on EFS remained unchanged: adjusted HR for EFS were 0.51 (0.33–0.79) for CK elevation. Other significant variables were intermediate and high sokal risk, SG-TKI (better EFS); higher comorbidities (worse EFS).

Overall survival in chronic myeloid leukemia patients according to CK elevation (n=283)



Summary/Conclusion: The cumulative incidence of CK elevation in CML patients on TKI is 72% with no difference between imatinib and SG- TKI. CK levels correlated with MSK symptoms but rhabdomyolysis was rare. CK elevation independently predicted better OS and EFS. These results inform clinicians on not discontinuing TKI based on laboratory elevation of CK alone.

EP676 FRONTLINE TREATMENT APPROACHES FOR CML IN MYELOID BLAST PHASE: A SINGLE-CENTER EXPERIENCE OVER 2 DECADES

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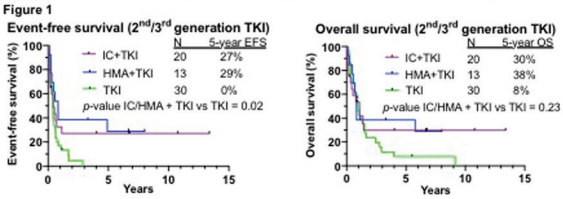
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Background: The natural course of untreated or TKI-resistant chronic myeloid leukemia (CML) is progression to a blast phase (BP), which may be myeloid (MBP) or lymphoid. Over the past 20 years, the advent of tyrosine kinase inhibitors (TKIs) against the BCR-ABL1 fusion protein has dramatically reduced the incidence of CML-BP. However, CML-BP still occurs in some patients, and outcomes remain exceedingly poor with no consensus frontline treatment approach.
Aims: We retrospectively evaluated the outcomes with different frontline treatment approaches in patients with CML-MBP who were treated at our institution over 2 decades.
Methods: Patients were included if they were diagnosed with CML-MBP as defined by ≥20% bone marrow myeloblasts (WHO criteria) between 2000-2019, with or without the presence of concomitant extramedullary (EM) disease, and received frontline therapy for CML-MBP. Patients with EM-only disease were excluded. Patients could have received prior therapy for CML in chronic phase (CP) or accelerated phase (AP) but no prior therapy for BP aside from hydroxyurea. Patients were divided into 4 frontline treatment approaches: 1) intensive chemotherapy (IC)+TKI, 2) hypomethylating agent (HMA)+TKI, 3) TKI alone, or 4) IC alone. We assessed morphologic/hematologic responses per AML IWG 2003 criteria and cytogenetic/molecular responses per CML ELN 2020 criteria. We assessed cumulative incidence of relapse (CIR), event-free survival (EFS), overall survival (OS), and the benefit of allogeneic stem cell transplantation (ASCT).
Results: 104 patients were identified who received frontline treatment for CML-MBP (IC+TKI, n=20; HMA+TKI, n=20; TKI alone, n=56; IC alone, n=8). Baseline patient characteristics are shown in Table 1. Patients who received IC+TKI were younger than other groups. The majority of patients in each group had received at least one prior TKI for treatment of CML CP/AP. A 2nd/3rd generation TKI was used for CML-MBP in 100% of patients treated with IC+TKI, 65% with HMA+TKI, and 54% with TKI alone.
Hematologic, cytogenetic and molecular response rates are shown in Table 1. Given similarities in outcomes between IC+TKI and HMA+TKI, these two groups were combined for analysis (IC/HMA+TKI, n=40). Compared to TKI alone, IC/HMA+TKI resulted in a higher CR/CRi rate (57.5% vs 33.9%, $p<0.05$), higher complete cytogenetic response (CCyR) rate (45% vs 10.7%, $p<0.001$), and led to more patients proceeding to ASCT (32.5% vs 10.7%, $p<0.01$). These superior outcomes with IC/HMA+TKI were observed despite a higher 60-day mortality with combination therapy compared to TKI alone (15% vs 1.8%, $p<0.05$).
With a median follow-up of 6.7 years, long-term outcomes were similar between the IC+TKI and HMA+TKI groups, and both were superior to TKI alone when all patients were considered as well as when analysis was limited to those treated with a 2nd/3rd generation TKI (Figure 1). When using a 2nd/ 3rd generation TKI, IC/HMA+TKI led to improved 5-year CIR (44% vs 86%, $p<0.05$), 5-year EFS (28% vs 0%, $p<0.05$), and 5-year OS (34% vs 8%, $p=0.23$) compared to TKI alone.
Landmark analysis was performed to assess the benefit of ASCT in patients who achieved an objective response (CR/CRi/MLFS). Median time to ASCT was 4.7 months, and long-term survival was superior for patients who proceeded to ASCT (58% vs 22%, $p=0.12$) compared to those who did not proceed to ASCT at the landmark timepoint.

Table 1

	N (%); Median [Range]			
	IC + TKI (N=20)	HMA + TKI (N=20)	TKI (N=56)	IC (N=8)
Age, years	47 [29-83]	56 [37-89]	57 [21-79]	56 [27-74]
De novo CML-MBP	5 (25%)	5 (25%)	3 (5.3%)	0
Year of treatment initiation for MBP	2013 [2007-2018]	2013 [2003-2019]	2004 [2000-2012]	2003 [2000-2003]
Prior TKI exposure for CML	14 (70%)	14 (70%)	32 (60%)	7 (87.5%)
BM blast %	37 [21-64]	40 [28-79]	49 [21-87]	30 (20-60)
Cytogenetic clonal evolution	12 (60%)	15 (75%)	42 (75%)	6 (75%)
Best Response				
CR/CRi	12 (60%)	11 (55%)	19 (33.9%)	1 (12.5%)
CR/CRi/MLFS	16 (80%)	14 (70%)	27 (48.2%)	1 (12.5%)
Time to best response, months	0.9 [0.7-6.9]	2.2 [0.8-5.5]	2.1 [0.6-16.3]	0.6 [0.6-0.6]
CCyR achieved	8 (40%)	10 (50%)	6 (10.7%)	0
Best molecular response				
MMR	3/17 (17.6%)	2/16 (12.5%)	1/47 (2.1%)	0
CMR	2/17 (11.8%)	1/16 (6.3%)	1/47 (2.1%)	0
Proceeded to SCT	7 (35%)	6 (30%)	6 (10.7%)	1 (12.5%)
60-day mortality	3 (15%)	3 (15%)	1 (1.8%)	3 (37.5%)
5-year outcomes				
EFS	27%	19%	5%	0%
OS	30%	28%	13%	0%
5-year outcomes with a 2nd/3rd generation TKI				
EFS	27%	29%	0%	N/A
OS	30%	38%	8%	N/A

Figure 1



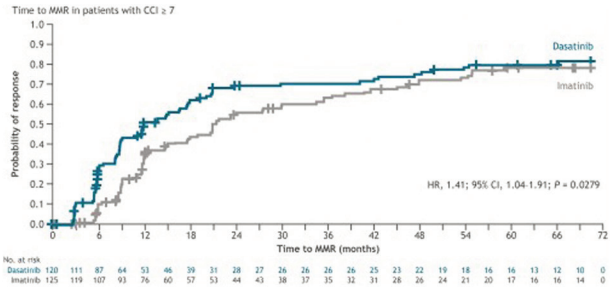
Summary/Conclusion: Compared to patients treated with TKI alone for CML-MBP, treatment with IC+TKI or HMA+TKI leads to improved response rates, CIR, EFS, and OS, particularly for patients treated with a 2nd/3rd generation TKI.

EP677 EFFECT OF COMORBIDITIES ON PATIENT RESPONSES WITH FIRST-LINE DASATINIB VERSUS IMATINIB IN CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE: EXPLORATORY POST HOC ANALYSIS OF DASISION

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Background: Tyrosine kinase inhibitors (TKIs) have dramatically improved the standard of care for patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). In the 5-y follow-up of the phase 3 DASISION study (NCT00481247), dasatinib (DAS) was associated with faster and deeper molecular responses than imatinib (IM) as first-line (1L) therapy for CML-CP. The NCCN guidelines recommend considering multiple factors independent of risk score when selecting TKI therapy, including the presence of comorbidities. Over 50% of pts with CML-CP have ≥1 comorbidity at diagnosis; as such, comorbidities may influence 1L treatment (Tx) choice for most pts.
Aims: Investigate the effect of comorbidities on response outcomes with DAS vs IM via an exploratory post hoc analysis of DASISION at 5-y follow-up.
Methods: DASISION was a multinational, open-label, phase 3 trial assessing DAS vs IM for newly diagnosed CML-CP. Pts were randomized to receive 100 mg DAS (n=259) or 400 mg IM (n=260) QD. Charlson Comorbidity Index (CCI) was retrospectively calculated for each pt at diagnosis. Efficacy and safety data were retrospectively stratified based on CCI score categories 2–4, 5–6, and ≥7 (higher scores indicate higher comorbidity burden). Rates of major molecular response (MMR) and $MR^{4.5}$ were compared between Tx arms using unstratified Cochran–Mantel–Haenszel tests. Time to MMR and $MR^{4.5}$ were evaluated using Kaplan–Meier method with HRs based on Cox proportional hazards models and *P* values from unstratified log-rank tests. CIs for median time to response were calculated using the Brookmeyer and Crowley method. *P* values are descriptive and unadjusted for multiple comparisons.
Results: In total, 14 (3%) pts had CCI 2–4 (DAS 7, IM 7), 260 (50%) had CCI 5–6 (DAS 132, IM 128), and 245 (47%) had CCI ≥7 (DAS 120, IM 125). Baseline characteristics were balanced between groups. Dose reductions of DAS and IM occurred in 14% vs 29% (CCI 2–4 group), 23% vs 12% (CCI 5–6 group) and 54% vs 22% (CCI ≥7 group) of pts, respectively. Responses were greater with DAS vs IM in the CCI 2–4 group (MMR: 85.7% vs 57.1%, *P*=0.2542; $MR^{4.5}$: 71.4% vs 14.3%, *P*=0.0374), and were significantly higher in the CCI 5–6 group (MMR: 81.1% vs 64.8%, *P*=0.0033; $MR^{4.5}$: 42.4% vs 29.7%, *P*=0.0329). Median time to MMR in the CCI 5–6 group was significantly shorter with DAS vs IM (15.0 vs 24.0 months; HR,1.64; *P*=0.0006). In the CCI ≥7 group, response rates were numerically higher (MMR: 70.8% vs 64.0%; $MR^{4.5}$: 45.0% vs 39.2%) and median time to MMR was significantly shorter with DAS vs IM (12.0 vs 21.4 months; HR, 1.41; *P*=0.0279; **Figure**). Rates of grade (gr) 3–4 Tx-related adverse events (TRAEs) were (DAS vs IM): 0% vs 14% (CCI 2–4); 8% vs 9% (CCI 5–6); 24% vs 13% (CCI ≥7). Gr 3–4 TRAEs leading to discontinuation did not occur in the CCI 2–4 group, and were reported with similar frequency with DAS and IM in CCI 5–6 and ≥7 groups. No deaths occurred in the CCI 2–4 group; a similar percentage of pts treated with DAS and IM died in the CCI 5–6 and ≥7 groups.



Summary/Conclusion: In this exploratory post hoc analysis, DAS was effective in all CCI groups, in line with previous findings, suggesting that comorbidities do not negatively affect TKI activity. Response rates were significantly higher with DAS than IM in pts with CCI 5–6, but comparable between Txs in pts with CCI ≥7. Time to response was significantly faster with DAS than IM in both the CCI 5–6 and ≥7 groups, while the frequency of gr 3–4 TRAEs leading to discontinuation was similar between Txs. These findings highlight the benefit of 1L Tx with DAS in pts with CML-CP and a high comorbidity burden.

EP678 HYDROXYUREA PRE-TREATMENT IN CHRONIC MYELOID LEUKEMIA PATIENTS: MORE HARM THAN GOOD?

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Background: The current role of hydroxyurea (hydrea) as a treatment modality in chronic myeloid leukemia (CML) is limited. However, many clinicians still use it as a bridging therapy before starting treatment with tyrosine kinase inhibitors (TKI).
Aims: The objectives of this analysis were to evaluate the use of hydrea in clinical practice in the treatment of CML, and assess the benefits of hydrea pre-treatment on achieving early response milestones and disadvantages such as the occurrence of hematotoxicity during subsequent TKI therapy.
Methods: We performed a retrospective analysis on data from a real-world population-based Dutch registry (The PHAROS CML Registry combined with HemoBase) of newly diagnosed chronic phase CML patients between 2008 and April 2013. Patients were stratified based on having received pre-treatment with hydrea. All time-dependent analyses were performed using the cumulative incidence competing risk (CICR) method with death and progression considered as competing events. The start date of first-line TKI treatment was used as time-point zero in the time-dependent analyses.
Results: From a total of 432 evaluable patients, 194 (45%) patients had received hydrea pre-treatment. Hydrea-treated patients had a higher mean leukocyte count and more often reported presence of

hyperviscosity symptoms (3 *vs* 9%, p = 0.009), constitutional symptoms (36 *vs* 26%, p = 0.049), or symptomatic splenomegaly (26 *vs* 12%, p < 0.001) at diagnosis. However, the majority of hydrea-treated patients had no symptoms of hyperleukocytosis or splenomegaly (66%). Surprisingly, the hydrea-treated group had a significantly longer interval between diagnosis and start of first-line TKI treatment (22 *vs* 15 days, p = 0.002). Also, after the start of TKI therapy, hematotoxicity occurred more frequently in hydrea pre-treated patients (23 *vs* 11%, p < 0.001). There was no benefit observed of hydrea pretreatment for patients achieving a CHR at 1 or 3 months, nor for CCyR and MMR at the ELN-set response milestones during the first year of treatment. The proportion of patients achieving MMR at 12 months was significantly higher in the non-hydrea group (55% *vs* 43%, p = 0.05), however this difference was no longer significant when correcting for ELTS-score and type of first-line TKI in a cox-regression model.

Summary/Conclusion: Hydrea pre-treatment is used in nearly half of newly diagnosed CML patients, including many patients without a high leukemic load and/or symptom burden. We observed a significantly longer delay in starting first-line TKI treatment in hydrea-treated patients. Furthermore, hydrea pre-treatment was associated with a higher rate of hematotoxicity during first line TKI treatment and no apparent benefit in achieving the ELN-defined response milestones. Our data suggest an unneeded pre-treatment use of hydrea when a diagnosis of CML is under consideration and recommend restricting the use of hydrea pre-treatment to patients with clinically significant (symptomatic) hyperleukocytosis or symptomatic splenomegaly. More restrictive use of hydrea may shorten the delay of TKI treatment initiation at diagnosis and help limit hematotoxicity of TKI therapy.

EP679 FRENCH REAL–LIFE OBSERVATIONAL STUDY "TOPASE" EVALUATING SAFETY AND EFFICACY OF PONATINIB CONFIRMS INDUCTION OF DEEP MOLECULAR RESPONSES IN 110 RESISTANT OR INTOLERANT CML PATIENTS

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Background: Ponatinib is a 3rd generation tyrosine kinase inhibitor (TKI) indicated in chronic phase (CP), accelerated phase (AP) and blast phase (BP) CML as well as in patients (pts) with T315I mutation.

Aims: TOPASE is an observational cohort, designed to evaluate, with a 2 to 4 years follow-up period, the efficacy and safety of ponatinib in routine clinical practice.

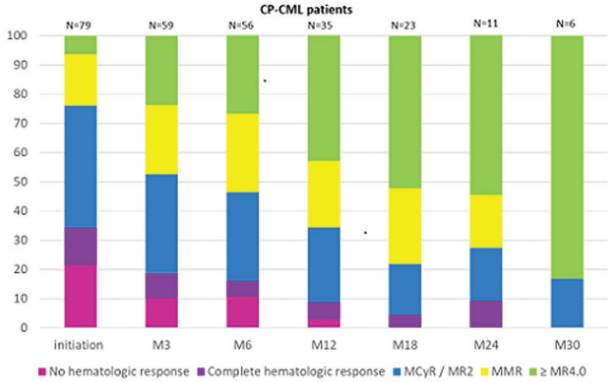
Methods: This interim analysis reports results from data of pts included in 42 CML French centers from February 2018 to December 2020.

Results: 110 pts were registered, 97 in CP and 13 in AP/BP; median age was 58.7 [20-90] years. Reason for prescription was resistance in 73% and intolerance in 26% of pts. Ponatinib was prescribed in 14 % of cases in second line and in 53% in third line of treatment. Last treatment administered prior to ponatinib was dasatinib (39%), bosutinib (24%), nilotinib (24%), imatinib (10%) and ABL001 (2%). Twenty seven of the 69 pts screened for mutations harbored a BCR-ABL mutation (T315I in 13). Thirty two per cent had an history of hypertension and 30% were treated for hypertension at inclusion. In CP-CML pts, ponatinib starting dose was 15mg/d in 37%, 30 mg/d in 43% and 45 mg/d in 20%. Respectively in each subgroup the percentage of intolerant pts were: 42, 24 and 10 %.Considering AP/BP pts, ponatinib initiating dose was 45 mg/d in 62%, 30 mg/d in 23% and 15 mg/d in 15% of pts. At the initiation of ponatinib, out of 93 CP-CML pts evaluable for response, 26% of pts were in MMR or beyond, 39% were in MCyR and/ or MR2, 14% were in CHR and 21% were not in CHR. Efficacy analysis was performed on all the 59 CP-CML pts with BCR-ABL1 > 0.1% at ponatinib start and with at least one evaluation under treatment, as defined in the protocol.After a median treatment duration of 10.7 months [0.4; 36.4], MMR was achieved in 30 pts (51%) (Table 1). Overall, the global responses in all evaluable patients showed a shift towards deeper responses up to 30 months (Table 2). In 37 pts (34%) [31 in CP and 6 in AP/BP] ponatinib was discontinued early after a median exposure of 5.8 months. Reasons for discontinuation were lack of response or progression (n=15), adverse event (n=14) or another reason (n=8). Treatment related adverse events (TRAE) were reported in 52% of pts (n=52) (serious = 11% [n=11]). Most common TRAE (all/serious) were hypertension (9/1), constipation (5/1), dry skin (5/0), lipase increase (4/0).Cardiovascular events (5/4) included acute coronary syndrome (1), angina pectoris (1), aortic insufficiency (1), atrial fibrillation (1), pericardial effusion (1) and cerebrovascular events (2/2) included ischemic stroke and cerebrovascular accident. Four pts died during follow-up: 1 from disease progression (pt included in AP/BP) and 3 from AE (1 general status alteration, 1 pancytopenia [pt included in AP/BP] and 1 from pulmonary embolism, the only AE considered as related to ponatinib). More complete data analysis on the incidence of TRAEs according to the dose of ponatinib are currently conducted and will be presented.

Table 1: Pts in CP and without MMR at ponatinib initiation who achieved MMR or above at least once on therapy according to initial daily dose of Ponatinib.

CP phase at initiation	Dose at initiation (mg/day)			
	15 mg (n=17)	30 mg (n= 28)	45 mg (n=14)	Total (n=59)
MMR (or above) at least once during follow-up	6 (35%)	17 (61%)	7 (50%)	30 (51%)

Figure 1:Therapeutic response during follow-up



Summary/Conclusion: Results from this real-world French cohort confirm the high efficiency of ponatinib in TKI-resistant and intolerant CML pts. Ponatinib induces deep molecular responses, with an acceptable safety profile. Vascular events rate seems low in this study, which is the largest prospective observational study on ponatinib use in Europe.

EP680 WITHDRAWAL SYNDROME AFTER TYROSINE KINASE INHIBITORS DISCONTINUATION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Background: Withdrawal syndrome (WS) - a musculoskeletal pain after discontinuation of tyrosine kinase inhibitors (TKI) in patients (pts) with chronic myeloid leukemia (CML) - was described in the treatment-free remission (TFR) studies with a weighted mean incidence of 27% [Chen et al, Front Oncol., 2019]. The pathophysiological mechanisms of WS and predisposing factors have not been well established.

Aims: To characterize the outcomes of WS and evaluate factors associated with WS in a large cohort of CML pts who discontinued TKI therapy.

Methods: WS was evaluated in prospective pts group (PG, n=109) and in retrospective group (RG, n=74). The key inclusion criteria: CML chronic phase, any TKI therapy ≥ 3 years, deep molecular response (DMR) duration ≥2 years in PG and ≥1 year in RG. DMR was defined as at least MR4 (BCR-ABL ≤ 0,01% IS). TKI were restarted in both groups in case of major MR (MMR, BCR-ABL>0,1% IS) loss. In 34 pregnant pts (24 and 10 in RG and PG accordingly) TKI were restarted in case of MR2 (BCR-ABL>1%) loss.

WS was defined as a musculoskeletal pain newly observed after TKI cessation or as a worsening of previously observed symptoms in pts with medical history of locomotion system diseases. WS was registered In PG every month (mo) during first 6 mo after TKI cessation, every 2 mo from 6 to 12 mo and every 3 mo thereafter. The data in RG were collected according to medical records.

Age, gender, Sokal score, duration and the type of TKI therapy, presence of locomotion system diseases and pregnancy were evaluated in pts with and without WS. Comparison was done with Mann–Whitney U-test and Chi-squared test. The survival without MMR loss was evaluated by Kaplan-Meier method.

Results: Median (Me) time of observation was 33 mo (range 1-136). MMR loss free survival at 36 mo was 49% and 43% in PG and RG respectively (p=0,96).
WS was observed in 49(27%) of 183 pts: 41(38%) in PG and 8(11%) in RG. WS was presented as arthralgia, myalgia, ossalgia or combination of symptoms in 37(76%), 17(35%), 4(8%) and 35(71%) pts. Newly observed and worsening symptoms were in 35(71%) and 14(29%) pts respectively. Me time to WS appearance was 2 mo (range 1-7). Me duration of WS was 5 mo (range 1-35). WS grade 1-2 was in 45(92%) pts, grade 3 in 4(8%) pts.
TKI therapy was resumed in 15(31%) of 49 pts with WS: in 13 pts with MMR loss, in 1 pt with 3rd grade WS symptoms and in 1 pt due to physician decision. WS was resolved in all 15 pts at 1-3 mo after TKI restart. Thirty-four (69%) pts with WS remained in TFR. WS completely resolved in 31 and gradually decreased up to 1st grade in 3 pts at the time of analysis.
WS was resolved spontaneously or with nonsteroidal anti-inflammatory drugs in 14(45%) and 17(55%) pts accordingly. Two of 17 pts also received glucocorticoids. The outcomes of WS are presented on figure 1. An older age (p<0,0001), longer duration of TKI therapy (p<0,0001) and the presence of locomotion system diseases (p=0,022) were observed in pts with WS (table 1). The development of WS was not registered in any of pregnant pts (p<0,001).

Figure 1.
Withdrawal syndrome outcomes in 49 CML patients

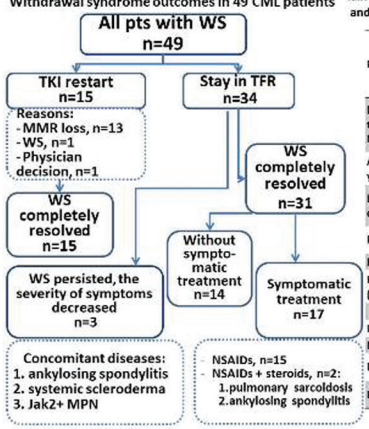


Table 1. Comparative analysis of patients with and without withdrawal syndrome (n = 183)

Parameters	Pts with WS n=49	Pts without WS n=134	P value
Duration of TKI treatment, Me (range), years	119 (40-218)	72 (6-181)	<0,0001
Age, Me (range), years	53 (24-80)	37 (21-86)	<0,0001
Locomotion system diseases, n (%)	18 (37)	27 (20)	0,022
Pregnancy, n (%)	0 (0)	34 (25)	<0,001
Female, n (%)	28 (57)	84 (63)	0,496
High Sokal risk, n (%)	3 (6)	19 (14)	0,188
TKI before discontinuation:			
Imatinib, n (%)	37 (76)	86 (64)	0,149
Nilotinib , n (%)	11 (22)	36 (27)	0,545
Dasatinib, n (%)	1 (2)	11 (8)	0,136
Bosutinib, n (%)	0 (0)	1 (1)	0,545

Summary/Conclusion: The rate of WS in the large CML cohort was 27%. We evaluate a higher WS incidence in PG compared to RG (38% vs 11%). The differences may be cause by methods of data collection: prospective observation probably allowed to more accurately identifying the presence of WS. On the other hand, there were more pregnant pts in RG, and we found for the first time that WS doesn't develop in pts with pregnancy. A longer period of TKI exposure, older age and the history of locomotion system diseases were associated with the development of the WS.

EP681 FIRST INTERIM RESULTS OF THE RUSSIAN PROSPECTIVE STUDY OF REDUCTION AND DISCONTINUATION TREATMENT OF TKI (READIT) IN CHRONIC MYELOID LEUKEMIA PATIENTS WITH DEEP MOLECULAR RESPONSE

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Background: TKI dose reduction may be safely used for AE correction or prevention in pts with optimal response. The feasibility of TKI dose reduction as a step before treatment-free remission (TFR) phase has been confirmed in several trials. However, no unified scheme has been developed for each TKI. The connection of plasma blood TKI concentration with the AE and response preservation has not been studied.
Aims: To provide the first interim results of the «Study of REduction And DIscontinuation Treatment of TKI (READIT)» (NCT 04578847): evaluation of the response rates and first data of imatinib (IM) plasma blood concentrations after dose reduction.

Methods: Two consecutive phases are planned in the trial: 1) TKI dose reduction phase for at least 12 months (mo), 2) TFR observation (24 mo). The TKI dose reduction phase consists of two 6 mo steps: 1st step (300 mg for IM, 400 mg for nilotinib (NIL), 50 mg for dasatinib (DAS) and 300 mg for bosutinib (BOS)) and 2nd step (25 mg for DAS and 200 mg for IM, NIL and BOS) of TKI dose reduction. Inclusion criteria: adult CML in chronic phase (CP), TKI therapy ≥ 3 years, major molecular response (MMR, BCR-ABL1 ≤0,1%) ≥2 years and deep molecular response (DMR, BCR-ABL1 ≤0.01%) ≥1 year. Recruitment of patients in reduced doses was possible, provided that the duration of the current therapy is at least 6 mo. Treatment by TKI doses of previous step was resumed in case of confirmed MMR loss (BCR-ABL>0.1% in two samples).
Plasma blood concentration was measured for IM (24±2 hours (Cmin) and 4 hours (Cmax) after drug intake). We used the Mann-Whitney U-test for comparative analysis.
Results: A total of 70 CML pts were included from Dec.2019 till March 2021. The baseline characteristics: male 41%, Median (Me) age 56 years (range 23-74); Me TKI therapy duration 6,3 years (range 2.5-18.9); Me duration of MMR and DMR was 3,3 years (range 2-11,2) and 2 y (range 1-11,2), respectively. At baseline 46 (66%) pts received IM (39 pts-400 mg, 3 pts–300 mg, 4 pts–200 mg) and 24 (34%) pts - second-generation (2G) TKI: NIL - 13 pts (6 pts-800-600 mg, 6 pts-400 mg, 1 pt–200 mg), DAS- 6 pts (4 pts-100-70 mg, 2 pts–50 mg), BOS- 5 pts (1 pt–500 mg, 2 pts–300 mg, 2 pts–200 mg).
Thirty-six pts have completed 1st dose reduction step. Three pts on IM lost DMR (1 pt-after 3 mo, 2 pts-after 6 mo dose reduction), no cases of DMR loss in the 2G TKI group. Twenty-one pts completed 2nd step of dose reduction. Two pts lost DMR after 3 mo: 1 pt on IM and 1 pt on DAS. *(Fig.1)*. Of those 5 pts 4 were restored DMR at the same dose. There were no cases of confirmed loss of MMR during the dose reduction phase.
We analyzed the IM concentration in 98 plasma blood samples (Cmax-in 32, Cmin–in 66). There was a significant difference in Cmin of IM 400 mg, 300 mg and 200 mg (p=0.0019) and no difference in Cmax of IM 300 mg and 200 mg. (p=0.078) *(Fig.2)*.
No difference in IM concentration (Cmin and Cmax on 300 and 200 mg) was in 5 pts who lost DMR compared to pts without DMR loss. No significant difference IM 400 mg Cmin was in pts with and without AE (p=0.26).

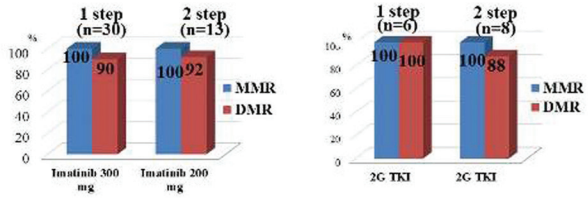
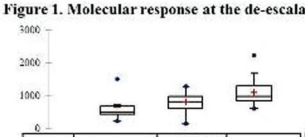
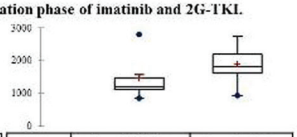


Figure 1. Molecular response at the de-escalation phase of imatinib and 2G-TKI.



	Cmin IM 200 mg (ng/ml)	Cmin IM 300 mg (ng/ml)	Cmin IM 400 mg (ng/ml)
No pts.	6	28	32
Min	232,8	150,5	621,7
Max	1515	1284	2231
Me	506,75	815,4	989,4



	Cmax IM 200 mg (ng/ml)	Cmax IM 300 mg (ng/ml)
No pts.	6	26
Min	852,8	927,1
Max	2800	3167
Me	1217	1810,5

Figure 2. Concentration (Cmin and Cmax) of IM 400 mg, 300 mg and 200 mg.

Summary/Conclusion: No MMR loss was detected during therapy with 1st and 2nd step of TKI dose reduction and about 90% of pts remained in DMR. This proves the safety of TKI treatment at reduced doses. The results will be updated within a longer follow-up in order to evaluate the impact of de-escalation phase on TFR rates. The role of different TKI concentrations will be studied.

EP682 A SURVEY OF HEALTHCARE PROFESSIONALS IN THE UNITED KINGDOM TO DESCRIBE CURRENT PATHWAYS AND MANAGEMENT PRACTICES IN CHRONIC MYELOID LEUKAEMIA: THE ADAPT CML SURVEY

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Background: A survey of healthcare professionals in the UK to describe current pathways and management practices in chronic myeloid leukaemia:the ADAPT CML survey.
Aims: To understand the current diagnosis (Dx), treatment (Tx) and management, including unmet need, landscape for UK patients (pts) with chronic phase chronic myeloid leukaemia (CML-CP).
Methods: We conducted a survey with 46 Haematology consultants (27 from district general hospitals [DGH]; 19 from tertiary centres [TC]). Structured interviews with Medical Science Liaisons from Novartis, were conducted between July and October 2020. Responses were descriptively analysed.
Results: Most (70%) respondents saw 5-10 newly diagnosed CML-CP pts per year (43%, 39%, 17% had a current total CML-CP pts population estimate of ≤50, >50 ≤100, and >100 respectively). All respondents stated they routinely use physical examination, white blood counts, platelet counts, haemoglobin counts and blood film in their CML diagnostic work-up, although only 89% used chromosome banding analysis (CBA). Information on cardiovascular (CV) risk most commonly captured routinely in pt notes prior to tyrosine kinase inhibitor (TKI) initiation were comorbidities (98%), smoking status (98%) and CV history (91%), while total cholesterol (61%) and blood glucose (52%) were less frequently captured. Only 32% used QRisk assessment. Sokal remained the most commonly used prognostic scoring tool (76%).
The median (interquartile range) estimated percentage of pts on different lines of treatment (LoT) at DGH were 1st line (1L): 66% (55%–75%); 2nd line (2L): 25% (20%–32.5%); 3rd line (3L): 10% (5%–10%). At TC, 1L: 57.5% (50%–61.5%); 2L: 30% (21.25%–30%); 3L: 16.5% (10%–20%). Regardless of LoT or reason for prior TKI discontinuation (intolerance [INT]/resistance [RES]), major molecular response was the main response goal in 1L, 2L and 3L. INT was the most cited reason for switching to 2L (67%) or 3L (54%) TKI, while switch to 4L was RES (80%). Impact on quality of life (QoL) (85%) and tolerability affecting compliance (80%) were the most cited definitions of TKI INT. The most commonly reported choice of TKI was imatinib (98%) for 1L, dasatinib (50%) or nilotinib (41%) for 2L and a 2nd generation TKI (39%), TKI based on mutation profile (37%), or bosutinib (22%) for 3L. Additional factors influencing TKI choice at each LoT (not mutually exclusive) are listed in Table 1. In the first and subsequent years of TKI use, all respondents reported frequent monitoring of response by RQ-PCR or cytogenetics (78% using BCR-ABL1 RQ-PCR only); in line with ELN recommendations.
Most respondents (70%) used ELN2020 to guide patient management. Increased frequency of monitoring (65%) and evaluation of compliance (65%) were the most cited actions following an ELN warning response. For pts with >1 warning response or a failure response, a switch in therapy (72%/93%, respectively) and mutation analysis (76%/89%, respectively) were the most cited actions taken. Most frequently cited unmet needs in CML per line were improving QoL (1L, 48%), TKI toxicity (2L, 63%) and RES to current options (3L,72%).

Table 1. Factors influencing choice of tyrosine kinase inhibitor by line of treatment

Factors that play a part in decision-making process when selecting a TKI for a patient with CML-CP [1]	Line of treatment (L), N (% [n=46])				
	1L	2L (after 1L INT)	2L (after 1L RES)	3L (after 2L INT)	3L (after 2L RES)
Efficacy	31 (67%)	31 (67%)	36 (78%)	29 (63%)	34 (74%)
Safety profile	32 (70%)	34 (74%)	32 (70%)	32 (70%)	25 (54%)
Tolerability	35 (76%)	39 (85%)	29 (63%)	37 (80%)	29 (63%)
Quality of life	22 (48%)	28 (61%)	23 (50%)	23 (50%)	17 (37%)
Dosing regimen	16 (35%)	20 (43%)	15 (33%)	12 (26%)	8 (17%)
Comorbidities	45 (98%)	41 (89%)	37 (80%)	39 (85%)	32 (70%)
Age	33 (72%)	22 (48%)	24 (52%)	23 (50%)	20 (43%)
CML progression risk score	28 (61%)	13 (28%)	16 (35%)	10 (22%)	10 (22%)
CV risk score	31 (67%)	30 (65%)	33 (72%)	24 (52%)	24 (52%)
Patient choice	19 (41%)	23 (50%)	16 (35%)	16 (35%)	12 (26%)
Cost	14 (30%)	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Guidelines	27 (59%)	25 (54%)	25 (54%)	20 (43%)	20 (43%)
Aiming for TFR	24 (52%)	16 (35%)	9 (20%)	4 (9%)	2 (4%)
Standard local management choice	16 (35%)	8 (17%)	8 (17%)	6 (13%)	7 (15%)
Physician experience	13 (28%)	19 (41%)	18 (39%)	19 (41%)	19 (41%)
Mutational profiling/screening	0 (0%)	0 (0%)	5 (11%)	2 (4%)	5 (11%)
Other	1 (2%)	0 (0%)	0 (0%)	2 (4%)	2 (4%)

1 not mutually exclusive

Summary/Conclusion: The survey suggests TKI tolerability remains an unmet need in both 1L and 2L CML treatment while TKI resistance is more a concern in later lines. The survey also suggests management of CML in UK is broadly in line with ELN recommendations. However, it also highlights areas for improvement for optimal pt management including the need for well documented CV risk assessment, CBA in all diagnostic workup, mutation analysis in all warning/failure, and increased evaluation of TKI compliance.

EP683 TREATMENT ADHERENCE IN CHRONIC MYELOID LEUKEMIA PATIENTS

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RECEIVING TYROSINE KINASE INHIBITORS

Background: Oral tyrosine kinase inhibitors (TKIs) are the standard of care for chronic myeloid leukemia (CML). TKIs are administered in an outpatient setting for an indefinite period which may negatively impact adherence. Non-adherence to TKIs is associated with disease progression.
Aims: This study was designed to determine the proportion of CML patients non-adherent to their TKIs regimen and their outcome. The secondary objective was to identify the influence of patient characteristics on TKIs adherence.
Methods: Cross-sectional retrospective chart and dispensing record reviews were performed to identify patients receiving a TKI (imatinib, nilotinib and dasatinib) from January 2012 to December 2018. Adherence was evaluated using the medication possession ratio.
Results: With a median follow-up of 72 months, 83 patients with CML were included in our study. 16 (19%) patients were considered non-adherent to treatment. At 18 months of treatment, a major molecular response (MMR) was obtained in 61 (73.5%) patients. The 5-year event-free survival (EFS) of adherent patients was better than those who did not adhere to TKIs: 86% vs 61% (p = 0.0039). The rate of MMR was higher in adherent patients: 89% vs 6% (p <0.0001). 7 (44%) of non-adherent patients had grade 3 or 4 TKIs toxicity (p <0.001), while a low level of education was found in 11 (69%, p = 0.01). After multivariate analysis, only the occurrence of severe side effects of TKIs was predictive of patient non-adherence.
Summary/Conclusion: Non-adherence to TKIs of patients with CML should always be considered as a cause of treatment failure. It requires a good therapeutic education of the patients, and a better management of TKIs side effects.

EP684 THE EFFECT OF BODY MASS INDEX ON EFFICACY AND SAFETY OF BOSUTINIB OR IMATINIB IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA

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Background: Bosutinib is approved for the treatment of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML. Body mass index (BMI) was shown to influence treatment response with front-line dasatinib vs imatinib.
Aims: We report the efficacy and safety of bosutinib and imatinib by BMI in patients with newly diagnosed CP CML.
Methods: In the open-label BFORE trial (NCT02130557), patients were randomized to receive 400 mg once daily bosutinib or imatinib. Outcomes were assessed according to baseline BMI ≥25 or <25 kg/m^2. This post hoc analysis was based on the final 5-y analysis (database lock: June 12, 2020).
Results: In the bosutinib and imatinib arms, respectively, 149 (56.4%) vs 115 (43.6%) patients and 145 (54.3%) vs 122 (45.7%) patients had BMI ≥25 vs <25. In both the bosutinib and imatinib arms, median

Treatment duration and time on study was 55 mo for patients with BMI ≥25 or <25; respective median dose intensity was 394 vs 393 mg/d and 400 vs 400 mg/d. Molecular response (MR) rates are shown in the table. Cumulative incidence of major MR was similar in patients with ≥25 vs <25 receiving bosutinib (HR 0.99; 95% CI 0.74–1.31) or imatinib (HR 1.09; 95% CI 0.81–1.47). Event-free survival and overall survival rates at 60 mo are shown in the table. Most common reasons for treatment discontinuation were adverse events (AEs) (bosutinib 28.2 vs 20.0%; imatinib 13.3 vs 10.7%) and lack of efficacy (bosutinib 5.4 vs 5.2%; imatinib 16.1 vs 19.8%). In patients with BMI ≥25 vs <25, dose reductions and interruptions due to treatment-emergent AEs (TEAEs) occurred in 43.6 % vs 46.2% and 66.4% vs 69.7% of patients with bosutinib and 24.5% vs 24.6% and 40.6% vs 50.8% with imatinib. Any grade TEAEs in ≥30% of patients with BMI ≥25 vs <25 were diarrhea (73.8 vs 73.1%), nausea (40.9 vs 31.9%), thrombocytopenia (30.9 vs 41.2%), increased alanine (37.6 vs 28.6%) and aspartate aminotransferase (30.2 vs 20.2%) with bosutinib and diarrhea (49.0 vs 29.5%), nausea (46.2 vs 37.7%), muscle spasms (33.6 vs 26.2%), neutropenia (14.7 vs 32.0%) and thrombocytopenia (10.5% vs 30.3%) with imatinib.

	Bosutinib			Imatinib		
	BMI ≥25 n=149	BMI <25 n=115	OR (95% CI)*	BMI ≥25 n=145	BMI <25 n=122	OR (95% CI)*
Cumulative rate by 60 mo, %						
MMR	73.2	74.8	0.84 (0.48–1.50)	66.2	68.1	1.18 (0.69–2.01)
MR[4]	57.0	59.1	0.89 (0.54–1.47)	49.7	46.7	1.06 (0.64–1.75)
MR[4,5]	45.6	50.4	0.76 (0.46–1.25)	39.3	33.6	1.30 (0.76–2.21)
			HR (95% CI)*			HR (95% CI)*
Cumulative incidence of on-treatment progression/death at 60 mo, %	5.4	8.7	0.69 (0.28–1.70)	1.4	18.9	0.07 (0.02–0.30)
Kaplan-Meier OS at 60 mo, %	97.1	91.9	0.36 (0.11–1.18)	98.5	90.0	0.17 (0.04–0.76)

Note: OR >1 and HR <1 favor BMI ≥25 kg/m².
* Adjusted for Sokal risk group and region as determined at randomization.
MMR=major molecular response; OS=overall survival

Summary/Conclusion: Efficacy of bosutinib was consistent in patients with BMI ≥25 or <25; however, with imatinib a low (vs high) BMI appeared to be associated with worse survival outcomes. Differences in certain TEAEs were observed between BMI subgroups in both treatment arms.

Enzymopathies, membranopathies and other anemias

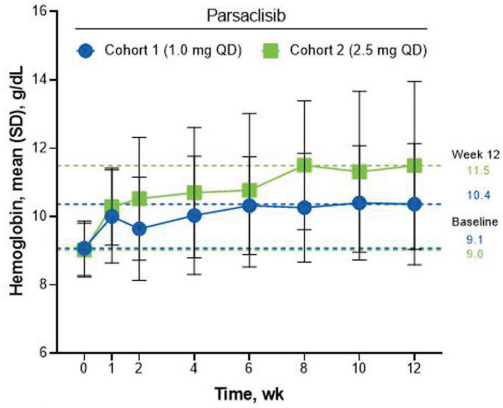
EP685 EFFICACY AND SAFETY RESULTS FROM AN OPEN-LABEL PHASE 2 STUDY OF PARSACLISIB FOR THE TREATMENT OF AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

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Background: There are no approved therapies for AIHA, a rare acquired condition caused by autoantibody-mediated decompensated destruction of red blood cells. The phosphatidylinositol 3-kinase δ inhibitor parsaclisib has shown efficacy in preclinical models of autoantibody-mediated diseases.
Aims: To describe preliminary 12-week efficacy and safety from an ongoing, multicenter, open-label phase 2 trial (NCT03538041) of parsaclisib in patients with primary AIHA.
Methods: Eligible patients were aged ≥18 years; had a diagnosis of warm AIHA (wAIHA), cold agglutinin disease (CAD), or mixed-type AIHA without an underlying lymphoproliferative malignancy; hemoglobin (Hgb) ≥7–≤10 g/dL; and failure of ≥1 standard therapy. Concomitant use of low-dose corticosteroids (≤20 mg/d prednisone equivalent) was permitted. After providing informed consent, patients received parsaclisib for 12 weeks at a starting oral dose of 1.0 mg once daily (QD; cohort 1) or 2.5 mg QD (cohort 2; enrolled after ≥6 patients with wAIHA in cohort 1 completed 6 weeks). Patients in cohort 1 could have their dose increased to 2.5 mg QD after 6 weeks if they had not achieved meaningful clinical response and/or required transfusions; those in cohort 2 could have dose reductions to 1.0 mg QD for tolerability. Patients achieving clinical benefit could continue to receive parsaclisib in an extension period. Primary endpoints were efficacy (proportion of patients with complete response [CR; Hgb ≥12 g/dL] or partial response [PR; Hgb 10–12 g/dL or ≥2 g/dL increase from baseline] at any visit from Week 6–12) and safety (treatment-emergent adverse events [TEAEs]).
Results: A total of 21 patients (cohort 1, n=10 [8 patients had a dose increase]; cohort 2, n=11) were enrolled and received parsaclisib; 17 patients (81%) completed 12 weeks of treatment. Mean (SD) age was 58.8 (16.6) years; 11 patients (52%) were female and 20 (95%) were White. Fourteen (67%), 4 (19%), and 3 (14%) patients had wAIHA, CAD, and mixed AIHA, respectively, and 6 (29%) had transfusions in the past year. Mean (SD) Hgb at baseline was 9.0 (0.8) g/dL and was similar between cohorts. Overall, 7 patients (33%) achieved CR (cohort 1, n=2 [20%]; cohort 2, n=5 [45%]) and 14 (67%) had PR (cohort 1, n=6 [60%]; cohort 2, n=8 [73%]) at any visit from Week 6 to 12. Dose-dependent increases from baseline in Hgb were observed over time, with cohort 2 (2.5 mg QD) achieving mean Hgb >10 g/dL by Week 2 (**Figure**). Other hemolytic markers including haptoglobin, reticulocytes, indirect bilirubin, and lactate dehydrogenase trended toward normalization. TEAEs occurred in 18 patients (86%). Five patients (24%) had grade ≥3 TEAEs, with only neutropenia occurring in >1 patient (n=2 [10%]). One patient (5%) had a serious TEAE (hemolytic anemia; deemed unrelated to treatment). Treatment-related AEs (TRAEs) were reported in 6 patients (29%); pruritic rash was the only TRAE occurring in >1 patient (n=2 [10%]), and neutropenia and thrombocytopenia were the only grade ≥3 TRAEs (n=1 [5%] each). TEAEs led to dose interruption in 4 patients (19%) and included neutropenia (n=2 [10%]), diarrhea (n=1 [5%]), and hepatotoxicity (n=1 [5%]; deemed unrelated to parsaclisib). One patient (5%) in cohort 1 discontinued parsaclisib due to a TEAE (thrombocytopenia). There were no fatal TEAEs.

Figure. Hemoglobin Levels at Each Study Visit



QD, once daily.
Dashed lines indicate mean hemoglobin (g/dL) at baseline and Week 12 for each cohort.

Summary/Conclusion: Parsaclisib was generally well tolerated, and treatment resulted in durable normalization of Hgb levels as early as Week 2. Parsaclisib has the potential to be an effective oral treatment for both wAvIHA and CAD and warrants further clinical investigation.

EP686 RARE ANEMIA DISORDERS EUROPEAN EPIDEMIOLOGICAL PLATFORM (RADEEP): DISTRIBUTION OF PATIENTS AFFECTED BY PYRUVATE KINASE DEFICIENCY IN EUROPE

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Background: Pyruvate kinase deficiency (PKD) is an ultra-rare chronic hereditary hemolytic anemia of variable severity, ranging from mild anemia to life-long transfusion dependence. Conventional treatment consisting of transfusions and splenectomy is challenged by clinical trials of PK activators (e.g. Mitapivat) and lentiviral gene therapy. Mild cases are often not monitored for long-term complications resulting from permanent haemolysis. In addition, lack of standardized diagnostic procedures combined with a low prevalence results in a significant number of undiagnosed or misdiagnosed patients. Consequently, this hampers access to proper treatment options for PKD patients in Europe.

Aims: The aim of this study was to assess the distribution of PKD patients in Europe in order to improve diagnosis and follow-up rates and to facilitate access to available treatment options by patients suffering from PKD.
Methods: The study was conducted through RADeep, which is endorsed by ERN-EuroBloodNet. Up to 145 centres dealing with RADs from 16 European countries were included in the study. Data on PKD patients in follow-up was requested, stratified by age range, adult and paediatric (<18) and by severity according to two main variables: splenectomy and regular transfusion, which was defined as >6 transfusions per year. Data on number of diagnosis in the last 25 years was requested only from diagnostic centres. Data was correlated to a country's total population (2020). Based on highest frequency, estimations were calculated for the expected number of PKD patients in all participating countries.
Results: Data on 499 PKD patients in follow-up and 611 diagnosed PKD patients retrieved from 84 medical centres from 15 European countries is shown on figure 1. Highest frequency for both PKD patients in follow-up and PKD diagnosis was found in Denmark, respectively 4,47 and 4,81 per million. This is in line with previous published data on PKD prevalence, with estimations ranging between 3,2 and 8,5 per million. Based on the PKD diagnosis frequency in Denmark, we calculated the expected number of PKD patients in the rest of participating countries. Results showed an expected number of PKD patients of 1.995, meaning that our study is covering on average 25% of PKD patients in follow-up and 31% of diagnosed PKD cases. Important differences on PKD patients in follow-up coverage are found among countries, from 63% in France to less than 25% in most of participating countries. Diagnostic coverage was highest in the Netherlands, France and Portugal. According to stratification of PKD patients based on severity, 267 adult patients were stratified as follows; 18% splenectomised on regular transfusion, 4% non-splenectomised on regular transfusion, 43% splenectomised on occasional or non-transfusion and 35% non-splenectomised on occasional or non-transfusion. Finally, % of PKD patients genotyped was found to be on average 90% and 86% for adults and pediatrics respectively (range 20-100%).

Figure 1. European distribution of PKD patients and estimations on expected number of PKD patients based on reference frequency

Country	Population	Nº Centres	Nº PKD patients follow-up	Frequency PKD patients follow-up per million	PKD diagnosis last 25 years	Frequency PKD diagnosis last 25 years per million	Nº Expected PKD patients based on reference frequency	% PKD patients follow-up vs Expected PKD	% PKD diagnosis vs Expected PKD
DK	5.822.800	3	26	4,47	28	4,81*	28	93%	100%
LT	2.794.100	1	2	0,72	2	0,72	13	15%	15%
IE	4.963.800	1	7	1,41	0	0,00	24	29%	0%
FI	5.525.300	1	2	0,36	0	0,00	27	8%	0%
PT	10.295.900	6	21	2,04	25	2,43	50	42%	50%
SE	10.327.600	3	5	0,48	2	0,19	50	10%	4%
CZ	10.693.900	3	11	1,03	21	1,96	51	21%	41%
GR	10.709.700	3	6	0,56	0	0,00	51	12%	0%
BE	11.549.900	6	11	0,95	27	2,34	56	20%	49%
NL	17.407.600	5	30	1,72	66	3,79	84	36%	79%
ES	47.330.000	17	55	1,16	103	2,18	228	24%	45%
IT	60.244.600	12	52	0,86	104	1,73	290	18%	36%
UK	67.025.500	5	31	0,46	7	0,10	322	10%	2%
FR	67.098.800	8	203	3,03	167	2,49	323	63%	52%
GE	83.166.700	10	37	0,44	59	0,71	400	9%	15%
Total	414.956.200	84	499	1,20	611	1,47	1.995	25%	31%

Summary/Conclusion: This study clearly shows the need to improve and standardize PKD patients' pathway at the national level across Europe in order to ensure adequate and timely diagnosis, and proper access to best treatment for any PKD patient. National recognition of centres of expertise for PKD for follow-up (i.e. France), centralized diagnosis (i.e. Netherlands) and/or existing registries (i.e. France, Netherlands, Denmark) dramatically improve disease coverage. Therefore, important efforts are needed in most other European countries to improve PKD diagnosis and follow-up rates.

EP687 FOSTAMATINIB FOR THE TREATMENT OF WARM ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIA (WAIHA): UPDATES FROM THE PHASE 2 AND PHASE 3 CLINICAL TRIALS

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Background: Warm antibody autoimmune hemolytic anemia (wAIHA) currently has no approved treatment options and is a rare, potentially serious disorder. The disease is characterized by red blood cell (RBC) phagocytosis in macrophages via a spleen tyrosine kinase (SYK) dependent signaling pathway. Fostamatinib, a potent oral SYK inhibitor, prevents SYK-dependent platelet phagocytosis in immune thrombocytopenia (ITP) and is an approved treatment for ITP. Fostamatinib may also prevent SYK dependent RBC phagocytosis in wAIHA.
Aims: We conducted subgroup analyses of the phase 2, open-label study (NCT02612558) to better understand factors related to response to fostamatinib in patients with wAIHA. We also provide an update on the phase 3, randomized, double-blind, placebo-controlled, global study (NCT03764618) of fostamatinib for wAIHA including a Data Monitoring Committee (DMC) review of blinded data.
Methods: Both studies enrolled (or are enrolling) adult patients with a diagnosis of primary/secondary wAIHA (documented by a positive direct antiglobulin test); baseline hemoglobin level ≤10 g/dL. Exclusion Criteria include (but are not limited to): presence of other forms of AIHA; uncontrolled hypertension. Hemoglobin (Hgb) response was defined as Hgb ≥10 g/dL with a ≥2 g/dL increase from baseline without rescue therapy. The Phase 2 study treated patients for up to 24 weeks at 150 mg BID. The phase 3 study is currently enrolling patients. During the 24-week study, eligible patients are randomized 1:1 to received fostamatinib or placebo. Randomization is stratified by concomitant steroid use and severity of anemia at baseline. The starting dose of 100 mg BID is increased to 150 mg BID after 4 weeks if drug is tolerated. Two concurrent wAIHA therapies are permitted during the study. A steroid taper protocol is implemented in patients with a Hgb response, and rescue therapy is allowed as needed. Patients can rollover to an open-label extension study upon completion of the randomized phase.
Results: In the phase 2 studies, 44% (11/25) of patients had a Hgb Response by Week 24. In total, 48% responded as there was one late responder at Week 30 (12/25). Common adverse events (AEs) were diarrhea and hypertension. In a subgroup analysis, patients with secondary wAIHA (4/5 [80%]) appeared to respond better than patients with primary wAIHA (7/19 [37%]). Patients who received fostamatinib as second-line therapy (one prior wAIHA treatment) (6/9 [67%]) appeared to respond better than those who received fostamatinib as third-or-later-line therapy (>1 prior treatment) (5/15 [33%]). Female patients (8/14 [57%]) appeared to respond better than male patients (3/10 [30%]). Small sample sizes make it difficult to draw conclusions.
Patient enrollment in the phase 3 study began last year. The study will enroll approximately 90 patients at 103 sites in 22 countries. As of January 11, 2021, 62 of 99 sites are open to screening (subject to local COVID-19 regulations), and 64 of 90 patients (71%) have been randomized. The DMC Review of data in 43 patients is shown in the table below.

DMC Review of Blinded Data on 43 Patients from Phase 3 Study (as of July 14, 2020)	
Percent of patients who discontinued study	16%
Due to AEs	7%
Due to loss of response	2%
Subject decision	7%
Mean age (range), years	60 (28-87)
Female	63%
Median duration of wAIHA (range), years	2.7 (0.1-28.3)
Median number of unique prior AIHA therapies (range)	2 (1-9)
Percent of patients on glucocorticoids	91%
Percent of patients on daily concomitant steroid use	
<20 mg/day	70%
≥20 mg/day	30%
Median Hgb	8.6 g/dL
Percent of patients with baseline Hgb <9 g/dL	61%
Percent of patients with primary wAIHA	88%
All patients provided informed consent. Fostamatinib is investigational (off-label) in wAIHA.	

Summary/Conclusion: Fostamatinib markedly improved Hgb levels in 48% of 25 evaluable patients with wAIHA in phase 2 studies. The AEs observed in the phase 2 study are consistent with the fostamatinib safety database of >3500 patients across different diseases. The subgroup analyses in the phase 2 study were consistent with response rates in the larger ITP studies with regard to improved response rates with earlier line fostamatinib use. The results of the larger phase 3 study may help identify factors associated with better outcomes.

EP688 COMPLEX MODES OF INHERITANCE IN HEREDITARY RED BLOOD CELL DISORDERS: A CASE SERIES STUDY OF 155 PATIENTS

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Background: Hereditary anemias are a heterogeneous group of conditions that are characterized by complex genotype-phenotype correlations. Based on clinical manifestations and morphological red blood cell (RBC) alterations, hereditary anemias can be broadly classified into four different subtypes: (i) disorders of hemoglobin synthesis, such as thalassemia and hemoglobinopathies; (ii) hypo-regenerative and hypo-productive anemias, such as Diamond-Blackfan anemia and congenital dyserythropoietic anemias; (iii) RBC membrane defects that are due to either alterations to the structural organization of the membranes, such as hereditary spherocytosis and hereditary elliptocytosis, or to alterations to membrane transport functions, such as hereditary stomatocytosis; and (iv) nonspherocytic hemolytic anemias, due to RBC enzyme defects.
Next-generation sequencing (NGS) has revolutionized the framework of the diagnosis of hereditary anemias by reducing both time and cost. Nevertheless, it remains a challenge to diagnose many hereditary anemia phenotypes according to phenotypic features and conventional diagnostic testing.
Aims: To identify complex modes of inheritance in hereditary red blood cell disorders by NGS analysis.
Methods: In this study, we evaluated a large case series of 155 consecutive patients with different of forms hereditary erythrocyte defects who were referred to the Medical Genetics Unit ('Federico II' University Hospital, Naples, Italy) from January 2018 to September 2020. All of the cases followed a diagnostic workflow based on a targeted-NGS panel of 86 genes known to be causative of hereditary RBC defects.
Results: We obtained an overall diagnostic yield of 83% of tested patients. Monogenic inheritance was seen for 67% (104/155), and multi-locus inheritance for 17% (26/155). *PIEZO1* and *SPTA1* were the most mutated loci among the other causative genes identified. The high frequencies of mutations in both of these genes were mainly related to their low genic intolerance, as suggested by the high values of the Residual Variation Intolerance Score percentiles for both genes. Accordingly, 18/26 patients with multi-locus inheritance showed dual molecular diagnosis of hereditary stomatocytosis (mainly dehydrated hereditary stomatocytosis type 1) and hereditary spherocytosis. These dual inheritance cases were characterized by analysis of their inheritance patterns, hematological indices, iron balance parameters, and hemolytic markers. Of note, dual inheritance patients were clinically indistinguishable from patients with hereditary spherocytosis. Additionally, their Osmoscan profiles were analyzed, which highlighted alterations of the ektacytometry curve of dual inheritance patients compared to both dehydrated hereditary stomatocytosis and hereditary spherocytosis.
Summary/Conclusion: One of the major advantages of the NGS approach is the identification of both polygenic conditions and modifier variants associated with causative mutations. Studies of Mendelian conditions have revealed the extent to which many rare diseases can be characterized by complex modes of inheritance, such as digenic inheritance and dual molecular diagnoses. Our findings expand the genotypic spectrum of red blood cell disorders and indicate that multi-locus inheritance should be considered for analysis and counseling of these patients. Of note, the genetic testing was crucial for diagnosis of patients with a complex mode of inheritance.

EP689 INHIBITION OF COMPLEMENT C1S WITH SUTIMLIMAB IN PATIENTS WITH COLD AGGLUTININ DISEASE (CAD): 1-YEAR INTERIM RESULTS OF THE PHASE 3 CARDINAL STUDY LONG-TERM FOLLOW-UP

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Background: CAD is a rare chronic autoimmune hemolytic anemia characterized by classical complement pathway–mediated hemolysis (predominantly extravascular occurring in the liver), anemia, and fatigue. Sutimlimab (formerly BIVV009) is a first-in-class humanized monoclonal antibody and C1s inhibitor that selectively targets the classical complement pathway, while leaving the lectin and alternative pathways intact.
Aims: CARDINAL (NCT03347396) evaluated sutimlimab efficacy and safety in adults with CAD and a recent transfusion history. One-year interim results of the long-term follow-up are reported.
Methods: CARDINAL is a Phase 3, open-label, single-arm study with a 26-week treatment period (Part A) and ongoing extension (Part B) for 2 years after the last patient finishes Part A. Interim data are available for Part B (data cut: January 16, 2020). Adult patients with confirmed CAD diagnosis, baseline hemoglobin (Hb) ≤10 g/dL, and ≥1 blood transfusion in the past 6 months were enrolled after providing informed consent. Sutimlimab was administered intravenously on Days 0 and 7, then biweekly. Interim Part B analysis assessed long-term efficacy and safety of sutimlimab, and durability of response (including laboratory parameters and quality of life [QOL]). Efficacy endpoints were change from baseline in hemolytic markers and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Descriptive statistics, frequency, or percentage were used to analyze outcomes.
Results: Overall, 24 patients enrolled and 22 finished Part A and entered Part B. Of enrolled patients, 62.5% were female; mean (standard deviation [SD]) age was 71.3 (8.2) years; mean (SD) number of transfusions <6 months before enrollment was 3.2 (4.0); 62.5% had received ≥1 targeted therapy in the last 5 years. Sutimlimab treatment led to rapid improvement in mean Hb level after the first dose; Hb remained >11 g/dL from Weeks 5 (Part A) to 53 (Part B; **Table**). Mean total bilirubin rapidly normalized by Week 3 and was maintained <20 µmol/L through Week 53. Mean FACIT-Fatigue scores rapidly increased by Week 1 and remained >40 points from Weeks 3 to 51; mean increase from baseline to Week 51 was 11.4, consistent with a clinically meaningful improvement. Improvements in Hb, bilirubin, and FACIT-Fatigue correlated with the normalization of C4 and near-complete inhibition of classical complement pathway activity (by Wieslab assay). Mean C1q levels were unaffected. Normalization of absolute

reticulocyte count from baseline to Week 3 was also observed, alongside normalized haptoglobin levels and reductions in lactate dehydrogenase. Of patients who entered Part B, 86.4% were transfusion-free from Weeks 26 to 53. From baseline to the data cutoff date, all 24 patients experienced ≥1 treatment-emergent adverse event (TEAE), with one serious TEAE (viral infection; treatment related). No meningococcal infections or TEAEs of meningitis were reported. One TEAE of device-related thrombosis (unrelated to sutimlimab) was reported in Part B; there were no other vascular thromboembolic TEAEs. No patients developed systemic lupus erythematosus.

Table. Long-term efficacy outcomes and laboratory parameters following sutimlimab treatment during the CARDINAL study

	Part A (N=24)				Part B (N=22)	
Hemolytic markers	Baseline		Week 26		Week 53	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hb, g/dL	24	8.6 (1.6)	20	11.3 (2.4)	16	11.8 (1.4)
Total bilirubin, µmol/L	21	53.3 (24.0)	17	18.7 (12.3)	19	16.9 (8.7)
LDH, U/L	24	438.1 (284.6)	20	332.9 (155.54)	21	367.2 (253.64)
Absolute reticulocytes, ×10⁹/L	22	138.3 (68.0)	17	87.0 (41.6)	15	87.2 (38.9)
Haptoglobin, g/dL	24	0.27 (0.28)	20	0.33 (0.34)	22	0.45 (0.49)
Complement parameters	Baseline		Week 25		Week 51*	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Total C4, g/L	23	0.04 (0.07)	20	0.29 (0.07)	3	0.24 (0.19)
Classical complement pathway activity, %	24	19.8 (16.7)	21	3.0 (3.1)	21	3.2 (3.4)
C1q, ng/mL	24	84906.2 (35723.0)	21	77885.9 (26305.9)	21	63137.2 (20151.9)
QOL outcome	Baseline		Week 26		Week 51*	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
FACIT-Fatigue	22	32.5 (10.6)	17	42.5 (8.3)	18	44.3 (8.7)
Transfusions	Baseline to Week 5 n (%)		Weeks 5 to 26 n (%)		Weeks 27 to 53 n (%)	
Patients with 0 transfusions	19 (79.2)		17 (70.8)		19 (86.4)	

C4, complement protein 4; C1q, complement component 1q; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; QOL, quality of life; SD, standard deviation.
*Last data collection.

Summary/Conclusion: Sutimlimab, a first-in-class selective anti-C1s classical complement pathway inhibitor, maintained Hb levels >11g/dL, sustained normalization of bilirubin, and continued to improve FACIT-Fatigue scores, with no newly identified safety concerns at 1 year. These results of the ongoing CARDINAL Part B long-term study demonstrate that continued upstream inhibition of the classical complement pathway with sutimlimab provides sustained and durable treatment effects in chronic CAD.

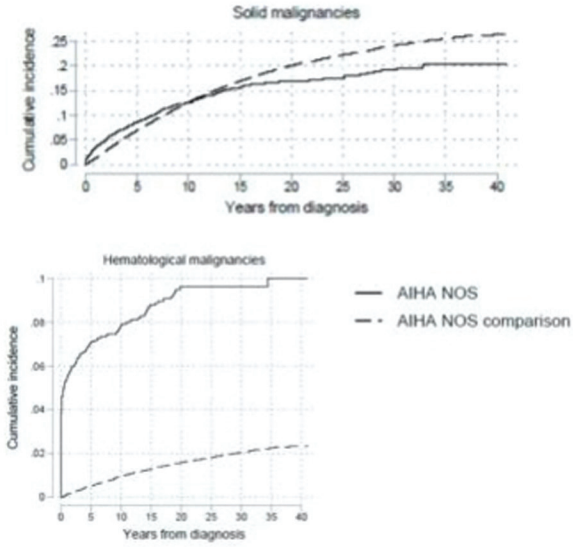
EP690 CANCER RISK IN PATIENTS WITH WARM AUTOIMMUNE HAEMOLYTIC ANAEMIA - A NATIONWIDE COHORT STUDY

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Background: Warm autoimmune haemolytic anaemia (wAIHA) is an acquired blood disorder characterized by antibodies directed against own RBCs. wAIHA is either primary or secondary due to cancers or other diseases. The presence of an underlying disease in wAIHA is associated with an overall reduced prognosis, compared with primary wAIHA. The association between wAIHA and some cancers, especially B-cell malignancies, have been established, but accurate risks are missing. To our knowledge, no studies have investigated the cumulative incidence of cancer following diagnosis of primary or secondary wAIHA.
Aims: The aim of this study is to evaluate the prevalence of any cancer amongst patients with wAIHA at time of diagnosis, compared with the general population, and whether patients with wAIHA have a higher incidence of cancer after wAIHA-diagnosis.
Methods: Patients with wAHIA diagnosed 1980-2016 were identified in the nationwide Danish Haemolysis Cohort. Each patient was age-sex-matched with up to 50 comparisons from the general population without haemolysis. Patients and comparisons were followed from index date, corresponding to date of wAIHA diagnosis or an assigned matched date for comparisons. We identified incident and prevalent cancer diagnoses using the Danish Cancer Registry. Patients and comparisons were followed until a cancer diagnosis, death, emigration or end of study, whichever came first. Any registered cancer diagnosis before index-date + 30 days were considered prevalent, thereafter, all cancer diagnoses were defined as incident cancer diagnosis. We present cumulative incidences (CIs) of cancer diagnoses after one year, five years, and ten years.
Results: We identified 2,700 patients with wAIHA and 133,730 sex and age-matched comparisons. Out of the 2,700 patients with wAIHA, 1,589 (58.9%) were primary wAIHA, and 1,111 (41.1%) patients were secondary wAIHA due to defined underlying diseases – most frequently haematological cancers. Women accounted for 56% of patients, and this uneven sex distribution were most prominent in primary wAIHA. Median age was 58.8 years for patients with primary wAIHA and 68.2 years for secondary wAIHA patients. The mean age at death for the patients diagnosed with primary wAIHA was 77.6 years, 75.0 years for patients diagnosed with secondary wAIHA, and 83.9 and 83.8 years in the respective comparison groups.
The CI of haematological cancer was higher for patients diagnosed with wAIHA vs. general population comparisons (Figure). For all haematological malignancies, except multiple myeloma, the CI remained higher in wAIHA vs. comparisons. For solid cancer the CI was higher the first 10 years following wAIHA diagnosis vs. comparisons, after time point incidences equalized (Figure).

Figure: The cumulative incidences of all solid and haematological cancers combined in patients diagnosed with wAIHA and comparisons



Summary/Conclusion: Patients diagnosed with wAIHA have a higher risk of developing malignancies after the wAIHA diagnosis. The increased risk for subsequent cancer development after wAIHA-diagnosis is most prominent for haematological malignancies.

EP691 BASELINE CHARACTERISTICS BY AGE OF A GLOBAL COHORT OF PATIENTS DIAGNOSED WITH PYRUVATE KINASE DEFICIENCY – A DESCRIPTIVE ANALYSIS FROM THE PEAK REGISTRY

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Background: Pyruvate kinase (PK) deficiency is the most common hereditary red cell glycolytic enzyme defect leading to lifelong hemolytic anemia. Despite current supportive interventions, patients (pts) may develop serious complications, such as iron overload, regardless of their age or transfusion history. Information describing the real-world burden of disease among the pediatric population is limited.
Aims: This analysis aimed to characterize the clinical manifestations and disease management strategies for the pediatric cohort (<18 years [yrs]) and the adult cohort (≥18 yrs) with PK deficiency enrolled in the Peak Registry (NCT03481738).
Methods: The Peak Registry is an ongoing, global prospective and retrospective cohort study of adult and pediatric pts diagnosed with PK deficiency. Demographic, medical history, laboratory, and treatment data for this analysis were collected from eligible pts who enrolled in the Registry as of the latest data cut (24Mar2020). All analyses reported are descriptive and based on non-missing data as of the time of enrollment in the Registry. Continuous variables are summarized as means (SD) or medians (range), while categorical variables are summarized as counts and percentages.
Results: A total of 140 pts (56 pediatric and 84 adult) were included in this analysis. The mean age of participants at enrollment was 7.8 yrs (SD 4.6) for the pediatric cohort vs 37.4 yrs (SD 15.5) for adults. Hemoglobin levels (median [range]) were 8.4 g/dL (5.8–12.3) in the pediatric cohort and 9.5 g/dL (6.7–12.9) in adults. Ferritin levels (median [range]) in the pediatric cohort were 772 ng/mL (78–2499) and 404 ng/mL (19–2263) in adults. History of chelation therapy was 50.0% (0–5 yrs), 54.5% (6–11 yrs), and 63.6% (12–17 yrs) in pediatric subgroups and 30.6% in adults. The median age at splenectomy for pediatric and the adult groups were at 5 yrs (2–12 yrs) and 6 yrs (1–27 yrs), respectively. The higher frequency of splenectomy (0% [0–5 yrs], 52.2% [6–11 yrs], 61.5% [12–17 yrs]) with increasing age across pediatric cohorts matches a decreased frequency in those who were treated with regular transfusions (≥6 transfusions within 1 yr prior to enrollment), 46.7% (0–5 yrs), 14.3% (6–11 yrs), and 10.0% (12–17 yrs). The frequency of splenectomy and regular transfusions was similar between the 6–17 yrs old cohort (55.6% and 12.9%) and the adult cohort (51.3% and 9.4%).

Table:	Overall Population		Pediatric Subgroups		
	Adult, ≥18 yrs N=84	Pediatric, <18 yrs, N=56	0–5 yrs N=19	6–11 yrs N=24	12–17 yrs N=13
Demographic and Medical History					
Gender, N	84	56	19	24	13
Female, n (%)	48 (57.1)	30 (53.6)	11 (57.9)	11 (45.8)	8 (61.5)
Age at diagnosis, N	76	51	18	22	11
Median (range), yrs*	16 (0–68)	1 (-1–11)	0 (-1–2)	0.5 (-1–11)	4 (-1–11)
Genotype, N	65	27	8	11	8
Missense/Missense, n (%)	41 (63.1)	11 (40.7)	2 (25.0)	5 (45.5)	4 (50.0)
Missense/Non-missense, n (%)	21 (32.3)	11 (40.7)	5 (62.5)	4 (36.4)	2 (25.0)
Non-missense/Non-missense, n (%)	3 (4.6)	5 (18.5)	1 (12.5)	2 (18.2)	2 (25.0)
Splenectomy history available, N	80	54	18	23	13
Ever received splenectomy n (%)	41 (51.3)	20 (37.0)	0 (0)	12 (52.2)	8 (61.5)
Age at splenectomy, N	38	19	0	12	7
Median (range), yrs	6 (1–27)	5 (2–12)	–	5 (2–10)	6 (4–12)
Chelation therapy history available, N	72	51	18	22	11
Ever had chelation therapy, n (%)	22 (30.6)	28 (54.9)	9 (50.0)	12 (54.5)	7 (63.6)
Transfusions history available, N	76	54	18	23	13
Ever transfused, n (%)	48 (63.2)	50 (92.6)	17 (94.4)	22 (95.7)	11 (84.6)
Transfusion history 12 months prior to enrollment, N	64	46	15	21	10
Regularly transfused pts (≥6 transfusions), n (%)	6 (9.4)	11 (23.9)	7 (46.7)	3 (14.3)	1 (10.0)
Number of transfusions, mean (SD)	9.2 (2.8)	9.5 (3.1)	10.0 (3.6)	8.7 (3.1)	9.0 (–)
Non-regularly transfused pts (never or 0–5), n (%)	58 (90.6)	35 (76.1)	8 (53.3)	18 (85.7)	9 (90.0)
Number of transfusions, mean (SD)	0.4 (1.1)	0.9 (1.5)	1.1 (1.9)	1.0 (1.5)	0.7 (1.3)
Lab Parameters					
Hemoglobin, N	38	36	12	16	8
Median (range), g/dL	9.5 (6.7–12.9)	8.4 (5.8–12.3)	8.6 (5.8–12.3)	8.3 (7.1–10.9)	8.2 (6.8–11.4)
Percent reticulocyte count, N	17	13	5	6	2
Median (range), %	5.3 (2.6–40.7)	9.3 (2.2–42.5)	3.4 (2.2–29.1)	25.3 (3.6–42.5)	24.1 (13.4–34.8)
Indirect bilirubin, N	25	18	6	9	3
Median (range), mg/dL	3.3 (0.8–23.1)	3.1 (1.4–12.0)	3.4 (1.4–3.9)	2.9 (1.5–12.0)	3.9 (2.9–6.2)
Lactate dehydrogenase, N	22	12	3	5	4
Median (range), IU/L	225 (133–849)	654 (135–2949)	710 (552–2949)	568 (206–1551)	677 (135–1798)
Ferritin, N	26	16	6	6	4
Median (range), ng/mL	404 (19–2263)	772 (78–2499)	847 (123–2000)	430 (78–925)	1474 (264–2499)

N represents number of patients with data available; *-1 age at diagnosis denotes presumably diagnosed in utero pt=patient; SD=standard deviation; yrs=year.

Summary/Conclusion: This analysis provides early insight into the disease manifestations experienced by pediatric pts with PK deficiency. Prior research has revealed that adult pts with PK deficiency experience a high disease burden. This analysis confirms that complications start early on, with pediatric pts experiencing significant anemia and treatment with transfusions and chelation before age 6. The timing of the decrease in regular transfusions matches the timepoint of an increased frequency of splenectomy, possibly reflecting the known impact of splenectomy on partially ameliorating the anemia in PK deficiency. However, despite the high rate of splenectomy in this cohort, many children and adults continue to have substantial anemia and disease burden. The Registry will continue to collect data in pts to better understand the clinical manifestations and complications of PK deficiency over time.

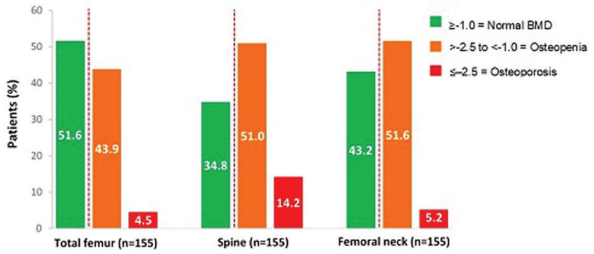
EP692 EARLY-ONSET OSTEOPENIA AND OSTEOPOROSIS IN PATIENTS WITH PYRUVATE KINASE DEFICIENCY

H. Al-Samkari [1,*], R. F. Grace [2], A. Glenthøj [3], O. Andres [4], W. Barcellini [5], F. Galactéros [6], K. H. M. Kuo [7], D. M. Layton [8], M. Morado Arias [9], V. Viprakasit [10], Y. Dong [11], F. Tai [11], P. Hawkins [11], S. Gheuens [11], C. Bowden [11], J. Porter [12], E. J. van Beers [13]

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Background: Hereditary pyruvate kinase (PK) deficiency results in lifelong hemolytic anemia and several significant comorbidities, the epidemiology of which are not well characterized. Among these is reduced bone mineral density (BMD), which can result in premature osteopenia, osteoporosis, and fractures.
Aims: To better characterize the bone density abnormalities in patients (pts) with PK deficiency, this study evaluated pooled pre-treatment baseline data from 3 clinical trials involving pts with PK deficiency investigating mitapivat (AG-348), an allosteric activator of PK: DRIVE-PK (NCT02476916), ACTIVATE (NCT03548220), and ACTIVATE-T (NCT03559699). This is the first large PK deficiency cohort in which dual-energy x-ray absorptiometry (DXA) scores were systematically and consistently assessed.
Methods: DRIVE-PK is a completed phase 2, global, randomized, open-label study. ACTIVATE is an ongoing phase 3, global, randomized, double-blind, placebo-controlled study. ACTIVATE-T is an ongoing phase 3, global, open-label, single-arm study. In all 3 studies, pts ≥18 years (yrs) of age with a confirmed diagnosis of PK deficiency were eligible to participate. Pts were eligible to participate in DRIVE-PK and in ACTIVATE if they were not regularly transfused (DRIVE-PK: ≤3 units of red blood cells in the prior 12 months [mos]; no transfusions in the prior 4 mos; ACTIVATE: ≤4 transfusion episodes in the previous yr; no transfusions in the prior 3 mos) and in ACTIVATE-T if they were regularly transfused (≥6 transfusion episodes in the previous yr). BMD was measured using DXA at baseline; scans were obtained locally for all 3 studies. Scans were interpreted locally for DRIVE-PK and centrally for ACTIVATE and ACTIVATE-T. Osteopenia and osteoporosis were identified on DXA according to standard definitions, and prevalence of each was compared to prevalence ascertained via medical history.
Results: Of 159 pts evaluated (DRIVE-PK, n=52; ACTIVATE, n=80; ACTIVATE-T, n=27), median age was 34 yrs (range, 18–78) and majority were female (n=88; 55.3%). Of 155 pts who had baseline T-scores for total femur, spine, and femoral neck, 38 (24.5%) had a T-score of ≥–1.0 at all locations, indicating normal BMD; 91 (58.7%) had a T-score of >–2.5 to <–1.0 at 1 or more locations, indicating osteopenia; and 26 (16.8%) had a T-score of ≤–2.5 at 1 or more locations, indicating osteoporosis. The proportion of pts in each T-score range for each of the 3 locations is shown in the Figure. In contrast to the DXA scan findings, only 28 (17.6%) pts had a known medical history of osteopenia and 23 (14.5%) had a known medical history of osteoporosis. Taking together DXA scan results and medical history for all 159 pts, 85 (53.5%) had osteopenia and 33 (20.8%) had osteoporosis. Median age for pts with either osteopenia or osteoporosis (n=118) was 36 yrs (range, 18–78). Of these, 20 pts (16.9%) were regularly transfused and 98 pts (83.1%) were not regularly transfused.

Figure. Pooled T-scores at Baseline†



BMD: bone mineral density.
†Pooled population includes patients with PK deficiency from DRIVE-PK, ACTIVATE, and ACTIVATE-T trials.

Summary/Conclusion: In this large cohort, universal DXA scanning revealed that over three-quarters of adults with PK deficiency had osteopenia or osteoporosis, irrespective of transfusion requirements. Given the young median age of the cohort (34 yrs), these findings have considerable significance and implications for the screening and care of pts with PK deficiency throughout their adult lives. Early monitoring of these pts with DXA scans in order to ensure a prompt diagnosis of bone density abnormalities and indicated treatment may be warranted.

EP693 PHARMACOLOGIC INHIBITION OF PI3KΔ REDUCES AUTOANTIBODY FORMATION AND IS EFFICACIOUS IN A PRECLINICAL MODEL OF AUTOIMMUNE HEMOLYTIC ANEMIA

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Background: Autoimmune hemolytic anemia (AIHA) is a rare acquired disorder in which autoantibodies directed against red blood cell (RBC) membrane antigens lead to accelerated RBC destruction. The disease can be distinguished on the basis of the autoantibody class and thermal characteristics: warm AIHA (immunoglobulin [Ig]-G–mediated) and cold agglutinin disease (IgM-mediated). The mortality rate is approximately 11%, and there are currently no regulatory approved AIHA treatments. Phosphatidylinositol 3-kinases (PI3Ks) are divided into 3 classes (Class I, II, and III) according to their structure, regulation, and substrate specificity. The Class I PI3K delta isoform (PI3Kδ) has been implicated in autoimmune diseases associated with aberrant B-cell and antibody responses. Parsaclisib is an oral, small-molecule PI3Kδ selective inhibitor without known adverse off-target toxicities that is being clinically evaluated in AIHA and hematologic malignancies.
Aims: To evaluate the efficacious potential of small-molecule PI3Kδ inhibition in preclinical models of antibody-mediated immunity, including spontaneous AIHA.
Methods: The relevance of PI3Kδ inhibition on de novo antibody production was characterized in 2 preclinical mouse models. Intravenous 2,4,6-trinitrophenyl lipopolysaccharide (TNP-LPS) triggers a rapid antigen-specific, B-cell–mediated IgM response. In contrast, intraperitoneal injection of 2,4-dinitrophenyl-keyhole limpet hemocyanin (DNP-KLH) drives an antigen-specific, T-cell–dependent, B-cell–mediated IgG immunity. The interleukin-2 knockout (IL-2 KO) mice spontaneously develop a systemic autoimmune disease, dying from complications of AIHA mediated by autoantibodies. The pharmacologic effect of PI3Kδ inhibition was quantified using antigen-specific enzyme-linked immunosorbent assays, complete blood count, and flow cytometry.
Results: In vitro enzymatic selectivity screening revealed that parsaclisib potently inhibited the PI3Kδ kinase enzyme (50% inhibitory concentration [IC_{50}] = 1.1 ± 0.5 nM) with ~20,000-fold selectivity over the other PI3K family member enzymes. Oral prophylactic PI3Kδ inhibitor treatment dose-dependently reduced antigen-specific IgM and IgG antibody titers. The modulation of antigen-specific IgM and IgG responses following parsaclisib treatment was fully consistent with previously published data using TNP-LPS and DNP-KLH stimuli in PI3Kδ knockout mice. Selective pharmacologic inhibition of the PI3Kδ isoform ameliorated AIHA symptoms in the IL-2 KO mouse model, with disease modulation associated with the reduced presence of Ig-bound RBC. Hemoglobin and RBC levels were unaffected by PI3Kδ inhibition in healthy age-matched wild-type mice.
Summary/Conclusion: In preclinical models, PI3Kδ inhibition dose-dependently inhibited de novo IgM and IgG humoral responses and was highly efficacious in a spontaneous AIHA mouse model. These experimental data support the scientific rationale for clinically evaluating parsaclisib in AIHA (NCT03538041).

EP694 IMPACT OF OLIPUDASE ALFA ENZYME REPLACEMENT THERAPY ON PULMONARY, VISCERAL AND HEMATOLOGIC MANIFESTATIONS OF ACID SPHINGOMYELINASE DEFICIENCY: 1-YEAR RESULTS OF CLINICAL TRIALS IN CHILDREN AND ADULTS

M. Scarpa [1,*], L. Arash-Kaps [2], A. Barbato [3], G. A. Diaz [4], R. C. Gallagher [5], R. Giugliani [6], N. B. Guelbert [7], N. Guffon [8], C. Hollak [9], T. Ikezoe [10], S. A. Jones [11], R. Lachmann [12], O. Lidove [13], P. Mabe [14], E. Mengel [15], E. Senates [16], M. Tchan [17], J. Villarrubia [18], M. Wasserstein [19], Y. Chen [20], S. Furey [20], C. Ortemann-Renon [21], Q. Zhang [21], M. Kumar [20]

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Background: Acid sphingomyelinase deficiency (ASMD) is a rare, debilitating lysosomal storage disease with no approved treatment. Deficient ASM activity results in progressive pulmonary, hepatic, visceral, and hematologic dysfunction across a disease spectrum that includes central nervous system manifestations in the most severe patients. Disease awareness is low and diagnostic delays are common. It may fall to hematologists to evaluate and identify undiagnosed patients. Olipudase alfa (recombinant human ASM) is an enzyme replacement therapy in development for the non-central nervous system manifestations of ASMD.
Aims: Present safety and efficacy outcomes of 2 international clinical trials of dose-escalated olipudase alfa in children and adults with chronic ASMD.
Methods: ASCEND (NCT02004691/Sanofi Genzyme) is a Phase 2/3, multicenter, randomized, 52-week, double-blind, placebo-controlled trial in 36 adults with chronic ASMD randomized 1:1 to receive olipudase alfa or placebo. Independent primary efficacy endpoints were % change in % predicted lung carbon monoxide diffusing capacity (DL_{CO}) and % change in spleen volume (for the USA, combined with change in Splenomegaly Related Score [SRS]) at Week 52. ASCEND-Peds (NCT02292654/Sanofi Genzyme) is a Phase 1/2 multicenter, open-label trial evaluating olipudase alfa in 20 children with chronic ASMD. Primary objective was safety over 64 weeks. Efficacy outcomes at 52 weeks included change in spleen volume, DL_{CO}, and height Z-score. Both trials also evaluated changes in liver volume, platelet count, lipid profile, and biomarkers. Informed consent was obtained.
Results: In ASCEND (adult), least-square mean % change from baseline to Week 52 favored olipudase alfa over placebo for % predicted DL_{CO} (+22.0% vs. +3.0%, p=0.0004), spleen volume (-39.4% vs. +0.5%, p<0.0001), liver volume (-31.7% vs. -1.4%, p<0.0001), and platelets (+16.8% vs. +2.5%, p=0.019), with differences seen by Week 26. SRS decreased in both groups (-8.0 for olipudase vs. -9.3 for placebo at Week 52, p=0.70). Biomarker and lipid profiles improved in olipudase-alfa compared to placebo-treated patients. No patient had a

treatment-related serious adverse event or discontinued due to a treatment-emergent adverse event; 35/36 patients continue in an open-label extension.
In ASCEND-Peds (pediatric), splenomegaly and hepatomegaly improved in all patients at Week 52 (mean decrease ±SD: 49.2% ±9.7% and 40.6% ±9.4%, respectively, p<0.0001). Among 9 patients able to perform baseline DL_{CO} testing, mean % predicted DL_{CO} improved by 32.9% ±29.1% (relative change from baseline, p=0.0053). Platelet count improved by a mean ±SD of 34% ± 36% after 52 weeks of olipudase alfa (p=0.0003). Median height Z-score improved from -2.0 to -1.5 (p<0.0001). Biomarker and lipid profiles also improved. Treatment response was similar across age groups (<6 years, 6 to <12 years, 12 to <18 years). Eleven of 20 patients had infusion-associated reactions (mainly urticaria, pyrexia, and/or vomiting). Three patients had treatment-related serious adverse events: transient alanine aminotransferase increases in 1 patient, urticaria and rash in 1 patient, and anaphylactic reaction in 1 patient that was treated with a desensitization protocol. All patients completed the study and continue in an extension trial.
Summary/Conclusion: Olipudase alfa was well-tolerated in children and adults and, after 1 year of treatment, resulted in improved lung function, reductions in spleen and liver volumes, improved platelet counts and lipid profiles, reductions in disease biomarkers, and (in children) improved growth.

EP695 MITAPIVAT AMELIORATES RED CELL FEATURES AND DECREASES ANEMIA IN BAND 4.2-/- MICE, A MODEL OF HEREDITARY SPHEROCYTOSIS

A. Matte' [1,*], A. Recchiuti [2], E. Federti [1], C. Kung [3], A. B. Wilson [1], A. Pomilio [2], P. Kosinski [3], V. Riccardi [1], I. Iatcenko [1], L. Dang [3], A. Iolascon [4], R. Russo [4], C. Brugnara [5], A. Janin [6], C. Leboeuf [6], N. Mohandas [7], L. De Franceschi [1]

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Background: Hereditary spherocytosis (HS) is the most common cause of inherited red cell membranopathy, due to mutations in genes encoding membrane or cytoskeletal proteins, including band 3, ankyrin, spectrin or band 4.2. Loss of membrane cohesion results in surface area loss and generation of spherocytic red cells with decreased cellular deformability and reduced red cell survival due to splenic sequestration. A diagnostic test for HS is the incubated osmotic fragility implying a role for red cell ATP content in maintaining normal RBC function including membrane stability. Recently, relative PK deficiency has been observed in HS red cells (Andreas O et al. BJH 187: 386, 2019).
Aims: To understand whether the oral pyruvate kinase activator, mitapivat, by modulating ATP content, might have potential beneficial effects for HS RBCs in band $4.2^{-/-}$ mice, a well-established model of HS (Peters LL et al JCI 103: 1527, 1999).
Methods: Mitapivat was administrated to band $4.2^{-/-}$ mice at dosages of 100 mg/kg/day over 6 months. We analysed: hematologic parameters, red cell indices and osmotic fragility, markers of hemolysis, phagocytic index and iron homestasis.
Results: In band $4.2^{-/-}$ mice, Mitapivat resulted in (i) decreased anemia with reduced reticulocyte count (Hb 11.6±0.035 g/dL, n=17 *vs* 13.104±0.09 g/dL, n=9; P<0.05; retics: 11.4±0.1%, n=16 vs 7.6±0.2%, n=7 % P<0.05) and decreased hemolytic indices (LDH, total bilirubin) with decreased spleen weight/mouse weight ratio (8.41±0.08 vs 6.53±0.06, n=8 each group; P<0.05); (ii) reduction in the proportion of phosphatidylserine positive RBCs, measured with Annexin V binding (2.4±0.02% *vs* 1.5±0.06% n=5-6; P<0.05); (iii) reduction of naturally occurring antibody (NAb) bound to band $4.2^{-/-}$ RBC membrane; (iv) improvement of osmotic fragility. The decreased hemolysis was associated with reduction in serum erythropoietin (EPO: 1001.2±41.7 U/L vs 472 ± 12.5 U/L, n=7, P<0.05). We also documented *in vivo* reduction of erythrophagocytosis and *in vitro* decreased phagocytic index, supporting the improvement in HS red cell features by Mitapivat. The improvement of anemia in Mitapivat treated band $4.2^{-/-}$ mice was associated with decreased liver iron overload.
Summary/Conclusion: Our data indicate that Mitapivat ameliorates anemia of band $4.2^{-/-}$ mice, reduces chronic hemolysis and improves band $4.2^{-/-}$ mouse RBC features. Thus, Mitapivat might represent a potential therapy to be explored in patients with HS.

EP696 BONE MINERAL DENSITY IS STABLE IN ADULTS WITH PYRUVATE KINASE DEFICIENCY RECEIVING LONG-TERM TREATMENT WITH MITAPIVAT

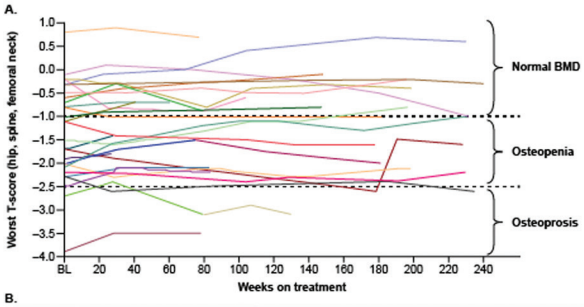
H. Al-Samkari [1,*], E. J. van Beers [2], W. Barcellini [3], F. Galactéros [4], B. Glader [5], K. H. M. Kuo [6], D. M. Layton [7], Y. Ravindranath [8], H. Yaish [9], Y. Dong [10], F. Tai [10], P. Hawkins [10], V. Beynon [10], K. Gilroy [10], R. F. Grace [11]

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Background: Hereditary pyruvate kinase (PK) deficiency results in chronic hemolysis that can lead to reduced bone mineral density (BMD). A recent analysis of 159 patients (pts) with PK deficiency showed that >75% of adult pts had osteopenia or osteoporosis at a median age of 34 years (yrs). Mitapivat (AG-348) is an investigational, first-in-class, allosteric activator of PK that has been shown to improve hemoglobin and other hemolysis markers for up to 42 months (mos) in pts with PK deficiency. Mitapivat has mild aromatase inhibition effects; however, it is not clear whether this carries a negative impact on BMD in pts with PK deficiency. Conversely, reducing hemolysis through PKR activation with this agent may have a positive effect on BMD.
Aims: To report BMD over time in pts with PK deficiency receiving long-term treatment with mitapivat in the DRIVE-PK study.
Methods: DRIVE-PK (NCT02476916) is a phase 2, global, randomized, open-label, dose-ranging study in pts ≥18 yrs of age with a confirmed diagnosis of PK deficiency and not receiving regular transfusions (≤3 units of red blood cells ≤12 mos and no transfusions ≤4 mos). Pts were randomized 1:1 to 50 mg or 300 mg of mitapivat twice daily (BID) during a 24-week (wk) core period; eligible pts could enter an extension period to receive mitapivat for up to 8 yrs. Dose adjustments were permitted based on safety and efficacy; following an amendment, doses >25 mg BID were tapered to the lowest effective dose in the extension. BMD was measured using DXA scans at baseline (BL), every 6 mos through month 30, and then annually. DXA changes over time were assessed for pts receiving mitapivat >12 mos. Pts were classified as having normal BMD, osteopenia, or osteoporosis based on DXA T-scores.
Results: Of 52 participants in DRIVE-PK (median age 34 yrs [range, 18–61]), 31 (32% female) received mitapivat >12 mos and had on-treatment DXA monitoring for up to 56 mos. Of 30 pts who had BL T-scores for total hip, spine, and femoral neck, 12 (38.7%) had a T-score ≥–1.0 (normal BMD) at all locations, 13 (41.9%) had a worst T-score >–2.5 to <–1.0 (osteopenia) at 1 or more locations, and 5 (16.1%) had a worst T-score ≤–2.5 (osteoporosis) at 1 or more locations. As of the latest assessment during the extension period, 12 (38.7%), 11 (35.5%), and 5 (16.1%) of 31 pts had a T-score indicating normal BMD, osteopenia, and osteoporosis, respectively. None of the 12 pts with BMD in the normal range at BL showed worsening of BMD at latest assessment. Of 13 pts with a worst BL T-score of >–2.5 to <–1.0 at 1 or more location(s), 9 remained stable, 1 worsened, and 3 improved to a T-score of ≥–1.0, indicating normal BMD. Of 5 pts with a worst BL T-score of ≤–2.5 at 1 or more location(s), 4 remained stable and 1 improved to a T-score of >–2.5 to <–1.0 (Figure and Table). No fractures were reported during this study.

Figure. A. Individual longitudinal plot[a] of worst DXA T-score in pts treated with mitapivat for >12 mos[b,c]; B. Shift of worst DXA T-score category across hip, spine, or femoral neck from BL to last study assessment

A.



B.

Baseline		T-score at last assessment, n (%)		
Prior category[d]	n (%)	Normal BMD ≥-1.0	Osteopenia ≥-2.5 to <-1.0	Osteoporosis ≤-2.5
Normal BMD ≥-1.0	12 (38.7)	12 (38.7)	0	0
Osteopenia ≥-2.5 to <-1.0	13 (41.9)	3 (9.7)	9 (29.0)	1 (3.2)
Osteoporosis ≤-2.5	5 (16.1)	0	1 (3.2)	4 (12.9)

= stable = improved = worsened

[a]Each colored line represents an individual pt's longitudinal T-score results; [b]Safety Analysis Set: Pts who received mitapivat for >12 mos (365 Days); only pts with evaluable post-BL DXA T-score are included in the analysis; [c]Two pts are included who were treated for >12 mos, but only have evaluable post-BL T-score results up to 6 mos; one pt is included who has no evaluable T-score results from BL to 18 mos; [d]Safety Analysis Set: Subjects Who Received Mitapivat for >12 Months (365 Days); only patients with evaluable post-baseline DXA T-score are included in the analysis.
BL=baseline; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; mos=months; pt=patient
Note: One patient did not have BL DXA, so the table shows results for 30/31.

Summary/Conclusion: DXA scanning revealed that BMD was largely stable over time in adult pts with PK deficiency receiving long-term treatment with mitapivat for up to 56 mos, despite a substantial degree of reduced BMD at BL. Therefore, mitapivat does not appear to promote progression of BMD abnormalities in these pts and could halt this process by decreasing hemolysis and ineffective erythropoiesis. Additional BMD data will be collected as part of this ongoing extension study.

EP697 WARM AUTOIMMUNE HEMOLYTIC ANEMIA IS ASSOCIATED WITH A REGULATORY T CELL DEFICIENCY AND A TH17 POLARIZATION

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Background: Warm autoimmune hemolytic anemia (wAIHA) is a rare acquired autoimmune disease mediated by antibodies targeting red blood cells. Until now, the involvement of T helper (Th) lymphocytes has been scarcely studied in humans, most of the conclusions being extrapolated from animal models. Although still debated, a skewing to a pro-inflammatory Th17 polarization seems to be associated with AIHA. On the other hand, a quantitative regulatory T cell (Treg) deficiency has been shown in one study, but their suppressive functions were not assessed. Importantly, the balance between the pro- and anti-inflammatory T cell responses has never been measured simultaneously.
Aims: Assuming that an imbalance between the pro- and the anti-inflammatory T cell responses could participate to AHAI pathogenesis, we quantified the different circulating helper T cell (Th) subsets, Tregs and assessed their functional capabilities and their transcriptomic profiles.
Methods: Newly diagnosed wAIHA patients (n=20) were compared to sex- and age-matched healthy donors (n=30). Cells were quantified at baseline by flow cytometry, and polarization was determined by intracellular cytokine staining after stimulation with PMA and ionomycin. Treg functions were evaluated by their capability to inhibit effector T cell proliferation. Cytokines were measured by luminex assays in culture supernatants and sera. RNA sequencing was performed on Treg isolated from 4 patients and 4 controls by fluorescence-activated cell sorting ($CD4^+CD25^{Hi}CD127^-$).
Results: AHAI patients have a decrease in circulating Treg ($CD4^+CD25^{Hi}Foxp3^+$, 3.20% *vs.* 4.45%, p=0.008), mostly affecting activated Treg ($CD4^+Foxp3^{hi}CD45RA^-$), known to arbor high suppressive capabilities. Moreover, Treg have a functional deficiency in AIHA, as shown by their lower ability to inhibit T cell proliferation (51% *vs.* 73%, p=0.03) associated to a trend to a lower inhibition of the secretion of pro-inflammatory cytokines (TNF-α, IFN-γ and IL-2) measured in coculture supernatants. Treg transcriptomic revealed an activated profile, as supported by an engagement in transcriptional and translational processes, an activation of TCR and IL-2 signaling, and an increased expression of CTLA-4 mRNA. Interestingly, TNF signaling pathway was also engaged, probably due to the increase in TNF-α in the sera of patients (2.29 *vs.* 1.24 pg/ml, p=0.002).
Although, Th polarization assessed by flow cytometry did not differ between patients and controls, the production of IL-17 by effector T cells measured in supernatants was higher during AHAI. Considering the Th17/Treg ratio, we observed an unbalance (0.023 *vs.* 0.01, p=0.01) of the pro-inflammatory over the anti-inflammatory T cell response during AIHA.
Summary/Conclusion: This work is the first to provide a concomitant evaluation of effector and regulatory T cells in human AIHA, showing an imbalance in the Th17/Treg ratio, associated with a quantitative and functional deficiency of Treg. Most interestingly, our results pointed out TNF-α as an interesting cytokine to target as its concentration is elevated in the sera and could participate to the inhibition of Treg functions.

EP698 SEVERE NEONATAL HAEMOLYTIC ANAEMIA AND SPHEROCYTIC-ELLYPTOCYTOSIS PHENOTYPE DUE TO THE INTERACTION OF THREE NOVEL SPTA1 MUTATIONS

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Background: RBC morphology is a key diagnostic feature for hereditary spherocytosis (HS) and hereditary elliptocytosis (HE). However, this phenotypic diagnosis may not be readily available in patients requiring frequent transfusions and does not predict disease course or severity. However, RBC deformability measured by osmotic gradient ektacytometry (OGE) allows a clear differentiation between HS and HE, where the truncated osmoscan curve reflects the inability of the already elliptical cells to deform further under shear stress. In Hereditary Pyropoikilocytosis (HPP), the RBCs appear to have a significantly decreased ability to maintain deformability in the face of hypotonicity and the classical trapezoidal profile of HE is less evident
Aims: We aim to demonstrate that in patients with HPP and SPTA1 variants, the implication of a canonical splicing site, may explain not only the marked defect of spectrin chains tetramerization and elliptocytosis, but also the weakness of skeleton attachment to the lipid bilayer and the loss of RBC membrane, microvesiculation and spherocytosis. As most of the SPTA1 gene variants described, so far, in patients with HE or HPP, only one or few nucleotides are affected, the resulting protein involvement could be variable, ranging from a slight clinical form (the most frequent) associated with moderate elliptocytosis to a more severe form (the rarest) leading to poikilocytosis, depending on the degree of tetramerization failure
Methods: The diagnosis of HHA was performed via a step-wise process including RBC morphology, Hb electrophoresis, and measurement of common RBC enzyme activities. RBC deformability and other rheological parameters were studied by OGE, using the osmoscan module of the Laser-assisted Optical Rotational Deformability Cell Analyser (LoRRca; MaxSis. RR Mechatronics) as previously described. The genetic diagnosis of membranopathies was performed by gene capture followed by t-NGS that includes a panel of 35 genes responsible for membranopathy hemoglobinopathy, enzymopathy and CDA. NGS and Whole exome sequencing (WES) have been performed using an Illumina HiSeq2000 device.
Results: Both patients studied here showed severe neonatal hemolytic anemia and jaundice, that required phototherapy and transfusion. One patient was a typical case of HPP splenectomized at the age of 30 years, and the other patient a newborn with a severe clinical form of HS. In both cases, the t-NGS study demonstrated a complex set of five variants

in the SPTA1 gene. Three of these variants were novel, two leading to abnormal splicing, and one to a microdeletion of chromosome 1, confirmed by WES, that removes the entire gene. In the patient with HPP, we have observed that, in addition to ellyptocytes and other bizarre forms, a high number of typical spherocytes are present. This effect is also demonstrated by the Osmoscan profile that is characteristic of HS, probably due to the masking of the HE trapezoid shape of the curve characteristic of ellyptocytes by the more severe rheological abnormalities of spherocytes.
Summary/Conclusion: Our study demonstrates that in HPP, associated with a high percentage of spherocytes and typical HS osmoscan profile, the interactions between both SPTA1 gene variants, in addition to the loss of shape recovery after elongation (ellyptocytes), a membrane instability leading to spherocytosis can also be observed, depending on the severity of tetramerization failure. This highlights the importance of molecular diagnostic in patients with no family history of RBC cytoskeleton disorders.

EP699 PYRUVATE KINASE DEFICIENCY IN THE RUSSIAN FEDERATION: AN OVERVIEW OF CLINICAL CHARACTERISTICS AND MOLECULAR DEFECTS.

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Background: Non-spherocytic hemolytic anemia due to erythrocyte pyruvate kinase deficiency (PKD) is an autosomal recessive disorder associated with more than three hundred mutations in *PKLR* gene. PKD characterized by anemia, jaundice, and splenomegaly.
Until now we have no data on the incidence and prevalence of this disease in Russia. Due to the technical difficulties of conducting a study of erythrocyte pyruvate kinase activity, genetic research is currently the main method for diagnosing this disease in Russia.
Aims: The aim of our study was to create an overview of the PKD population in the Russian Federation.
Methods: We performed a retrospective analysis of data from 43 genetically confirmed cases of PKD. All patients had undergone at least one assessment at our center. The diagnosis was confirmed by next generation sequencing using the Hemolytic Anemia Panel, a 75-gene panel for inherited anemias. Clinical and genetic characteristics were collected from patient records.
Results: Forty-three patients were enrolled. The median age is 5 years old (4 month – 26 years old). The age at diagnosis varied between 4 month and 26 years. The ratio male: female was 1:1.53. At least once transfusion of erythrocyte suspension was required to 42 (97.67%) patients. The minimum age at the debut of transfusion dependence was the first day of life, the maximum – 4 years. Exchange blood transfusion was performed for 14 children, transfusion of packed red blood cells during the first year of life was noted for 40 children; 2 children underwent single transfusions on the background of infectious episodes at 3 and 4 years respectively. Clinically, 43 patients (100%) had an anemia, 29/37 (78,38%) had a splenomegaly and 132 (74,42%) had a jaundice. Iron overload, requiring the chelation therapy, was found in 11 (25.58%) patients. Splenectomy due to high transfusion dependence was performed in 10 patients: transfusion independence was achieved in 5 of them, for the rest cases – an increase of the interval between blood transfusions. Median of surgical intervention is 7 years 4 months, (min – max 1 year 4 months – 14 years 4 months).
The homozygous mutations in the *PKLR* gene were found in 11 patients (25.58%), compound heterozygous mutations in 32 patients (74.42%), 78.67% of them were missense mutations. 36 genotypes were described in 43 patients, among them were: c.1529G>A/c.1529G>A (n=4), c.1137_1139del/c.1456C>T (n=2), c.1079G>A/c.1529G> A (n=2), c.1130T>C/c.1456C>T (n=2), c. c.1174G>A/c.1456C> T (n=2), other genotypes occurred once. Two mutations were the most frequent: c.1529G>A (17.33%) and c.1456C>T (17.33%). Previously not described mutations were identified for 19 (44.19%) patients.
Summary/Conclusion: Patients with PKD are characterized by a predominance of severe course of the disease with early onset and transfusion dependence. PKD is rare for our country with a total number of 43 pediatric patients (2013-2021). The observed clinical and genetic heterogeneity in our cohort highlights the need for interdisciplinary approach and further studies.

EP700 MOLECULAR HETEROGENEITY OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY IN PORTUGAL

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Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect in the world, affecting more than 350 million people. The *G6PD* gene is localized on the X chromosome (Xq28), spanning over 18 kb, and is composed of 13 exons and 12 introns. Until now, almost 400 allelic variants had been reported. The enzyme is responsible for the first step of the pentose phosphate pathway, in which NADPH is produced; hence G6PD is an essential enzyme in red blood cell for defence against oxidative stress. G6PD deficiency can cause neonatal hyperbilirubinemia and chronic haemolytic anaemia, however, most of the individuals are generally asymptomatic, only experiencing episodic acute haemolytic anaemia (AHA) in the contexts of oxidative stress, such as with certain drugs or infection. Patients with chronic nonspherocytic haemolytic anaemia (CNSHA), the severe type of G6PD deficiency, present mutations (Class I variants), most of them located in exons 10 or 11, that encode aminoacids located at the dimer interface, and severely affect protein stability.
Aims: To analyse the molecular heterogeneity of G6PD deficiency in Portugal.
Methods: A total of 143 Portuguese G6PD deficient patients (104 males, 36 heterozygous females and 3 homozygous females, without known black ancestry, had been enrolled in molecular diagnosis of G6PD deficiency at the Haematology Unit from CHUC, between 1994 and 2020. Individuals were mainly from Central Portugal, but also from Southern, Northern and Azores regions. Diagnostic was made based on the clinical history, hematologic data and demonstration of a reduced erythrocyte G6PD activity. Enzyme quantification was addressed by quantitative spectrophotometric enzymatic assay. Molecular study was made by PCR-RFLP analysis or by direct Sanger sequencing of all the exons and adjacent intronic regions of the *G6PD* gene.
Results: Twenty-one different *G6PD* pathogenic mutations were found. Among them, 20 were missense and one was an in-frame deletion of 18 nucleotides in exon 10 (G6PD Tondela). The three most frequent mutations belong to the G6PD A (376G) African background haplotype, namely G6PD A- (202G>A; 68Val>Met) (59.6%), G6PD Betica (968T>C; 323Leu>Pro) (12.3%) and G6PD Santamaria (542A>T; 181Asp>Val) (4.1%). Despite the African background haplotype, most hemizygous patients have non-African Y-chromosomal lineages. From the 18 rare mutations, the most common was G6PD Coimbra (592C>T; 198Arg>Cys), found in 4 chromosomes (2.74%). Four were described as class I G6PD mutations (Shinshu, Tondela, Covão do Lobo and Figueira da Foz). The other rare mutations present in 1, 2 or 3 individuals were: G6PD Vanua Lava, Taipei, Mediterranean, Azores, Mexico City, Seattle, Chatham, Mira d'Aire, Anadia, Canton, Kamiube, Flores and Kaiping. Five G6PD deficient hemizygous individuals (G6PD activity at about 80% in accordance with class III) have the silent mutation 1311C>T (437Tyr=) in combination with the IVS11+93C>T polymorphism, with no other mutation within *G6PD* gene. Six of the rare *G6PD* mutations were found for the first time in the Portuguese population (G6PD Tondela, Anadia, Flores, Azores, Covão do Lobo and Figueira da Foz).
Summary/Conclusion: This report confirms a wide genetic heterogeneity of G6PD deficiency in the Portuguese population.

EP701 SYMPTOMATIC BONE MARROW RECONVERSION: A COMMON FEATURE IN HEREDITARY SPHEROCYTOSIS?

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Background: Hereditary spherocytosis (HS) is a genetic disorder due to red cell membrane protein abnormalities, characterized by chronic and acute hemolytic anemia of variable degrees of severity. Extramedullary hematopoiesis is a rare complication, which has been reported in several single case reports. It is diagnosed through compressive complications or found incidentally at radiographic controls. Bone marrow reconversion, process in which the yellow marrow is transformed back to red marrow in adults, is observed in various pathological situations such as medullary infiltration by oncological blood diseases (lymphomas, leukemias, myelomas, myelofibrosis), in patients receiving hematopoietic growth factors or in thalassemia and sickle cell anemia. It is not known as a common complication in HS. Here we describe for the first time bone marrow reconversion in two unrelated HS patients complaining with disabling knee pain.
Aims: Study clinical manifestations and genetic characteristics of patients with bone marrow complications in our cohort of HS patients.
Methods: We retrospectively collected clinical and biological data from a total of 137 pediatric or adult HS patients (79 females/58 males; median age at diagnosis 12.4 years, (1day-63 years)) followed in our Center, including genetic analyses of genes implicated in red cell membrane disorders. We focused on bone marrow complications, especially extramedullary hematopoiesis and bone marrow reconversion, based on the available radiological data.
Results: We found no case of extramedullary hematopoiesis in this cohort. By contrast, 2 unrelated patients were diagnosed with bone marrow reconversion at the knees. The first one was a 24-years-old male who complained of knee pain during sports activities. MRI found an iliotibial band syndrome and a knee bone marrow reconversion. This led to the diagnosis of fully compensated hemolysis (Hb 137 g/l, reticulocytes: 381G/L), which was confirmed to be HS in our center, using pink test, EMA test and ektacytometry. NGS analyses showed that the patient bore a known *SPTB* frameshift mutation SPTB:p.Lys1337Serfs*3.
After this unusual presentation, a second patient, a 59-year-old woman diagnosed with HS at the age of 11, following the fortuitous discovery of anemia, consulted in our center for the follow up of her disorder. She also had fully compensated hemolysis (hb 123 g/L, reticulocytes 513 G/l). She was not a heavy smoker. She had been complaining of chronic knee pain for several months. Again, MRI, found a typical bilateral bone marrow reconversion, with decreased T1 signal intensity and STIR hyperintensity in tibial and femoral diaphysis bone marrow, respecting epiphyses (Figure). The patient bore a potentially pathogeneous splice mutation disrupting the splice branch point of intron 38 of the *ANK1* gene: ANK1: c.5097-.

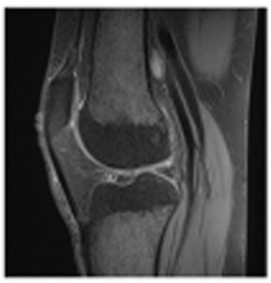


Figure 1A: Bone marrow STIR hyperintensity

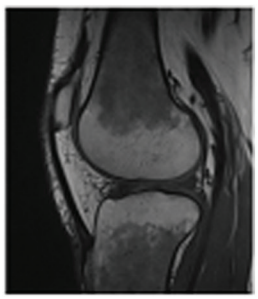


Figure 1B: Bone marrow T1 hypointensity

Summary/Conclusion: Unlike extramedullary hematopoiesis, bone marrow reconversion is an unrecognized bone marrow complication in HS. Extramedullary hematopoiesis is described in HS as mainly mediastinal, paravertebral, renal and splenic masses. Bone marrow reconversion found in 2 patients of this series should be searched more systematically in HS patients. It could be a common and underestimated process leading to chronic and disabling pain in HS patients. Apart from pain medication, the targeted management of this complication requires further investigations in non-anemic patients.

EP702 SOLUBLE CTLA-4 IN CHILDREN WITH IMMUNE CYTOPENIAS: RELATION TO DISEASE ACTIVITY

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Background: Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is a costimulatory receptor exhibiting a potent inhibitory signal on antigen-activated immune responses. A soluble form of CTLA-4 (sCTLA-4), resulting from an alternative splicing, has been identified and was found increased in several autoimmune diseases.
Aims: to evaluate serum levels of sCTLA-4 in different types of immune cytopenias and to determine its possible relation to the disease activity.
Methods: Serum levels of sCTLA-4 were assessed using enzyme linked immunosorbent assay in 47 children and adolescents with immune cytopenias and compared to 47 age- and sex-matched healthy controls.
Results: Among the 47 patients enrolled, 24 (51.1%) had chronic immune thrombocytopenia (ITP), 19 (40.4%) had autoimmune hemolytic anemia (AIHA), and 4(8.5%) patients with autoimmune lymphoproliferative disease (ALPS). sCTLA-4 levels were significantly higher in the sera of patients with immune cytopenias as compared to healthy controls ($p< 0.001$), however, levels were comparable between the different groups of immune cytopenias ($p=0.084$). Serum sCTLA-4 inversely correlated to the age at diagnosis, and hemoglobin level and ($p= 0.048$, and $p=0.039$ respectively), while it directly correlated with the disease duration ($p=0.023$) as well as markers of hemolysis including reticulocyte count, serum LDH and indirect bilirubin ($p=0.025$; $p=0.019$; $p=0.004$ respectively). Moreover, serum sCTLA-4 levels were significantly lower in patients with AIHA in remission compared to patients with active disease ($p=0.026$), however, this was not true among the ITP group ($p=0.523$).
Summary/Conclusion: Our results showed that Children with immune cytopenia exhibit significantly higher levels of circulating sCTLA-4 which correlated to the disease activity. The prognostic significance of the assessment of the circulating sCTLA-4 among patients with immune cytopenia and its use to tailor treatment regimen require additional studies.

EP703 IDENTIFICATION OF A WARM AUTOIMMUNE HEMOLYTIC ANEMIA (WAIHA) POPULATION USING PREDICTIVE ANALYTICS OF A KNOWN CLINICALLY PROFILED COHORT

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Background: The disease burden of warm autoimmune hemolytic anemia (wAIHA), a rare disorder characterized by the destruction of red blood cells (RBCs) by pathogenic IgG autoantibodies, has not been well studied. At the time this claims database analysis was carried out a diagnostic code specific for wAIHA did not exist, which presented challenges in identifying patients with wAIHA.
Aims: Despite the absence of a diagnostic code specific for wAIHA we aimed to 1) identify a wAIHA cohort using a collection of diagnostic codes, 2) bisect severe versus non-severe wAIHA patients, 3) compare the frequency of comorbidities, anemia symptoms, treatments, diagnostic tests, and healthcare provider visits in these two groups, and 4) use a predictive model to validate clinical variables and prevalence estimates.
Methods: A de-identified, longitudinal, patient-level claims database of >300 million US patients was used for this study. Patients with wAIHA were identified based on a diagnosis code of "autoimmune hemolytic anemia" (AIHA), chronic use of steroids (≥ 30 days) in the last 36 months, and chronic use of non-steroidal immunosuppressants. Patients were classified as severe if claims related to transfusion, high frequency of blood testing, high frequency interactions with a hematologist, and/or ≥ 2 ER visits per year were observed in the 36-month period. Codes for anemia symptoms, comorbidities, treatments, and diagnostic tests were

grouped and analyzed within the most recent 12 months for each patient. Prevalence was estimated using Artificial Intelligence/Machine Learning (AI/ML) lookalike modeling, using known patients with wAIHA as the positive training class.
Results: A cohort of 1,548 patients with wAIHA was identified (n= 631 were classified as severe while n= 917 as non-severe). Median patient age was > 65 years, and patients were evenly distributed by gender. The rate of disease-relevant claims was disproportionately higher in the severe cohort versus the non-severe cohort. Over the 12-month study period, there was a 61% higher rate for anemia symptomatology codes and a 570 % higher rate for wAIHA specific testing and monitoring codes in the severe cohort. Primary hypertension, hyperlipidemia, gastro-esophageal reflux, and evidence of chemotherapy use were also present in wAIHA patients. All these conditions were observed more frequently in severe patients with the exception of lupus. Almost 44% of wAIHA claims for the full cohort were associated with hospital/emergency care - 48% for the severe group. AI/ML modeling predicted patients using claims variables for hemolytic anemia, other blood count abnormalities, and medical procedure claims commonly used for the diagnosis and management of wAIHA. The predictedpopulation supports reported US prevalence estimates of 30,000-49,000 patients.
Summary/Conclusion: We developed and validated a method for defining wAIHA patients using de-identified claims data based on AIHA ICD-10 codes and relevant treatments. We observed that while disease manifestations are generally the same in the severe and non-severe wAIHA cohorts, there is an increased rate of occurrence in the severe cohort during the same 12-month period. This increase was also associated with higher utilization of healthcare resources. The comorbidity of lupus was more commonly associated with non-severe wAIHA patients. This may indicate that patients with a known diagnosis (in this case lupus) who are more closely monitored are less likely to reach the level of severity that would categorize them as patients with severe wAIHA.

EP704 CLINICAL FEATURES AND TREATMENT RESPONSES IN PEDIATRIC PATIENTS WITH WARM ANTIBODY IMMUNE HEMOLYTIC ANEMIA

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Background: Autoimmun hemolytic anemia (AIHA) is characterized with autoantibodies that target normal red blood cell membrane antigens and induce cell lysis. Although there have been both pediatric and adult patients with AIHA, its presentation in childhood is relatively rare. Based on this, treatment responses and clinical findings of children with AIHA are very important.
Aims: In this study, we aimed to evaluate the treatment responses and clinical features of pediatric patients with AIHA who were followed up in our center.
Methods: This is a 12 years retrospective cohort study of warm AIHA case collected at Hematology and Oncology Clinic of Dr. Behcet Uz Children's Hospital. We included 39 patients aged between 1 month and 18 years. These patients' demographic characteristics, laboratory findings at diagnosis and treatment responses were recorded. Patients with underlying immunodeficiency or autoimmune disease were classified as secondary AIHA, and the other patients as idiopathic AIHA. Idiopathic and secondary autoimmune hemolytic anemia groups were compared in terms of recurrence. The patients groups according to first-line treatment selection were also compared in respect of recurrence.
Results: Thirty-nine patients with warm AIHA were collected 16 (41%) girls and 23 (59%) boys. The mean age at diagnosis was 5.1 ± 4.5 years and the mean follow-up period from diagnosis was 7.2 ± 5.9 years. Distrubition of the patients according to classification is seen table 1. Twelve (30.7%) patients reported consanguinity and viral etiology was detected in four (10.2%) patients. At the time of diagnosis, 6 patients received IVIG, 17 patients received steroid, 15 patients received IVIG + steroid combined therapy and only one patient didn't need treatment. Twenty-three (59%) of them required blood transfusions with a mean hemoglobin level of 5,40 ± 1,83 g/dl. The mean hemoglobin level of 16 (41%) patients who were not transfused at diagnosis was 7,67 ± 1,92 g/dl. According to response criteria 19 (48.7%) of the patients had complete response, 19 (48.7%) had partial response, and one patient (2.6%) was unresponsive. There weren't difference among the 3 groups of patients who were received IVIG, steroid or IVIG + steroid combined therapy in terms of recurrence during diagnosis (p = 0.128). There were 18 (46.2%) and 2 (5.1%) patients in the secondary and idiopathic AIHA groups who relapsed after treatment response at the time of diagnosis, respectively (p <0.001). During follow up additional therapies which include cyclosporine (n=7), mycophenolate mofetil (n=7), rituximab (n=3) sirolimus (n=2) and danazol (n=1) were applied. Four (10.2%) patients were splenectomised. Two patients (DOCK 8 deficiency and Digeorge syndrome) died.

Table 1. Distrubition of the patients according to warm antibody AIHA classification

	n (%)
Idiopathic	18 (46)
Secondary	21 (54)
1. Autoimmune disease	
• Evans syndrome	6 (15)
• Systemic lupus erythematosis	2 (5)
2. Immun deficiency	
• CTLA-4 haplo insufficiency	1 (2)
• Transient hypogammaglobulinemia of infants	1 (2)
• Digeorge syndorme	2 (5)
• DOCK-8 deficiency	2 (5)
• PNP deficiency	1 (2)
• Hypogammaglobulinemia	3 (8)
3. Autoimmune lymphoproliferative disease	3 (8)
Total	39 (100)

AIHA: Autoimmun hemolytic anemia, CTLA-4 : T lymphocyte associated protein 4, DOCK-8: Dedicator of cytokines 8, PNP: Purine nucleoside phosphorylase,

Summary/Conclusion: This study highlights heterogenity, severity and response rate of first line therapy in pediatric patients with warm AIHA. First line therapy with steroids is effective. However challenges in management of reccurent case remain unresolved. Thus the findings in this study may contributed to clinical features of recurrence in pediatric patients with warm reactive AIHA.

EP705 AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH LYMPHOID MALIGNANCIES: REPORT FROM A FRENCH PROSPECTIVE REGISTER.

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Background: The incidence of autoimmune hemolytic anemia (AIHA) is estimated between 1 to 3/100,000 person-years and is associated to another disease in half of the cases, mostly hematological malignancies. The accurate incidence of lymphoid malignancy (LM)-related AIHA remains elusive as previous data have been obtained from cohorts from tertiary centers, with possible selection bias.
Aims: Determination of the frequency, clinical characteristics, and evolution of LM-related AIHA based on prospective data collected in the register of hematological malignancies of Côte d'Or (RHEMCO), a population-based register recording all incident hematological malignancies occurring in a restricted geographical area of 532,886 inhabitants.
Methods: Patients included in RHEMCO between 01/01/1995 and 31/12/2015 were considered to calculate incidences. The medical records of AIHA patients referred to our tertiary hospital during the same periods were also considered for the clinical description and the

evolution of LM-related AIHA. AIHA was defined as regenerative (reticulocytes >120 G/L) anemia (hemoglobin <11 g/dL) with hemolysis (haptoglobin <0.3 g/L, elevated LDH, free bilirubin >14 µmol/L) and a positive direct antiglobulin test. Response was defined as hemoglobin >10 g/dL.

Results: Based on RHEMCO, the frequency of AIHA during LM was 0.77% (n=27/3499): 1.10% for chronic lymphoid leukemia (CLL), 0.67% for B cell lymphoma, 0.87% for T cell lymphoma and 0.36% for Hodgkin lymphoma (HL). The frequency of Evans' syndrome (ES) was 0.29% (n=10/3499): 0.44% for CLL, 0.24% for B cell lymphoma and 0.43% for T cell lymphoma.

From RHEMCO and medical records, 56 patients with secondary AIHA were identified among which 17 had ES. The median age at diagnosis was 74 [interquartile range (IQR): 54-92] years and 54% were male. For ES, the median age was 62 [IQR: 29-85] years and 76% were male. AHAI was associated with B cell lymphoma in 54%, CLL in 30.5%, T cell lymphoma in 13% and HL in 2.5%. ES was also mostly associated with low grade B cell lymphoma (47%) and CLL (41%). Anemia occurred after the diagnosis of LM in 38% of the cases with a median delay of 3 [IQR:0.5-18.4] years and 65% for ES, with a median delay of 5.1 [IQR:0.3-10.1] years. LM and AIHA were diagnosed simultaneously (≤ 3 months) in 49% of the cases for isolated AIHA and 29% for ES. Splenomegaly was observed in 63% of the cases. At AIHA diagnosis, the median hemoglobin level was 7.5 [IQR:3.5-12.3] g/dL. Warm antibodies represented 87% of the cases. Monoclonal gammopathy was detected in 47% of the cases and a circulating lymphocyte clone in 89%.

Patients with LM-related AIHA were treated in 97% of the cases, with medications dedicated to AIHA in 90% of the cases and specifically for LM in 67%. AIHA responded to steroids in 53% (n=17/32), to rituximab in 82% (n=14/17) and to splenectomy in 43% (n=3/7). After a median follow-up of 5.6 years, AIHA was considered in remission in 56%.

Summary/Conclusion: LM-related AIHA is rare, with an incidence of 0.063/100,000 person-years for CLL, 0.081/100,000 for B cell lymphoma and 0.01/100,000 for T cell lymphoma and HL. These incidences are close to the ones observed for LM-related ITP although ITP is considered 3 times more frequent than AIHA, highlighting the frequent secondary nature of AIHA. The diagnosis of AHAI was made simultaneously or after LM in almost 90% of the cases. Rituximab seems to be a treatment of choice in LM-related AIHA as shown by a response rate close to the one of primary AIHA.

EP706 FACIT-FATIGUE SUBSCALE OUTCOMES FROM AN ONGOING PHASE 2, OPEN-LABEL STUDY OF THE PHOSPHATIDYLINOSITOL 3-KINASE DELTA (PI3KΔ) INHIBITOR PARSACLISIB IN PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

F. Pane [1,*], I. Murakhovskaya [2], L. Terriou [3], W. Barcellini [4], A. Patriarca [5], K. Bibeau [6], K. Butler [6], S. Moran [6], S. Wei [6], U. Jäger [7]

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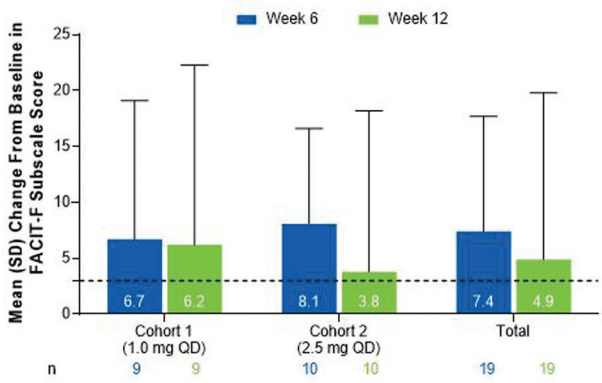
Background: AIHA is a rare acquired disorder resulting from decompensated autoantibody-mediated hemolysis of red blood cells. AIHA is characterized by low hemoglobin levels, which may lead to fatigue, one of the most common symptoms of AIHA. Fatigue has been associated with reduced overall quality of life (QoL) in anemia and other conditions, and a clinically meaningful reduction in anemia-related fatigue (ie, ≥3-point increase in the Functional Assessment of Chronic Illness Therapy–Fatigue subscale [FACIT-F]) may improve QoL. There are no approved treatments for AIHA. Aberrant signaling of PI3Kδ has been associated with autoimmunity. Parsaclisib is an orally administered selective PI3Kδ inhibitor that showed clinical antitumor activity in B-cell malignancies and ameliorated kidney and salivary gland pathology in autoantibody-mediated preclinical disease models of systemic lupus erythematosus and Sjögren's syndrome, respectively.

Aims: To describe FACIT-F outcomes from an ongoing, multicenter, open-label phase 2 study (NCT03538041) of parsaclisib for the treatment of patients with primary AIHA.

Methods: Eligible patients were aged ≥18 years; were diagnosed with primary warm AIHA (wAIHA), cold agglutinin disease (CAD), or mixed-type AIHA without an underlying lymphoproliferative malignancy or other autoimmune-related underlying conditions; had hemoglobin levels of ≥7–≤10 g/dL; and failed ≥1 prior treatment for AIHA. After informed consent was obtained, patients were enrolled into 1 of 2 successive cohorts and received parsaclisib for 12 weeks. In cohort 1, patients received parsaclisib 1.0 mg once daily (QD) with the option to have a dose increase (2.5 mg QD) at Week 6. In cohort 2, patients received parsaclisib 2.5 mg QD; a dose reduction to 1.0 mg QD was permitted for tolerability. Following completion of the initial 12-week treatment period, eligible patients achieving clinical benefit could continue into an open-label extension period. For the QoL assessment, patients responded to the FACIT-F subscale questionnaire at baseline, Week 6, and Week 12. An increase in FACIT-F score indicates less fatigue and better QoL.

Results: By the data cutoff date (October 12, 2020), 21 patients had enrolled (10 patients in cohort 1; 11 in cohort 2). The 2 cohorts were similar in age (median [range]: cohort 1, 62.0 [46–77] years; cohort 2, 60.0 [22–80] years), sex (male: cohort 1, 40%; cohort 2, 55%), AIHA subtype (wAIHA: cohort 1, 70%; cohort 2, 64%; CAD: cohort 1, 20%; cohort 2, 18%; mixed: cohort 1, 10%; cohort 2, 18%), baseline hemoglobin levels (mean [SD]: cohort 1, 9.1 [0.8] g/dL; cohort 2, 9.0 [0.8] g/dL), and baseline FACIT-F scores (mean [SD]: cohort 1, 32.6 [12.8]; cohort 2, 34.8 [11.7]). Both cohorts showed an increase in FACIT-F subscale score compared with baseline at Week 6 (mean [SD] change from baseline: cohort 1, 6.7 [12.4]; cohort 2, 8.1 [8.5]; total, 7.4 [10.3]) and Week 12 (mean [SD] change from baseline: cohort 1, 6.2 [16.1]; cohort 2, 3.8 [14.4]; total, 4.9 [14.9]; **Figure**). Mean (SD) percentage change from baseline in FACIT-F score was 40% (71.8) for all patients (cohort 1, 52% [100.7]; cohort 2, 29% [31.8]) at Week 6 and 35% (81.2) for all patients (cohort 1, 55% [111.2]; cohort 2, 17% [37.6]) at Week 12.

Figure. Change From Baseline in FACIT-F Subscale Score at Weeks 6 and 12



FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; QD, once daily.
Dashed line indicates a clinically meaningful improvement from baseline (≥3-point increase in FACIT-F score).

Summary/Conclusion: Parsaclisib treatment was associated with a clinically meaningful (ie, ≥3-point) improvement in fatigue-related QoL in patients with AIHA. This benefit was seen as early as Week 6 and persisted throughout the treatment period.

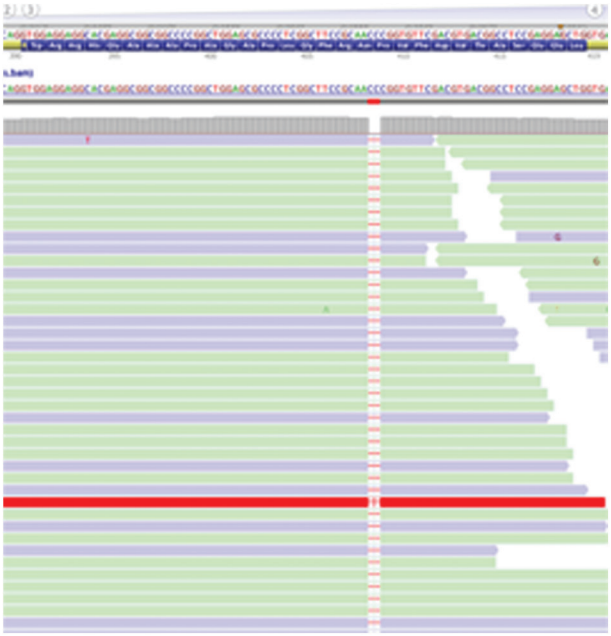
EP707 CLINICAL AND MOLECULAR CHARACTERISTICS OF IMERSLUND-GRÄSBECK SYNDROME: FIRST REPORT OF A NOVEL FRAMESHIFT VARIANT IN EXON 11 OF AMN GENE

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Background: Imerslund-Gräsbeck syndrome (IGS) is a rare autosomal-recessive disorder characterized by selective vitamin B12 malabsorption, megaloblastic anemia, and proteinuria. The precise incidence of this disorder is unknown in the Middle East and Arab countries. The

disease is caused by a homozygous variant in either AMN or CUBN genes. In addition, some compound heterozygous variants are reported.
Aims: To report the clinical, laboratory and molecular data of patients diagnosed with IGS in Oman.
Methods: All data were retrospectively collected. Mutation analysis for all genes involved in vitamin B12/folic acid metabolism and megaloblastic anemia was conducted using next-generation sequencing (NGS).
Results: Three siblings (2 girls and a boy) have been diagnosed with the condition. They exhibit a phenotypic variability with different age of presentation and different spectrum of disease. All patients harbor a novel biallelic frameshift mutation in exon 11 of AMN gene (p.Pro409Glyfs*), which was not reported previously in the literature (Figure). Both parents are heterozygotes for the same variant. All patients responded well to vitamin B12 parenteral therapy, but proteinuria persisted.



Summary/Conclusion: In communities with high incidence of consanguinity, cases of early-onset vitamin B12 deficiency should be thoroughly investigated to explore the possibility of Imerslund-Gräsbeck syndrome and other vitamin B12–related hereditary disorders. Further local and regional studies are highly recommended.

EP708 USE OF AN NGS PANEL FOR DE DIAGNOSIS OF HEREDITARY HEMOLYTIC ANEMIAS

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Background: Hereditary haemolytic anemias (HA) are a group of heterogeneous, low frequency entities characterized by the premature destruction of red blood cells (RBC). They are usually secondary to genetic mutations leading to alterations in hemoglobin or membrane structure and enzimatic production, as well as RBC differenciation and proliferation. In many cases, attaining an accurate diagnosis is complex due to overlapping clinical presentation, variable clinical expression and great variety of implicated genes.
The recent use of next generation sequencing (NGS) has led to an improvement in our understanding of these entities by widening the knowledge of genetic alterations involved, and has proved a useful tool for both diagnosis and genetic advice.
Aims: The aim of this study is to evaluate the results of an NGS panel for congenital anemias and medullary aplasia in a single center in Madrid, Spain.
Methods: A total of 39 patients were included in the study, 71% had clinical suspicion of HA and 28% had familiar history of hereditary anemia. We performed NGS (Ion Torrent S5XL System – Thermofisher Scientific) of a panel comprising 55 genes related to metabolic enzymes (AK1, ALDOA, BPGM, G6PD, GPI, GSS, HK1, NT5C3A, PFKFB1, PGK, PKLR, TPI1), membrane and cytoskeleton proteins (ANK1, EPB41, EPB42, EPB72, SLC4A1, SPTA1, SPTB, PIEZO1, PIGA, PIGT), ribosomic proteins (RPL11, RPL15, RPL5, RPS19, RPS26, SBDS), telomeric regulators (RTEL1,TERT, TERC, TINF2, DKC1), DNA repair (FANCA, FANCC, FANCG, LIG4), transcription factors (GATA1, GATA2, MECOM), globin chains (HBA1, HBA2, HBB) and other non-classifiable genes (ANKRD26, ATRX1, DNAJC21, SRP72, TRS2, HAX1, SAMD9, SAMDL9, ADAMTS13, ELANE, ERCC6L2, DDX41).
Results: The median age was 31 years; R(0-72), 59% were female. Mean hemoglobin was 12.5 g/dL and mean reticulocyte count was 100650/ml. Hemolysis paramethers were slightly elevated (mean LDH 244 U/L, mean bilirubin 1.73 mg/dL).
81% of the patients presented at least one genetic variant in the NGS study (median of 3 variants per patient). Among these, 71% presented pathogenic/likely pathogenic variants which were considered useful for the diagnosis, and 6 had variants of undetermined significance. Single Nucleotide Variation (SNV) were the most common, present in all patients with any variant. Insertions or deletions (indels) were additionally present in 20% of them.
Most of the variants were detected in genes associated with membrane and cytoskeleton (24; 58.5%), others non-classifiable (10; 24.4%), DNA repair (8; 19.5%), enzymatic genes (6; 14.6%), globin chains (5; 12.2%), telomeric genes and transcription factors (both 4; 9.8%) and ribosomic genes (3; 7.3%).
Genotype-phenotype correlation was variable in each group. Erytrocite membrane defects were confirmed in 70% of the patients with this clinical suspicion, but only 38% of the patients who were suspected of an alteration in globin chains had a proven genetic variant in these genes with a high percentage presenting alterations in membrane and cytoskeleton genes. Among the 5 patients with unknown HA, 3 had likely pathogenic variants in membrane and cytoskeleton genes and 2 in metabolic enzymes genes. 5 patients had pathogenic/likely pathogenic variants in various genes pertaining to more than one group, a situation with uncertain clinical significance.

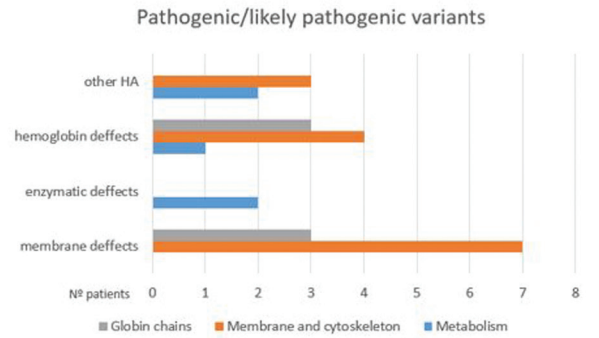


Figure 1. Correlation genotype-phenotype. Clinical suspicion (Y-axis) and gene affected in the NGS panel (color code).

Summary/Conclusion: NGS is a useful tool for the diagnosis of hereditary hemolytic anemias. However, there are still a lot of unknowns in the genetic landscape that must be addressed to improve our understanding of these diseases.

EP709 INFLAMMATION AND FATIGUE IN PATIENTS WITH COLD AGGLUTININ DISEASE (CAD): ANALYSIS FROM THE PHASE 3 CARDINAL STUDY

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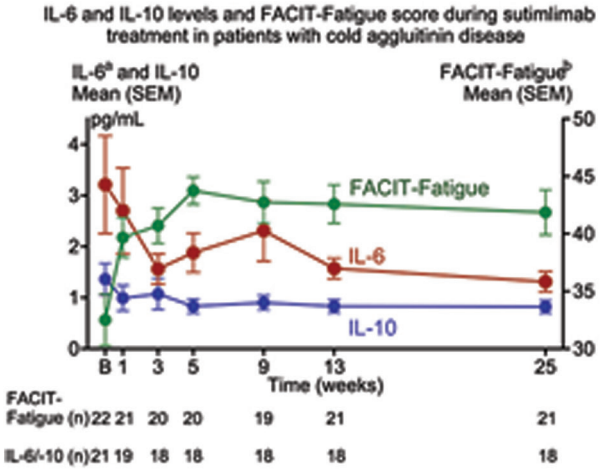
Background: CAD is a rare and chronic autoimmune hemolytic anemia driven by activation of the classical complement pathway. Complement activation increases vascular inflammatory markers via generation of anaphylotoxin C3a- and C5a-mediated response of increased cytokine production (eg, interleukins [IL]-6 and IL-10) (Cofiell et al. *Blood*.

2015; Landsem et al. *Clin Exp Immunol*. 2013). In CAD, classical complement pathway activation and resulting chronic inflammation may contribute to patient fatigue beyond anemia. A chronic complement-mediated proinflammatory state exists in other hemolytic diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (Cofiell et al. *Blood*. 2015; Weitz et al. *Thromb Res*. 2012) with cytokine levels associated with fatigue (Weitz et al. *Thromb Res*. 2012; Montoya et al. *Proc Natl Acad Sci USA*. 2017); however, this association has not been formally studied in CAD. Sutimlimab (formerly BIVV009) is a first-in-class humanized immunoglobulin G4 monoclonal anti-C1s antibody that selectively inhibits the classical complement pathway. Here we summarize the results of an analysis of inflammatory cytokine expression and fatigue over the Part A 26-week treatment period of CARDINAL.

Aims: To assess key inflammatory cytokine IL-6 and IL-10 activity and their relation to fatigue in patients with CAD and the effect of treatment with sutimlimab.

Methods: Twenty-four patients with CAD and recent history of transfusion were enrolled in CARDINAL Part A and received intravenous sutimlimab on Days 0 and 7, then biweekly infusions (6.5 g dose for weight <75 kg [n=17]; 7.5 g dose for weight ≥75 kg [n=7]). Cytokine profiles (IL-6 and IL-10) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores were assessed from baseline to Weeks 1, 3, 5, 9, 13, and 25 as represented by the treatment assessment time point after initiating sutimlimab treatment. Summary statistics were reported at each time point.

Results: In CARDINAL Part A, baseline mean FACIT-Fatigue score (mean pg/mL [standard error of the mean (SEM)]) was 32.5 (2.3), which is comparable to fatigue severity in another complement-mediated hemolytic anemia, paroxysmal nocturnal hemoglobinuria (Schrezenmeier et al. *Haematologica*. 2014), and cancer (Escalente et al. *Cancer Med*. 2019). Sutimlimab treatment rapidly inhibited the classical complement pathway with a rapid improvement in mean FACIT-Fatigue score by Week 1 that was maintained through to the treatment assessment time point (**Figure**). Mean IL-6 level was 3.21 pg/mL at baseline, decreased as early as Week 1 (2.70 pg/mL) after starting sutimlimab treatment and was 1.31 pg/mL at Week 25 (**Figure**). A similar pattern of change was observed for IL-10, with the mean values of 1.36 pg/mL at baseline and 0.82 pg/mL at Week 25 (**Figure**). Decreased inflammation, as demonstrated by IL-6 and IL-10 activity, inversely correlated with FACIT-Fatigue score improvements over time.



B, baseline; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; IL, interleukin; SEM, standard error of the mean.
[a]Normal values for IL-6 were <3.2 pg/mL. [b]Increased FACIT-Fatigue reflects decreased fatigue and improved quality of life, and a clinically meaningful improvement in cold agglutinin disease is≥5 points.

Summary/Conclusion: Sutimlimab treatment in the CARDINAL Part A study was associated with rapid and steady decrease in IL-6 and IL-10 levels that coincided with clinically meaningful improvements in fatigue. These results suggest that, in addition to anemia, complement-mediated inflammation may contribute to fatigue manifestation in patients with CAD and improve with complement inhibition. Furthermore, they highlight the influence of classical complement pathway inhibition on inflammatory activity in CAD.

EP710 MORTALITY AMONG VETERANS WITH A DIAGNOSIS OF PYRUVATE KINASE DEFICIENCY: A REAL-WORLD STUDY USING US VETERANS HEALTH ADMINISTRATION DATA

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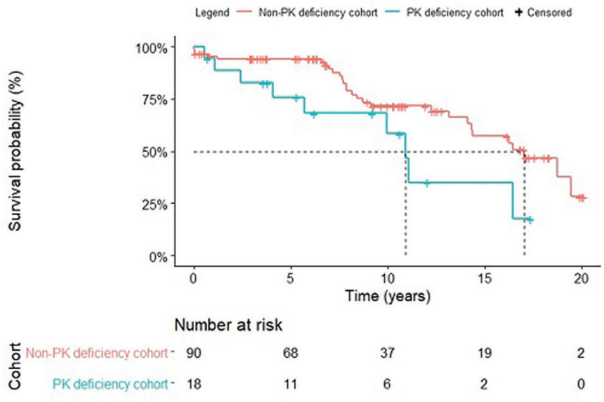
Background: Pyruvate kinase (PK) deficiency is a rare, hereditary disease caused by autosomal recessive mutations in the *PKLR* gene, where a glycolytic defect causes reduced adenosine triphosphate levels, leading to hemolytic anemia. Serious complications such as osteoporosis, pulmonary hypertension, sepsis, iron overload, and liver cirrhosis are associated with the disease and its therapy. Treatment is supportive only, and comprises splenectomy, blood transfusions, iron chelation, and management of disease-related morbidity. Identifying PK deficiency in real-world data is challenging due to a lack of diagnosis codes and treatments that are specific to the disease. Hence, population-based studies of PK deficiency using claims or electronic health record databases are limited. In addition, data on mortality in this patient (pt) population are lacking and limited to a few individual case reports.

Aims: This study aimed to identify pts with a PK deficiency diagnosis as documented by physicians and to compare their mortality to an age- and gender-matched cohort of individuals without the disease.

Methods: Pts with ≥1 diagnosis code related to PK deficiency (ie, anemia due to disorders of glycolytic enzymes, other hemolytic anemias due to enzyme deficiency, or unspecified hereditary hemolytic anemia) from January 1995–July 2019 were selected from the US Veterans Health Administration (VHA) database. Inclusion criteria required physicians' notes to contain the words "pyruvate", "kinase", and "deficiency." A manual review of these notes was performed to identify pts with a physician-documented diagnosis of PK deficiency (PK deficiency cohort). The index date for this cohort was defined as the date of the first medical record with a diagnosis code related to PK deficiency. Each pt in this cohort was matched 1:5 by age at index, sex, and index year (yr) (±1 yr) to pts from the general VHA population with no diagnosis codes related to PK deficiency (non-PK deficiency cohort). The index date for the non-PK deficiency cohort was defined as a random visit date during their match's index yr. Survival time from the index date was compared between the PK deficiency cohort and their non-PK deficiency cohort matches using a univariate Cox proportional hazards model with robust standard error estimation.

Results: A total of 18 pts met inclusion criteria for the PK deficiency cohort and were matched to 90 individuals in the non-PK deficiency cohort. For both cohorts, mean age at index was 57 yrs, 94% were male, 83–85% were white, and mean Charlson Comorbidity Index score was 0.4–0.5 (no significant differences between cohorts). The median follow-up was 6 yrs for the PK deficiency cohort and 8 yrs for the non-PK deficiency cohort. During this period, 9 (50%) and 28 (31%) deaths were observed in the PK deficiency and non-PK deficiency cohorts, respectively. The median time to death was 10.9 yrs for the PK deficiency cohort and 17.1 yrs for the non-PK deficiency cohort (hazard ratio: 2.3; p=0.0306); the Kaplan–Meier curves for both cohorts are shown in the Figure. Ten yrs post-index, 42% and 28% of pts had died in the PK deficiency and non-PK deficiency cohorts, respectively.

Figure. Kaplan–Meier survival estimates for both cohorts



Summary/Conclusion: Results of this study suggest that pts with PK deficiency may be at an increased risk of mortality. Further research to understand cause of death in this population is warranted, as is the replication of this study using larger sample sizes and other real-world data sources that better represent females and the pediatric and adolescent PK deficiency age groups.

EP711 FEASIBILITY STUDY: USING DRIED BLOOD SPOTS AS A DNA SOURCE TO SCREEN FOR PYRUVATE KINASE CAUSING VARIANTS

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Background: Pyruvate kinase deficiency (PKD) is a genetic blood disorder typically caused by mutations in the *PKLR* gene, leading to low levels of pyruvate kinase enzyme, which is required by red blood cells to make energy. PKD is inherited in an autosomal recessive fashion but in some individuals only one pathogenic variant can be identified after sequencing gene exons. Patient genotypes have been associated with severity of disease, with patients carrying a non-missense mutation having a more severe presentation. Therefore, understanding the underlying genetic defect in individuals is important as it can inform patient management. On rare occasions, PKD can arise from pathogenic variants in the *KLF1* gene, a transcription factor that controls *PKLR* gene expression.
We have developed a small NGS panel to sequence the entire footprint of the *PKLR gene* and exons of *KLF1*. Bloodspots have also been investigated as a sample source. They do not need expensive packaging like liquid blood samples, and can be sent through the post. This small change could help countries refer samples for analysis if they do not have access to *PKLR* gene sequencing.
Aims: To develop a targeted NGS assay capable of using DNA from liquid blood samples and from bloodspots to detect all known types of genetic variants that cause PKD (SNVs, small indels and deletions).
To cover the entire footprint of the *PKLR* gene to detect deep intronic variants which may contribute to the phenotype.
Methods: Residual clinical samples were used as positive controls from patients previously diagnosed with PKD. These individuals had undergone Sanger sequencing of the *PKLR* gene as part of their diagnostic work up. Bloodspots were created from liquid blood samples and DNA extracted from both for comparison.
Qiagen Qiaseq was used to target and amplify genomic regions of interest in all samples. This uses unique molecular indices to label each amplicon enabling duplicate reads to be discarded and CNV detection possible. All genetic variation was assed using the ACMG guidelines.
Results: Comparing the sequence between the new method and the existing Sanger sequencing method there was 100% concordance in the genetic findings. A minimum of 10ng of input DNA is required for the new methodology which can be extracted from a bloodspot. Liquid blood and bloodspot samples from the same primary sample identified the same genetic variants, indicating that bloodspots are a suitable sample for diagnosis.
Sequencing 80 patient cases (mostly liquid blood), identified 73 different genetic variants in total (19 class 1, 7 class 2, 22 class 3, 11 class 4 and 14 class 5). Most of the common variants were present in all cases. Six of the class 3 variants warrant further investigation, four of these are deep intronic variants which may affect *PKLR* gene splicing. These have been identified in individuals with PKD but with only one known pathogenic variant identified to date.
Summary/Conclusion: Our data show that bloodspots are a good source of DNA and are suitable for clinical diagnosis. The assay and the bioinformatic pipeline is able to identify all variant types which are known to cause PKD. The approach to sequence the entire *PKLR* gene may be clinically beneficial, but it does identify more variants of unknown clinical significance compared to exon only sequencing. Functional studies are required in order to investigate these further, to build the knowledge base and to make this data clinically useful.

EP712 USEFULNESS OF NGS TECHNIQUES FOR PYRUVATE KINASA DEFICIENCY (PKD) DIAGNOSIS IN SPAIN

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Background: PKD is the second most frequent enzymopathy and the first to produce chronic hemolytic anemia. Its prevalence is underestimated due to the low clinical suspicion, especially in mild cases, the low expressiveness of the peripheral blood smear and the limitations of enzymatic techniques. Next-generation sequencing techniques (NGS) allow simultaneous study of multiple causal genes in multiple patients, which provides the diagnosis of congenital hemolytic anemias.
Aims: During one year, all cases of undiagnosed chronic hemolytic anemias suspected to be PKD in Spain were remitted for NGS analysis.
Methods: DNA obtained from peripheral leukocytes was analyzed using a 40 genes panel covering congenital anemias at the Hematology Services of the Clínico San Carlos and Cruces University Hospitals. Ilumina platform (Truseq Custom Amplicon) was used. Pathogenic variants and those of uncertain significance were reported, using the GRCh37 / Hg19 genome as reference.
Results: Ninety-nine patients with congenital anemias from 23 national centers were analyzed. **PKD mutation was detected in 24 patients, 18 of them correctly suspected** of PKD (18/24, 75%), 3 of them were associated with a membranopathy, while 3 other suspected cases (12.5%) were finally diagnosed as hereditary membrane disorders, particularly xerocytosis (HX, 2 cases). Initial suspicion was different from PKD in 75 patients (18 membranopathies, 4 G6PD, 4 CDA and 49 with unknown origin). PKD explained **4% of the cases of undiagnosed anemias (2/49)** and was also detected in **two patients suspected of membranopathy (2/18),** interestingly with these two different diseases associated. It should be noted that **half (2/4) of the suspected cases of congenital dyserythropoietic anemia** (CDA) were eventually diagnosed as PKD. No cases of PKD were detected in patients suspected of G6PD deficiency.
Twenty-eight different gene variants were found in the 24 PKD confirmed cases. Six variants were constantly repeated in more than one patient, sometimes in combination: R486W (50% of patients), R337Q (17%), E241X (12.5%), R510Q (8%), I378X (8%), R559X (8%).
Summary/Conclusion: Our results confirms that NGS technique has become a powerful diagnostic tool, enabling a diagnoses in 78% of patients with congenital anemias in this study. Further, it allowed for the diagnoses of the majority of patients with clinical suspicion of PKD (75%), the detection of combined genetic alterations (in particular, 5 out of 24 PKD cases were combined with membranopathies), and the diagnosis of PKD in a high percentage of cases suspected of CDA (50%) or in a low percentage of unexplained anemias (4%). NGS also enabled the correct identification of two XH cases, initially suspected of PKD. The pathogenic variants detected in Spain are consistent with those previously reported, with the exception of the lower percentage of R510Q.

EP713 STUDY DESIGN OF A PHASE 2/3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF NIPOCALIMAB, AN FCRN ANTAGONIST, IN WARM AUTOIMMUNE HEMOLYTIC ANEMIA (WAIHA)

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Background: Warm autoimmune hemolytic anemia (wAIHA) is characterized by the destruction of red blood cells (RBCs) by pathogenic autoantibodies which bind to RBCs and lead to their clearance in the spleen and liver. Patients with wAIHA can experience acute worsening of anemia, which can be a medical emergency, and have an increased risk of thromboembolic events and premature death. Nipocalimab is a fully human, aglycosylated, effectorless IgG1 monoclonal antibody that targets the IgG binding site on the neonatal Fc receptor (FcRn) with high affinity. FcRn, which is expressed in endothelial cells, is responsible for recycling IgG into the circulation and for the relatively long half-life of IgG antibodies compared to other Igs. It is expected that nipocalimab,

by inhibiting IgG binding to FcRn, will prevent IgG recycling and lower pathogenic IgG autoantibodies that cause many autoimmune diseases including warm autoimmune hemolytic anemia (wAIHA).
Nipocalimab has been studied in multiple phase 1 studies in healthy subjects and in a recently completed phase 2 study in subjects with Generalized Myasthenia Gravis (gMG). In the gMG phase 2 study, nipocalimab was generally well tolerated at doses from 5 mg/kg every 4 weeks to 60 mg/kg every 2 weeks. Treatment with nipocalimab was associated with rapid and durable total serum IgG and pathogenic IgG autoantibody reduction and meaningful clinical response. A statistically significant relationship between IgG autoantibody reduction and clinical benefit was observed. This study provided proof-of-concept evidence that lowering pathogenic IgG autoantibodies can ameliorate the autoimmune condition these antibodies cause.
Aims: To share the rationale and study design for an adaptive, phase 2/3 multicenter, randomized, double-blind, placebo-controlled study in patients with wAIHA whose aim is to evaluate the efficacy, safety, tolerability, PK, and PD of nipocalimab compared with placebo[1].
Methods: Male or female subjects ≥18 years of age who have been diagnosed with primary or secondary wAIHA and have not experienced a sufficient response or have not tolerated currently available treatments will be included in the study. Subjects with cold antibody AIHA, cold agglutinin syndrome, mixed type (i.e., warm and cold) AIHA, or paroxysmal cold hemoglobinuria will be excluded. Patients will be randomized 1:1:1 to receive nipocalimab at two different dose schedules or placebo. Following completion of 24 weeks of double-blind treatment, patients may enter an open-label extension period to receive nipocalimab.
Results: The following endpoints will be analyzed:
Primary endpoint:
Percentage of participants achieving durable response of improvement in hemoglobin (Hgb).
Main secondary endpoints:
Change from baseline in the total score from the Functional Assessment of Chronic Illness Therapy-Fatigue Scale at the end of the double-blind period.
Number of participants who attain normal lactate dehydrogenase, normal haptoglobin, and normal indirect bilirubin levels at a minimum of 3 consecutive visits after baseline.
Summary/Conclusion: A phase 2 study investigating nipocalimab in subjects with gMG provided proof of concept for a phase 2/3 interventional study with nipocalimab in subjects with wAIHA. This phase 2/3 study is currently enrolling in the USA and Europe.
Reference: [1]https://clinicaltrials.gov/ct2/show/NCT04119050?cond=WAIHA&draw=2&rank=10

EP714 WARM AUTOIMMUNE HEMOLYTIC ANEMIA: A RETROSPECTIVE ANALYSIS OF 115 PATIENTS

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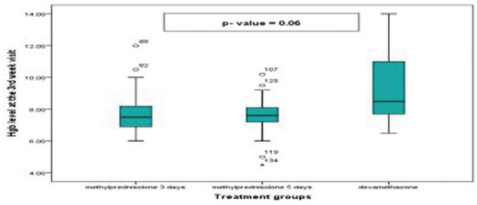
Background: Warm autoimmune hemolytic anemia (WAIHA) is a relatively rare hematologic disorder resulting from autoantibody directed against self-erythrocytes. There has been few studies about warm AIHA because of its low incidence.
Aims: We aimed to analyze 20-years' experience of WAIHA patients at a single referral center in Sousse. Clinical data, survival outcome of patients who were diagnosed with WAIHA were retrospectively analyzed.
Methods: This is a descriptive retrospective study. Data belonging to WAIHA in adult patients admitted in our department of hematology between January 2001 and December 2020 were analyzed.
Results: One hundred and fifteen patients (58.3% women) were included, the mean age at the time of wAIHA onset was 54 years (range 16-98), the mean hemoglobin level was 6.2 g/dL (range 2.1-10.9 g/dL). All the patients were direct antiglobulin test (DAT) positive (80 (69.6%) patients were IgG, 34 (29.6%) were IgG plus C3d, and only one was IgA DAT positive). wAIHA was considered "primary" for 53 patients (46%) and was associated with an underlying disorder in 62 (54%), including mainly lymphoproliferative diseases (31 patients) and connective tissue disease (25 patients). All patients received steroids at therapeutic dosages (corticosteroid 1 mg/Kg) as first line treatment (+/-chemotherapy for hematologic malignancy)). Hundred and one of them showed: complete response (68/59.1%) and partial response (33/28.7%). Thirty seven patients (32.2%) relapsed at least once and was retreated with corticosteroid in 15 patients because of anemic symptoms, or received cyclophosphamide in 12 patients, rituximab in only 4 patients and splenectomy in 6 patients. Twenty nine patients presented complication (11 cases of several infections, 3 cases of osteoporosis, 3 cases of thrombotic events, 9 cases of corticosteroid-induced diabetes, 3 cases of renal failure). After a median of follow-up of 44 months (1-188), 86 patients were in remission (eight in complete response, 60 in complete remission, 18 in partial remission), 11 patients were in relapse or refractory to a treatment and eighteen patients died (3 during poorly tolerated anemia, 4 due to infections, 1 related to metabolic acidosis for multiple myeloma, 1 ischemic stroke, and nine following a progression of hematologic malignancies or cancer).
Summary/Conclusion: This study indicates that secondary WAIHA are predominant. Oral corticosteroid is effective as first line therapy for warm AIHA, but several complication may arise. Despite a proven efficacy of rituximab as corticosteroid-sparing strategy, it is still little used as a second line therapy in our department for this immune disorders.

EP715 COMPARISON BETWEEN THE DIFFERENT REGIMENS AND PHARMACOLOGICAL FORMS OF CORTICOSTEROID AS FIRST-LINE THERAPY OF AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA): RESULTS OF THE PROSPECTIVE OBSERVATIONAL COHORT.

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Background: Autoimmune haemolytic anaemia (AIHA) is a critical health concern where myriad factors contribute to this autoimmune syndrome. There are no clear recommendations in the latest consensus of AIHA regard the different forms and regimens of corticosteroids in the treatment of the warm type.
Aims: we aim to compare the efficacy and safety of regimens started with intravenous corticosteroids and the regimen of prednisolone alone as first-line strategies for newly diagnosed adult warm AIHA.
Methods: The current study is a single-centre prospective cohort (NCT03269292, Clinical Trials.gov) conducted in a university-affiliated hospital (Assiut University Hospital, Assiut, Egypt). Subjects were enrolled if they have warm AIHA with positive direct antiglobulin (DAT) test either primary or secondary type and their age is more than 18 years. We excluded patients with previously treated AIHA and other types of immune haemolytic anaemia
The patients either administrated oral prednisolone 1mg/kg daily for 3 weeks or started therapy with one of three different regimens for the intravenous corticosteroid therapy: intravenous dexamethasone 40 mg daily for 4 days, Methylprednisolone 1 gram/day for 3 days, or Methylprednisolone 1 gram/day for 5 days then followed by oral prednisolone 1 mg/kg/day for the rest of the 3 weeks. Full clinical evaluation and CBC were done every 3 days for 3 weeks.
Results: 156 eligible newly diagnosed AIHA patients were recruited to the cohort and they receive corticosteroids as first line therapy.
The median hemoglobin level recorded at the baseline was significantly higher (p=0.001) in patients started the treatment with prednisolone orally (5.8g/dl) than patients started treatment with intravenous regimens (4.5g/dl). However, the median incremental increase of hemoglobin level from the baseline was significantly higher (p=0.003) in the patients started with intravenous regimens (3.1g/dl) than the other group (2g/dl). The analysis of the subgroups of patients started with intravenous regimens showed that no significant difference in the hemoglobin level at the baseline between the three treatment regimens (p=0.1). Although there was not any significant difference between these three groups regard the hemoglobin level at the end of the 3rd week but there was a trend to be higher in the dexamethasone group (figure 1).
There was not any significant difference between the regimens started with intravenous crticosteroids and the oral regimen alone as regard the frequency of the adverse events (p=0.3). The adverse events reported were either grade 1 or grade 2 and included hyperglycaemia, hypertensin, muscle weakness, hypokalaemia, abdominal pain and vomiting. They were not associated with long term sequalae or death.



Summary/Conclusion: In this study, we prove that regimens started with intravenous corticosteroids therapy are superior to oral regimen as they achieved higher levels of incremental increase in the hemoglobin levels from the baseline without increase of the incidence or increase the severity of the side effects. This is beneficial in cases of acute sever AIHA.

Gene therapy, cellular immunotherapy and vaccination - Biology & Translational Research

EP716 PHENOTYPIC, TRANSCRIPTIONAL AND FUNCTIONAL ANALYSIS OF CD19 CAR-T CELLS: SENESCENT/EXHAUSTED PHENOTYPE PREDICTS RESPONSE OF B CELL LYMPHATIC MALIGNANCIES

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Background: In spite of high rates of overall response following chimeric antigen receptor (CAR) T cell therapy its curative potential is jeopardized by exhaustion of the CAR T cells conceivably mediated by the immunosuppressive tumor microenvironment and excessive antigen exposure. However, cellular and molecular predictors of clinical response are not fully elucidated.
Aims: To identify phenotypic, transcriptional and cellular mediators of resistance to CAR T immune therapy.
Methods: We performed a broad immunophenotypic and transcriptomic analysis of the T cells from patients (pts) with relapsed/refractory B cell malignancies (n-39: NHL-28, ALL-5), and CLL-6) treated with locally produced CD19 CAR T cells in correlation with pts' day 28 clinical response. Intact CD3$^+$ T cells that were obtained from peripheral blood (PB) samples pre Flu/Cy lymphodepletion using negative magnetic sorting and the manufactured CAR T products were analyzed. The CD8$^+$ and CD4$^+$ T cells were individually assessed by a panel of 17 immune surface markers identifying different T cell subsets and underlying the T cell repertoire diversity. Transcriptional signature was assessed by NanoString technology.
Results: Phenotypic signature identified a higher proportion of exhausted CD57$^+$CD39$^+$ cytotoxic CD8$^+$ cells in CAR T products of non-responders (NR) in comparison to pts with complete response (CR). Furthermore, CD8$^+$ CAR T cells of NR pts were characterized by CD28 and IL-7R loss, and lower levels of CCR7. Expression of T cell checkpoint inhibitor PD1 was high in these exhausted CD8$^+$ cells. Importantly, higher proportion of exhausted cytotoxic CD8$^+$ cells was detected in PB of NR comparing to responders, suggesting the association of CAR T exhaustion with a dysfunctional phenotype of pts' T cells. In contrast, CD4$^+$ cells demonstrated low frequency of exhausted phenotype both in the PB as well as the CAR T product from both NR and CR pts, indicating that CD4$^+$ T cells are less prone to exhaustion compared to their CD8$^+$ counterparts, suggesting better persistence of CD4 CAR T cells following antigen exposure.
The transcriptional signature of the CAR T products overlaid with the phenotypic characterization. Higher levels of IL-7R, CD7, BATF3, IL15, FOS, MYC, CD69 and CD27 genes were detected in the CAR T cells of CR pts. In contrast, the CAR T cells of resistant pts were enriched with terminally exhausted population, upregulating CD57, TOX, EOMES, GZMB, GZMA, GZMH, CCL4 and LAG3 genes.
Finally, the functional capacity of the CAR T cells was evaluated in co-culture experiments with CD19$^+$ Raji cells. Stimulation with CD19$^+$ targets induced proliferation and cytokine secretion of the CAR T effectors. Importantly, reduced proliferation and reduced IL-2 secretion correlated with the exhaustion signature. Of note, CAR T cells with exhausted phenotype demonstrated killing capabilities comparable with the non-exhausted CAR cells. Similarly, CAR T cell degranulation, a prerequisite for target cell lysis did not differ as well. These data suggest that the in vitro cytolytic activity of exhausted CAR T cells may be preserved while their proliferation and cytokine production is clinically insufficient.

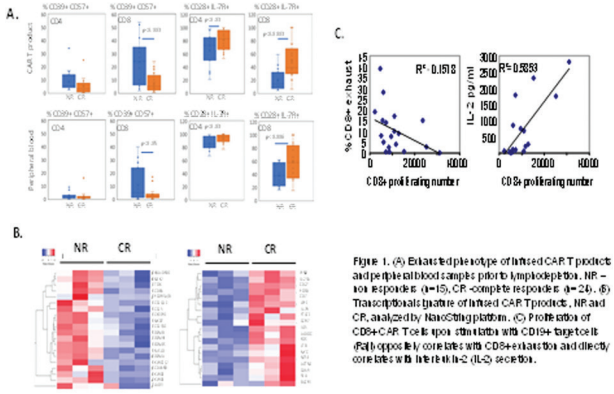


Figure 1. (A) Exhausted phenotype of infused CAR T products and peripheral blood samples prior to lymphodepletion. NR – non responders (n=15), CR -complete responders (n=24). (B) Transcriptional signature of infused CAR T products, NR and CR, analyzed by NanoString platform. (C) Proliferation of CD8+CAR T cells upon stimulation with CD19+ target cells (Pal) oppositely correlates with CD8+ exhaustion and directly correlates with interleukin-2 (IL-2) secretion.

Summary/Conclusion: Overall, these results reveal potential cellular and molecular mediators of resistance, identifying an enrichment of terminally exhausted CD8+ T cells as a main feature observed in PB and CAR T products of resistant patients. Delineating these mechanisms may guide future T cells engineering studies to enhance the efficacy and durability of CAR T therapy in B cell malignancies.

EP717 IMMUNE REGULATORY PROTEINS MODULATE FIBROSIS AND INFLAMMATION IN SCLERODERMATOUS GRAFT-VS-HOST DISEASE

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Background: Chronic graft-vs-host disease (cGVHD) is an immune related disease condition that is incompletely understood. It coincides with transplantation of non-purified Hematopoietic Stem Cells (HSCs) in up to 70% of patients and represents a major obstacle to the success of allogeneic hematopoietic stem cell transplantation (HCT). Sclerodermatous GVHD (Scl GVHD) is a more severe form of cGVHD and is associated with poor prognosis and low sensitivity to immune suppression which is the current first line therapy.
Aims: We hypothesized that there exist a range of inflammatory cells delivering profibrotic signals. Such signals while initially performing tissue repair following transplant-related injury of the skin, can eventually perpetuate uncontrolled pathologic fibrosis. Therefore, we aimed at identifying downstream fibrotic gene expression signatures in fibroblasts associated with chronic inflammation.
Methods: In skin biopsies, we show that JUN and CD47 are key regulatory molecules overexpressed and activated in Scl cGVHD patients. Mechanistically, using ChIP-seq and ATAC-seq we describe JUNs role in altering the transcriptional landscape of IL6 and CD47. Finally, using novel and conventional mouse models that recapitulate clinical Scl cGVHD we show the effect of anti-CD47 and anti-IL6 antibodies as promising therapeutics for the treatment of inflammation and fibrosis in Scl cGVHD patients.
Results: 1. Our combined expression and signaling data confirm that JUN activation is tightly linked to a profibrotic and immune dampening signature in Scl cGVHD.
2. JUN deletion alters chromatin accessibility and nucleosome positioning of immune regulatory and fibrosis genes in human Scl cGVHD.
3. We demonstrate that JUN, CD47 and IL6 are upregulated in a novel mouse model of Scl cGVHD demonstrating progressive disease.
4. Finally we show that CD47 and IL6 blockade are an effective therapeutic strategy for the treatment of sclerosis in the skin related to Scl cGVHD in mice.
Summary/Conclusion: In summary, we describe a novel mechanism through which chronic inflammation perpetuates fibrosis via activation

of JUN, CD47, IL6, which result in a profibrotic signature in Scl cGVHD. Our findings are of particular interest, as these pathways have been implicated in tissue sclerosis in other contexts and indicate potential targets for therapeutic intervention using anti-CD47 and IL6R antibodies.

EP718 IMPROVED LEUKEMIA CLEARANCE AFTER ADOPTIVE TRANSFER OF NK CELLS ENGINEERED WITH THE BONE MARROW HOMING RECEPTOR CXCR4

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Background: The overall survival in acute myeloid leukemia (AML) remains poor. New treatment options are needed. Early clinical trials have highlighted that adoptive transfer of natural killer (NK) cells can induce remission in patients with relapsed/refractory AML and high-risk myelodysplastic syndrome (MDS). Recent advances have now enabled investigators to explore the potential of genetically engineered NK cells to improve the efficacy.
Aims: The primary aim was to investigate whether *ex vivo* expanded human NK cells, engineered to overexpress the gain-of-function bone marrow (BM) homing receptor CXCR4^{R334X}, can be utilized for improved leukemia clearance *in vivo*. In addition, we further aimed to explore the role for the CXCR4/SDF-1α axis in NK cell BM homing by knocking out the CXCR4 gene.
Methods: A 4D-Nucleofector™ System (Lonza) was used to introduce CXCR4^{R334X}-coding mRNA, or RNP-complex for CRISPR/Cas9 mediated CXCR4 gene-knock-out (KO), into *ex vivo* expanded human NK cells. RNA transcript levels and cell surface expression of CXCR4 was determined by q-RT-PCR and flow cytometry staining respectively. KO efficacy was evaluated by ddPCR. CD107a degranulation experiments, and Calcein-AM-based killing assays, were used to evaluate the *in vitro* leukemia targeting potential post electroporation. *In vitro* migration was assessed by transwell migration assays whereas NSG-SGM3 mice were used to evaluate the *in vivo* migration capacity. To assess the *in vivo* anti-leukemic potential, NSG-SMG3 mice were inoculated intrabone with MOLM-14 cells prior to NK cell treatment.
Results: Here, we demonstrate that *ex vivo* expanded human NK cells, mRNA-transfected to overexpress the gain-of-function bone marrow (BM) homing chemokine receptor CXCR4^{R334X}, have a higher homing propensity for BM compartments *in vivo* leading to significantly improved leukemia rejection when adoptively infused into AML-bearing mice compared to control NK cells. Further, our data reveal that CXCR4^{R334X} mRNA-transfected NK cells more efficiently delayed leukemia spreading to non-tumor-inoculated BM compartments. Importantly, neither the CRISPR/Cas9 or the mRNA transfection approach used in this study affected the ability of NK cells to target AML cells.
Summary/Conclusion: Collectively, these data provide proof-of-concept that genetic engineering of human NK cells to promote homing to BM compartments is an independent modality that can be optimized to further enhance the efficacy of NK cell-based immunotherapy of myeloid leukemia.

EP719 HARNESSING EXHAUSTED, TUMOR-SPECIFIC T CELLS TO GENERATE A T-CELL RECEPTORS LIBRARY FOR ADOPTIVE T CELL THERAPY IN BLOOD MALIGNANCIES

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Background: Aggressive blood malignancies can benefit from the immune pressure imposed by allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT), able to eradicate cancer cells surviving chemo-radiotherapy. However, allo-HSCT may also mediate allo-reactions with potentially fatal outcomes. In order to boost HTSC efficacy while reducing toxicities, adoptive T cell therapy with genetically engineered T cells redirected against tumor antigens (ACT) is an appealing therapeutic candidate. However, ACT applicability in blood tumors is limited by the low number of known tumor-reactive T-Cell Receptors (TCRs).
Aims: We defined an experimental pipeline to isolate tumor-specific TCRs from allo-HSCT treated patients to widen the TCR repertoire for ACT by taking advantage of either multimers or inhibitory receptors surface markers expression.
Methods: Circulating Tumor-specific T cells in blood cancer patients who underwent allo-HSCT were phenotypically characterized, then purified and in vitro expanded by means of multimers directed toward immunodominant peptides of MAGE-A2, WT1, Survivin and hTERT tumor-associated antigens, restricted for HLA-A*0201 and HLA-A*2402 alleles. Tumor-Specific T cell TCR repertoire was studied by RNA sequencing.
Results: We successfully isolated and expanded markedly oligoclonal tumor-specific T-cell cultures from N=13/20 patients. Despite documented in vitro enrichment and expansion, cell cultures failed to lyse peptide-pulsed target cell lines during in vitro assays, suggesting that T cells were hypo-functional. To circumvent hypo-functionality, the dominant TCR from N=6 of those T-cell cultures was reconstructed and transferred into fit donor T cells which endogenous TCR have been previously knocked-down by means of CRISPR/Cas9 system. Newly engineered T cells proved able to specifically recognise and eliminate peptide-pulsed cell lines with different affinities in in vitro killing assays. A high-dimensional flow cytometry analysis performed on N=33 patients strengthened the hypothesis that tumor-specific T cells are hypo-functional ex vivo. Indeed, tumor-specific but not viral-specific T cells preferentially expressed multiple inhibitory receptors and showed an impaired differentiation program, with accumulation of stem cell-like memory T cells and terminal effectors. Interestingly, such phenotype was accentuated in those patients deemed to relapse after allo-HSCT. In order to take advantage such unique exhaustion signature, we exploited inhibitory receptors to segregate from three Acute Myeloid Leukemia patients a T cell fraction positive for multiple inhibitory receptors (IR+) and putatively enriched with tumor specificities. We then serially stimulated with autologous Leukemic-Antigen Presenting Cells (L-APCs) the IR+ and the control IR- fraction. In all the three tested patients, L-APCs promoted the occurrence of a dominant TCR clonotype in the IR+ but not in the IR- group. These dominant TCRs, when inserted into TCR-knocked-down donor T cells led to the generation of engineered T cells that efficiently lysed autologous leukemia in vitro while sparing healthy bone marrow cells.
Summary/Conclusion: Our data suggest the presence of circulating, though exhausted, tumor-specific T cells in patients after allo-HSCT. By exploiting multimers or the IR signature, we here provide a pipeline to isolate novel tumor-specific TCRs with different specificity, affinity and peptide sensitivity to be employed in ACT.

EP720 VALIDATION OF AN IL-1RAP CART-CELLS PRECLINICAL « GMP-LIKE » PRODUCTION PROCESS BEFORE AN UPCOMING FIRST IN HUMAN PHASE I CLINICAL TRIAL.

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Background: Use of Chimeric Antigen Receptor (CAR) T-cells have demonstrated excellent results in B-lymphoid malignancies. In myeloid malignancies, several other targets are investigated as the interleukin-1 receptor accessory protein (IL-1RAP). A limitation of CAR T-cells success is the persistence in patients over time without relapse. A central memory T-cells (T_{CM}) phenotype seems to be the best candidate for improving CAR T-cells efficiency.
Aims: The aim of this work is characterizing our preclinical "GMP-like" IL-1RAP CAR T-cells production, transferable for the clinic, in comparison to our experimental production.
Methods: Two arms were compared: CD4+/CD8+ cells were sorted from peripheral blood mononucleated cells of healthy donors on a ClinMACS Prodigy® device. Sorted CD4+/CD8+ cells were then activated by CD3/CD28 + IL-7/IL-15 before transduction, at day(D)1, using a IL-1RAP CAR lentiviral supernatant. In Comparison, for the experimental conditions, CD4+/CD8+ cells were activated using CD3/CD28 Beads + IL-2 before transduction at day 2. Cells were cultured for 9 days either in flask or in GMP approved device. Transduction efficiency was measure 4 days after the transduction by ΔCD19 reported gene labeling using flow cytometry. T-cells subsets phenotyping was perform on the fresh or thawed CAR T-cells final product (D9) and compared with untransduced T-cells (D0). Cytotoxicity was assessed by CD107a staining or IFNγ quantification by ELISA, after coculture with leukemic cell lines and IL-1RAP-coated recombinant protein. CAR T-cells metabolism was also assessed by Seahorse® analysis after IL-1RAP stimulation.

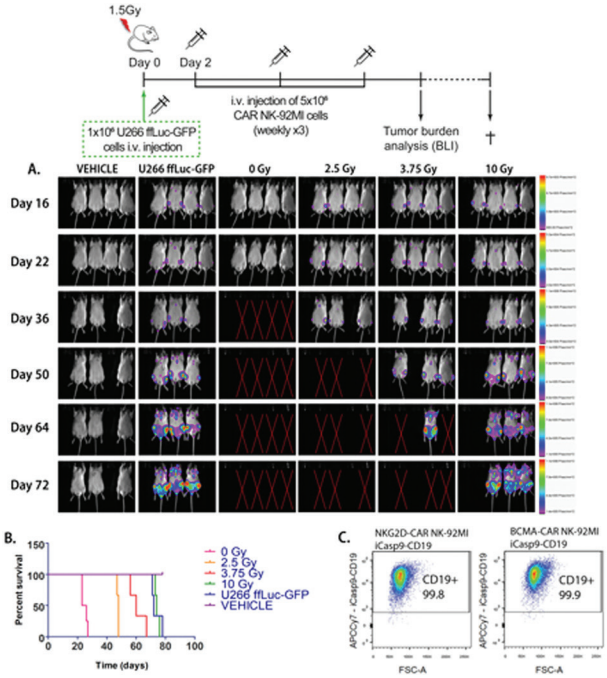
Results: Cells proliferation was similar between the two procedures of IL-1RAP CAR T-cells. However, the transduction efficiency was higher in the preclinical (64.6%±15.6%) than in the experimental process (45.6% ±10.4%). The CD4/CD8 ratio was maintained between D0 and D9 in the preclinical process in comparison to the experimental process (4.0±0.9, 4.0±1.9, and 1.7±0.7 respectively). At D9, the CAR T-cells product was mostly composed of stem cell-like memory T-cells (T_{SCM}) and T_{CM} in the preclinical GMP-like process in comparison with the experimental procedure (48.8%±0.8% and 30.9%±2.6% vs 30.1%±19,1% and 18.5%±6.5% respectively).
Better functionality was observed in the GMP-like process compare to the experimental one characterize by a higher CD107a positive CAR T-cells percentage, after coculturing against MonoMac-6 IL-1RAP tumor cell lines (34.1% ±9.8% vs 3.4% ±2.0% respectively, p=0.006%) or in presence of a IL-1RAP coated recombinant protein (55.7% ±4.6% vs 1.1% ±0.4% respectively, p<0.0001). These results were confirmed by IFNγ secretion quantitation (3708 pg/mL ±2176 pg/ml and 2535 pg/mL ± 1352 pg/mL respectively). Moreover, IL-1RAP coated recombinant protein stimulation show a basal glycolytic activation of CAR T-cells (fold rate at 2.0 ±0.2, p<0.001), but without difference of maximal glycolytic activity, suggesting a specific activation without exhaustion. Oxidative metabolism was similar with and without activation.
Summary/Conclusion: We have demonstrated that our IL-1RAP CAR T-cells preclinical GMP-like process meets standard requirements of production in term of T-cells subpopulation phenotype for anti-leukemia immunologic memory and cytotoxic functionality. It is ready for transfer in clean room in order to produce for AML patients in first in man phase I clinical trial.

EP721 EXPLORING A SAFE AND EFFECTIVE "OFF-THE-SHELF" CELL-BASED IMMUNOTHERAPY FOR THE TREATMENT OF MULTIPLE MYELOMA USING NON-IRRADIATED CAR NK-92MI CELLS

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Background: CAR-NK cells represent a safer approach than CAR- T cells. These ground-breaking CAR effectors exhibit some other immunological advantages, as they entail an 'off-the-shelf' strategy with no graft-versus-host disease. NK-92 is a universal, cheap and fast obtainable cellular therapy previously used in clinical trials. Although modest responses with these cells have been reported in Multiple Myeloma (MM), their cytotoxic potential can be enhanced by genetic modification. However, the products obtained so far offer some limitations and could be optimized in MM.
Aims: The aim of our study is to generate a risk-free and effective CAR NK-92MI immunotherapy for MM treatment.
Methods: NK-92MI cells were lentivirally transduced with a single second generation CAR, NKG2D-CAR or BCMA-CAR, both containing identical 4-1BB costimulatory domain, as well as dual BCMA-NKG2D CARs with different combinations of co-stimulators. CAR NK-92MI iCasp9-CD19 populations have been generated by retrovirus transduction with an SFG iCasp9.2A.ΔCD19 construct. All populations were purified by FACS sorting to obtain stable modified cell lines and vector copy number was measured by qPCR to ensure similar CAR expression. *In vitro* cytotoxicity assays were performed against an ensemble of MM cell lines with high and low expression of target ligands as well as a BCMA knock-out generated by CRISPR-Cas9 system: U266, $BCMA^{high}$ and $NKG2DL^{high}$; ARP-1, $BCMA^{dim}$ and $NKG2DL^{dim}$; XG-1, $BCMA^{high}$ and $NKG2DL^{low}$; $U266bcma^{KO}$, $BCMA^{KO}$ and $NKG2DL^{high}$. *In vivo*: $5x10^6$ CAR NK-92MI cell infusions were administered i.v. once a week for three weeks.
Results: We have demonstrated specificity, non-toxicity and higher *in vitro* antitumor activity of CAR NK-92MI cells compared to the parental cell line. Besides, we have noticed that the expression of both CARs in combination has not showed synergy, but a broadening of cytotoxic coverage against MM cell lines *in vitro* is remarked. *In vivo* MM orthotopic xenograft mouse model experiments have demonstrated that the irradiation dose used in the clinic completely abrogate the efficacy of this 'off-the-shelf' immunotherapy in our treatment schedule. Decreasing irradiation doses (2.5-3.75 Gy) has no impact on tumor elimination and leads to early NK-92MI-induced death in animals (Figure 1A-B). To settle these drawbacks, CAR NK-92 MI cells expressing suicide gene therapy have been generated (99.8% purity, Figure 1C) and it has been demonstrated that cells can be rapidly eliminated *in vitro* upon induction with Rimiducid (AP1903). This strategy will assure antitumor efficacy and safety of the immunotherapy, and all generated effectors displayed similar *in vitro* cytotoxic activity than their CAR NK-92MI counterparts. *In vivo* experiments are ongoing.



Summary/Conclusion: We have generated simple and combined stable CAR NK-92MI cells that improve the cytotoxic activity of the parental cell line. The co-expression of both CARs results in cytotoxic coverage against different MM targets. *In vivo*, these data show the futility of irradiation as an NK-92 CAR treatment strategy in our MM model and the further need of combinations with iCasp9 safety switch to ensure the safety and efficacy of the therapy.

EP722 CAR-TREG THERAPY FOR SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by an abnormal inflammatory response against nuclear antigens due to a loss of the immune tolerance with consequent damage to healthy organs. Auto-reactive B cells with autoantibody production and immune complex formation have a fundamental role in the pathogenesis of the disease. Regulatory T cells (Tregs) are a subset of T lymphocytes endowed with immune suppressive capabilities. Tregs control the activation of the immune system, preventing

unwanted inflammatory reactions and preserving the immune tolerance against self-antigens. An impaired Treg functionality is involved in SLE, where they do not manage to control the inflammatory response. Adoptive transfer of polyclonal Tregs has been employed to restore the immune tolerance in different autoimmune diseases, achieving unsatisfactory results due to a low frequency of antigen specific suppressive cells. Chimeric Antigen Receptors (CARs) are chimeric molecules capable of redirecting T cell specificity against target antigens, greatly enhancing T cell activity. CAR-Tregs proved effective in controlling the inflammation in pre-clinical mouse models of autoimmune diseases different from SLE.
Aims: The aim of the project is to employ the CAR technology to redirect and enhance Treg activity in order to exploit their immune suppressive capabilities to restore immune tolerance in Systemic Lupus Erythematosus.
Methods: We sorted CD4+CD25+ cells from peripheral blood of Healthy Donors using magnetic separation beads. Next, we expanded Tregs using anti-CD3/CD28 magnetic beads in the presence of IL-2 and rapamycin. Considering the role of B cells, we transduced CAR-Tregs with a Lentiviral Vector encoding for a second generation anti-CD19 CAR, constituted by the intracellular portion of both CD28 and CD3-zeta to provide a more physiological stimulation. GFP was employed as transduction marker. Starting from day +14 since the initial stimulation, we performed functional assays. Immune and suppression assays were evaluated with flow cytometry.
Results: We obtained a cell product highly enriched in Tregs and with a transduction efficiency of 50%. CAR-Tregs retained their immune suppressive capabilities and performed equal to untransduced Tregs in suppressing the proliferation of autologous lymphocytes upon polyclonal stimulation. Noticeably, CAR-Tregs, but not untransduced Tregs, suppressed autologous B cell proliferation, demonstrating an antigen-specific suppression capacity. When co-cultured with CD19+ tumor cells, CAR-Tregs did not display killing capacities, but rather an impressive proliferation activity. More strikingly, anti-CD19 CAR-Tregs suppressed conventional anti-CD19 CAR-T cell killing when co-cultured together in the presence of a CD19+ tumor cell line. Finally, we tested the immune suppressive capacities of anti-CD19 CAR-Tregs in a humanized mouse model of lupus. Engineered cells delayed the occurrence of leukopenia compare to untransduced regulatory lymphocytes.
Summary/Conclusion: In conclusion, we efficiently generated anti-CD19 CAR-Tregs and proved their efficacy both in vitro and in an in vivo humanized mouse model of lupus.

EP723 MONITORING COMMERCIAL ANTI-CD19 CAR T-CELL PRODUCT EXPANSION KINETICS: REAL-WORLD APPLICATIONS OF A NOVEL DROPLET DIGITAL PCR ASSAY AND OF MULTIPARAMETRIC FLOW CYTOMETRY

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Background: Two CD19-directed CAR T-cell products (Tisagenlecleucel/Tisa-cel and Axicabtagene ciloleucel/Axi-cel) have been approved for refractory/relapsed (R/R) diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL) whereas Brexucabtagene autoleucel (Brexu-cel) has been used for R/R mantle cell lymphoma (MCL). Real-world data on commercial CAR T-cell product expansion kinetics are still limited and homogeneous standardized approaches are required to in vivo quantify CAR T cells.
Aims: To monitor and compare the expansion kinetics of commercial anti-CD19 CAR T-cell products using multiparametric flow cytometry (MFC) and a novel digital PCR method (ddPCR) we have developed.
Methods: We prospectively collected samples from 42 pts, [23 Axi-cel(15 DLBCL and 8 PMBCL), 18 Tisa-cel(18 DLBCL)] and 1 MCL patient receiving Brexu-cel at our Institution between Oct 2019 and Jan 2021. CAR T cells were monitored in peripheral blood (PB) on days 0,4,7,10,14,21,28 and monthly post-infusion by MFC using the CD19 CAR Detection Reagent (Miltenyi). A unique ddPCR primer-probe assay we have developed was used to quantify CAR vectors on genomic DNA extracted from PB, infusion bag-leftovers, bone marrow (BM) samples, tissue biopsies and circulating cell-free DNA (cfDNA).
Results: By MFC, 550 time-points of the 42 pts were analyzed. Median time to maximal expansion (Tmax) was identical for both products (10 days, range 7-28 days). At the point of maximal expansion (Cmax), there was no difference between pts receiving Axi-cel and Tisa-cel, with a mean of 76 cells/ul (range 1-442) vs a mean of 186 cells/ul (range 6-591) (p, ns). At this time point, CAR+ cells were more abundant among CD3+ cells in pts receiving Axi-cel (33.06% vs 15.58% for Tisa-cel, $p<0.05$). Complete response (CR) at 30 days from infusion (n=18) was associated with significantly more CAR+ cells at day 10 than non-CR (mean 146 vs 18 CAR+ cells/ul, $p<0.05$) and the magnitude of expansion in the first 30 days was higher in CR vs non-CR pts (mean area under the curve (AUC 0-30) = 1431.2 vs 584.3; $p<0.05$) irrespective of the product they received. For 16 pts (10 DLBCL, 5 PMBCL and 1 MCL) CAR T copy numbers were evaluated by ddPCR in 122 PB samples already analyzed by MFC. By transgene copy evaluation, similar kinetics of expansion were observed in all pts including the MCL patient receiving Brexu-cel. Consistent with MFC data, the median Tmax was 10 days (range 7-28 days), comparable values of transgene copies per mg of DNA were detected in PB samples from Axi-cel and Tisa-cel treated patients at the Tmax (mean $24x10^4$ copies/ug vs $13x10^4$ copies/ug, respectively) and the mean AUC 0-30 was significantly higher in CR vs non-CR pts (mean 115.9 vs 29.9;$p<0,05$). Collectively, a significant correlation between all MFC and ddPCR data was observed ($r=0.95$,$p<0,0001$ by Pearson Correlation). The ddPCR assay was then used to evaluate CAR T cells in samples for which MFC analysis was not suitable such as infusion bag-leftovers ($34x10^4$-$755x10^4$ copies/ug,n=13), cryo-preserved BM samples ($360-1x10^4$ copies/ug,n=3) tumor biopsies (0-864 copies/ug,n=3) and cfDNA ($0-9x10^4$ copies/ug,n=3).
Summary/Conclusion: Both MFC and ddPCR, allow the reproducible enumeration of commercial anti-CD19 CAR T-cells with concordant results. The ddPCR assay has the advantage over MFC to allow transgene copy evaluation in samples with limited cellularity and/or cryopreserved. In our cohort Axi-cel and Tisa-cel treated pts have similar expansion kinetics and CAR peak expansion was associated with clinical responses irrespectively of the product used.

EP724 SELECTION, EXPANSION, AND NEW PRETREATMENT OF HUMAN NATURAL KILLER CELLS WITH ANTI-CD38 MONOCLONAL ANTIBODY FOR EFFICIENT TREATMENT OF MULTIPLE MYELOMA.

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Background: Though the outcome of patients with Multiple myeloma (MM) has significantly improved over the past decade, most of the patients eventually relapse, with a short progression-free survival period. Recent adoptive cellular immunotherapy is becoming a game-changer in cancer treatment after recent breathtaking outcomes in various clinical trials with chimeric antigen receptor T cells. Nevertheless, this novel therapy is not free from challenges such as affordability, tumor recurrence in heterogeneous tumors, and off-tumor toxicity. To overcome these roadblocks, we capitalize on the unique anti-tumor properties of Natural Killer (NK) cells to target MM in combination with approved

monoclonal antibody Daratumumab, applying CD16 polymorphism donor selection and straightforward new in vitro pretreatment to bypass undesired fratricide.
Aims: We propose to explore the feasibility of obtaining a clinically relevant amount of allogeneic NK cells derived from peripheral blood (PBNK) and assess their efficacy in combinatorial therapy with approved anti-CD38 monoclonal antibody Daratumumab to treat incurable MM.
Methods: PBNK cells were isolated from three healthy donors using NK cell isolation kit (Miltenyi). Phenotypic and functional analysis of PBNK cells was evaluated by flow cytometry with a defined panel of antibodies. Polymorphism analysis on FcγRIIIA-158 was performed by flow cytometry with the monoclonal antibody 3G8 clone and MEM-154 clone. Bioluminescence imaging was applied to assess the anti-tumor effectivity of PBNK cells alone, and in combination with Daratumumab, targeting the tumor cell lines RPMI and U266 labeled with the constitutive expression of Firefly Luciferase. In vivo studies were performed in mouse models of MM in four different groups: control group without treatment, single-agent treatment group with Daratumumab, single-agent treatment with PBNK cells, and combinatorial treatment group with Daratumumab and PBNK cells.
Results: We obtained a clinically relevant amount of PBNK cells (median of 14,050 million cells from a single donor) after five weeks of expansion in a GMP-grade feeder-free medium. In vitro studies confirmed the multi-tumor target capacity of expanded PBNK cells, achieving a maximum killing capacity in the fourth week of expansion. The increase in killing capacity may be explained, at least in part, by increased expression overtime of the activation receptor NKG2C. Combination of expanded PBNK cells with Daratumumab procures a synergistic therapeutic effect against MM, increasing more than 20% the therapeutic effect against CD-38 positive MM cell line after CD16 polymorphism donor selection and in vitro pretreatment of PBNK cells to avoid fratricide. Mice with human MM xenografts treated with this combination present tumor volumes 43-fold smaller than control ones.
Summary/Conclusion: Our in vitro and in vivo findings presented in this study demonstrate the feasibility of using allogeneic PBNK cells combined with Daratumumab for treating MM. Besides, CD16 polymorphism selection in PBNK cells and novel in vitro pretreatment to avoid fratricide procure a significant increase in the therapeutic effect against MM. Our results fully support and justify the continued development of allogeneic PBNK cells for the treatment of MM.

EP725 DETERMINANTS OF IN VIVO EXPANSION OF CD19 SPECIFIC CAR T-CELLS IN LARGE B-CELL LYMPHOMA: SINGLE CENTER IMMUNMONITORING RESULTS

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Background: Pivotal trials of Axicabtagene-Ciloleucel (Axi-cel) and Tisagenlecleucel (Tisa-cel) for the treatment of relapsed and refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL) demonstrated complete responses in 40%>58% of the patients with accompanied grade ≥3 adverse events in approximately 30% of the patients. Recently, others could associate high tumor volumne and low CAR T-cell expansion *in vivo* with poor treatment outcome. We hypothesize, that expansion of CAR T-cells and T cells in vivo depend on the composition and differentiation status of (CAR) T-cell subsets and that differential expansion of (CAR) T cell subsets determines response rate.
Aims: We performed a retrospective, single-center study in which we characterized potential determinants of CAR T-cell and T-cell expansion[MS1] and their association with treatment response at time of transfusion and 28 days thereafter: i) the distribution of CD4+ and CD8+ (CAR) T-cells subsets ii) the memory phenotype and immune checkpoint expression of (CAR) T-cells.
Methods: Patients with r/r DLBCL were treated with the CD19 specific CAR T-cell products Axi-cel or Tisa-cel at the LMU. Peripheral blood from 38 patients was collected before, during and after CAR T transfusion. Multi-parameter flow cytometry was done to detect CAR T-cells and assess marker for T-cell differentiation (CD3, CD4, CD8, CD45RA, CCR7) and immune checkpoints (PD-1, TIM-3, LAG-3). CAR T-cells were quantified based on a two step-staining approach with a biotinylated recombinant CD19 protein. Efficacy was evaluated through PET-CT scan three months and by CT scan six months after CAR T-cell transfusion and patients were categorized in Responder (complete remission) and Non-Responder (partial remission, stable or progressive disease).
Results: CAR T-cell expansion peaked between day 7 and 14 in the peripheral blood with a significantly higher expansion of CD8+ CAR T-cells compared to CD4+ CAR T-cells between day 4 and 28 (p=0.004-0.007). CAR T-cells were detectable in most patients until day 105 (sensitivity 1:1000). Responder (R) displayed a higher absolute number of CD8+ CAR T-cells over time after transfusion compared to Non-Responder (NR, p=0.02). CAR T-cells in R showed a higher frequency of an effector (p=0.004) and lower frequency of a central memory phenotype (p=0.002) compared to NR 28 days after CAR T-cell transfusion. Furthermore, assessment of immune checkpoints over time revealed a lower expression of PD-1 (p<0.0001), TIM-3 (p<0.0001), LAG-3 (p=0.001) on CAR T-cells in R compared to NR.
Summary/Conclusion: We have successfully established an Immunmonitoring platform for the assessment of CAR T-cell expansion and their immune phenotypes *in vivo* through flow cytometry. We observed relationships of CAR T-cell kinetics, memory subsets and immune checkpoint expression with efficacy. These findings might bear the potential to monitor treatment responses and prevent disease relapse together with other clinical variables.

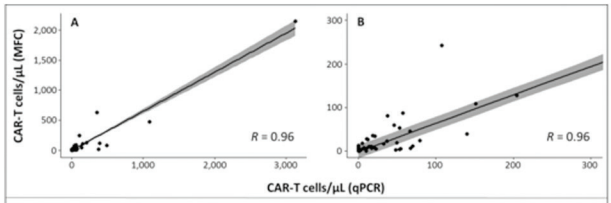
EP726 MONITORING CAR-T CELL IN B-CELL LYMPHOMA PATIENTS THROUGH SINGLE CHAIN VARIABLE FRAGMENT QPCR

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Background: CD19-targeted chimeric antigen receptor (CAR)-T cell is an approved cell therapy for the treatment of patients diagnosed with several subtypes of B cell lymphoma. Besides, monitoring CAR-T cell levels during follow-up is mandatory in order to ensure treatment success. Multiparametric flow cytometry (MFC) has proven to be an efficient method. However, improving follow-up with complementary approaches, such as qPCR could also be useful. CAR structure of both Tisagenlecleucel (Tisa-cel) (Kymriah®) and Axicabtagén Ciloleucel (Axi-cel) (Yescarta®) shares the FMC63 single chain variable fragment domain, which sequence is known, enabling their monitoring by qPCR.
Aims: To evaluate the utility of *FMC63*-specific qPCR for the detection of CAR-T cell levels during follow-up in patients treated with this therapy.
Methods: Twenty-nine patients diagnosed with a B-cell lymphoma who underwent CAR-T therapy with Axi-cel (8) and Tisa-cel (21) between June 2019 and January 2021 were included in this study. Peripheral blood (PB) samples were collected in EDTA tubes at days +7, +14, +30 and +90 (23, 24, 25 and 14 samples, respectively) from CAR-T administration, analyzing a total of 86 PB samples. In addition, nine tumor samples from eight patients were obtained from core needle biopsies. DNA was purified from PB samples using the *Maxwell 16 Blood DNA Purification Kit* (Promega, USA). Tumor samples were cut and disaggregated and DNA was purified using the QIAamp DNA Mini Kit (Qiagen). *FMC63*-specific qPCR was carried out in DNA samples, using primers and conditions previously described. For CAR-T quantification we first obtained the percentage of CAR-T cells through the ΔΔCt method (using a 100% CAR-T cell DNA sample) followed by a estimation of the absolute number of CAR-T cells from total cell count. MFC was performed on a DxFLEX cytometer (Beckman Coulter), using CD19 (20-291) protein-FITC (ACRO Biosystems). Quantitative variables were expressed as median and range. Comparison between

CAR-T cells detection by MFC and qPCR was analyzed using the Pearson correlation test.
Results: There was an optimal positive correlation between qPCR and MFC for the detection of CAR-T cells, demonstrating the usefulness of qPCR (Figure 1). Median number of CAR-T cells detected by qPCR was greater than those detected by MFC at days +7 and +14, as opposed to days +30 and +90 (Figure 1). This is probably because CAR-T cell contains a variable copy number of *FMC63* sequence and at the time of CAR-T expansion (days +7 and +14), these differences could be greater. At later stages, CAR-T cell percentage over the total number of cells is lower and the sensitivity of qPCR method is not comparable to MFC, which is able to analyze a greater number of cells. These facts may also explain the 22 samples in which CAR-T cells were detected by CMF and not by qPCR, since percentage of CAR-T in these samples was lower than 0.5% of total cells. (Figure 1). In respect of tumor samples, CAR-T cells were detected by qPCR in three out nine. Since fresh sample is not needed, qPCR demonstrates its superiority over MFC in terms of detection of CAR-T in tissue samples.



C

MFC \ qPCR	+	-
+	40	22
-	2	22

Days post CAR-T	Detected CAR-T cells/µL (median, range) qPCR	MFC
7	5 (0 - 351)	4 (0 - 627)
14	33 (0 - 3,128)	10 (0 - 2,147)
30	0 (0 - 1,085)	2 (0 - 476)
90	0 (0 - 494)	2 (0 - 76)

Figure 1. Correlation between multiparametric flow cytometry (MFC) and qPCR for CAR-T cell detection (Pearson correlation test). A. General overview of correlation. B. Zoom of samples with lower amount of CAR-T cells. C. CAR-T cells detected by microliter of peripheral blood by qPCR and multiparametric flow cytometry (MFC); positive and negative detection of CAR-T cells in patient samples through both methodologies.

Summary/Conclusion: Although qPCR is a reliable method for measuring CAR-T cell levels in patients undergoing this therapy, showing a good correlation with MFC, its sensitivity may not be sufficient at later stages of treatment. Approaches such as the application of qPCR in isolated T-cells or the use of digital PCR, could improve its usefulness in CAR-T cell monitoring.

EP727 CRISPR/CAS9 MEDIATED TCR EXCHANGE IN CORD BLOOD CD8+ T CELLS POTENTIALLY INCREASES GVL AND DECREASE GVHD

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Background: Hematopoietic cell transplantation (HCT) can potentially cure pediatric patients with acute myeloid leukemia (AML). However, a large proportion of transplanted patients eventually die due to relapse.
Aims: To improve overall survival, we propose a combined strategy based on the use of cord blood (CB) derived cells for cellular therapy and HCT.
Methods: We generated CB-CD8+ T cells expressing a recombinant T cell receptor (TCR) against Wilms tumor 1 (WT1) lacking endogenous TCR expression in order to avoid mispairing and competition. These cells were created through a highly efficient CRISPR-Cas9 multiplexing approach (up to 95% gene-editing efficiency) targeting the endogenous TCR alpha and beta chain. Next to this strategy, high lentiviral transduction efficiency resulted in high $WT1_{126}$-TCR expression levels with transduction enhancer LentiBOOST.
Results: By combining these approaches, we developed a tumor antigen-specific T cell product with robust expression of a $WT1_{126}$-specific TCR and very efficient elimination of endogenous TCR expression. TCR engineered T cells (TCR-T 2.0) show enhanced proliferation rate and cytokine production upon antigen recognition and express low levels of exhaustion markers (such as PD1, LAG3 and TIM3). Of note, TCR-T 2.0 show killing capacity when in coculture with AML blasts, but not in the presence of healthy cord-blood derived CD34+ hematopoietic stem cells.
Summary/Conclusion: Further drug product development could provide a potent off-the-shelf immune cell therapy approach to increase overall survival chances in pediatric relapse patients.

EP728 THE IMMUNOREGULATORY FUNCTIONS OF EXOSOME DERIVED FROM MESENCHYMAL STEM CELLS (MSCS) THAT GENETICALLY MODIFIED BY ADENO-ASSOCIATED VIRUS (AAV)

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Background: There exist kinds of limitations of MSCs during its application, while exosome derived from MSCs has shown promising future.
Aims: To verify the effects and mechanisms of natural MSCs-exosome in treating acute GVHD in mice, then explore and establish a method for targeted modification of MSCs-exosome and verify the functions of the modified MSCs-exosome.
Methods: In different doses of MSCs-exosome groups and MSCs group, the weight loss of acute GVHD mice was observed, then the proliferation levels of activated T cells were measured through T cell activation experiment in vitro and OVA antigen specific T cell activation experiment in vivo. AAV2YF3 mutants carrying PD-L1 and PD-L1-ITGB1 was obtained after the construction of recombinant expression vectors and then was applied to infect human MSCs to modify their exosome. The immunoregulatory functions of the modified MSCs-exosome were measured with methods as above.
Results: 1) Mouse MSCs-exosome (300ug*3 times) and MSCs (1e6*3 times) effectively alleviated the weight loss of acute GVHD mice. 2) Compared with IL2, 10ug, 25ug and 50ug human MSCs-exosome inhibited the proliferation of activated T cells in vitro, respectively 86.01% (IL2), 40%, 39.61% and 42.84%; compared with PBS, 50ug, 100ug and 200ug mouse MSCs-exosome inhibited the proliferation of antigen-specifically activated OT-1 cells in vivo, respectively 42.6%, 33.1%, 14.2% and 10.6%. 3) After the infection of AAV2YF3 mutant carrying PD-L1 or PD-L1-ITGB1, the positive proportion of MSCs-exosome exceeds 40% and 60%, respectively. 4) Compared with the natural state, human MSCs-exosome modified by PD-L1 or PD-L1-ITGB1 showed better proliferation inhibitory effect in vivo, and increased the proportion of Treg cells in vitro.
Summary/Conclusion: MSCs-exosome exhibited similar immunomodulatory effects with MSCs. MSCs-exosome after PD-L1 and PD-L1-ITGB1 targeted modification effectively inhibited the proliferation of activated T cells and increased the proportion of Treg cells.

Gene therapy, cellular immunotherapy and vaccination - Clinical

EP729 CAR-T CELL IN DIFFUSE LARGE B-CELL AND PRIMARY MEDIASTINAL LYMPHOMAS IN REAL LIFE SETTING: A REPORT FROM THE PROSPECTIVE OBSERVATIONAL STUDY OF THE ITALIAN SOCIETY OF HEMATOLOGY.

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Background: Relapsed/refractory (R/R) diffuse large B-cell (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) have a very poor prognosis with standard chemotherapy. The recently approved axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are anti-CD19 chimeric antigen receptor T cells (CAR-T) that proved very effective in clinical trials and real-life setting. The Italian Society of Hematology (SIE) is conducting a prospective observational trial to evaluate safety and efficacy in patients (pts) treated with axi-cel and tisa-cel.
Aims: of the study are: 1. to register all DLBCL and PMBCL pts candidate to CAR-T in the Italian authorized centers; 2. to evaluate the intention to treat overall response rate (ORR, complete [CR] and partial response [PR]); 3. to evaluate duration of response (DOR), progression free survival (PFS) and overall survival (OS); 4. to evaluate safety in terms of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and long-term cytopenia; 5. to evaluate different CAR-T products.
Methods: SIE designed a multicenter prospective observational study, approved by ethics committee of all centers. All pts treated since March 2019 to January 2021, were included into this national study.
Results: 126 pts were leukapheresed. Thirteen pts showed a rapid progression (10) or fatal infection (3) during the manufacturing and were not infused. The clinical characteristics of the 113 infused pts were: median age 53 years (19-70), male 64 (57%), stage III/IV 77 (68%), bulky disease 51 (45%); median number of prior lines was 3 (2-7); 33 patients (29%) failed a previous autologous stem cell transplantation and 81 (72%) were primary refractory. For histologies, 59 (52%) were DLBCL, 18 (16%) high-grade B-cell (HGBCL), 23 (20%) PMBCL, 13 (12%) transformed Follicular (tFL). Median lymphocyte count at the apheresis was 810/mm^3 (250-8900). Bridging therapy was delivered to 97 pts (86%). All pts received Flu-Cy lymphodepletion. Fifty-nine (52%) received axi-cel and 54 (48%) tisa-cel. Median follow-up time for infused pts was 6.9 months (IQR: 3.13-11.78). At 30-days after the infusion, all the 113 infused pts were evaluable for response: 45 (40%) CR, 35 (31%) PR, with and encouraging ORR of 71%. For the evaluable pts, DOR was 73% (95%CI:62-85) at 6-months and 58% (95%CI:44-77) at 12-months. In the whole series, 6 and 12-months PFS were 54% (95% CI:45-65) and 46% (95%CI:35-59); 6 and 12-months OS were 80% (95%CI:71-88) and 75% (95%CI:65-86), respectively. With the limitation of small number, 6-months PFS were 48% for DLBCL, 62% for HGBCL, 66% for PMBCL and 59% for tFL; 6-months OS by histotype were 78% for DLBCL, 80% for HGBCL, 80% for PMBCL and 92% for tFL. No differences between axi-cel and tisa-cel were reported in terms of OS and PFS. All grade CRS was observed in 87 (77%) of 113 pts, but only 6 (5%) were grade 3 or 4; ICANS was recorded in 31 (27%) patients, but only 11 (10%) were grade 3 or 4. Sixty-one (54%) pts received tocilizumab and 38 (34%) steroids. Cytopenia beyond 30 days was reported in 30 (27%) pts and 27 of them (24%) experienced viral or bacterial infections. No toxic deaths were recorded.
Summary/Conclusion: In the real-life, axi-cel and tisa-cel showed an ORR similar to those of the registrative trials, even if almost all pts underwent bridging therapy. The response rate is similar across histotypes and between products. CAR-T toxicity is manageable, relapse beyond 6 months is a rare event. Cytopenias as well as infections are an emerging problem in real-life setting.

EP730 CLINICAL OUTCOMES IN ADULTS WITH HEMOPHILIA B WITH AND WITHOUT PRE-EXISTING NEUTRALIZING ANTIBODIES TO AAV5: 6 MONTH DATA FROM THE PHASE 3 ETRANACOGENE DEZAPARVOVEC HOPE-B GENE THERAPY TRIAL

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Background: Etranacogene dezaparvovec is an investigational gene therapy for hemophilia B (HB) comprising an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) transgene with a liver specific promoter. Preliminary data suggest that anti-AAV5 neutralizing antibodies (NAbs) may not preclude successful transduction with etranacogene dezaparvovec.
Aims: A Phase 3 trial (HOPE-B; NCT03569891) was established to assess efficacy and safety of a single dose of etranacogene dezaparvovec (2x10^{13}gc/kg). Adult males with HB (FIX≤2%) receiving routine FIX prophylaxis, with/without AAV5 NAbs, were enrolled into this open-label, single-dose, single-arm trial, following a ≥6 month lead-in. Co-primary endpoints; change in FIX activity (measured by one stage assay) at 26 and 52wks and 52wk annualized bleeding rate compared to lead-in.
Methods: Outcomes at 26wks are analyzed using descriptive statistics and a correlation analysis.
Results: 54 participants were dosed and completed 26wks of follow-up, 23 (42.6%) of whom had AAV5 Nabs at baseline (BL) with a median titer of 56.9 (max titer 3212; 1st-3rd quartile 23.3-282.5) and a distribution representative of the general population. One participant (titer 198) received a partial dose and was excluded from efficacy assessments. One participant (titer 3212) did not respond and remained on prophylaxis. All other participants (n=52) discontinued prophylaxis. No correlation of pre-existing NAbs with FIX activity was observed up to a titer of 678 (n=52, r=-0.28 [95% CI -0.51, 0.00], R^2=0.078). Mean FIX activity at 26 weeks was 32.7 IU/dl (min <2, max 90.4, 1st-3rd quartile 16.3-42.6, n=22) in participants with NAbs versus 41.3 IU/dl (min 8.4, max 97.1, 1st-3rd quartile 31.3-52.7, n=31) in those without.
No deaths and no inhibitors to FIX were reported.

Table 1. Most common adverse events reported among participants with and without AAV5 NAbs at baseline

Adverse event (n)	With AAv5 NAbs at baseline (n=23)	Without AAv5 NAbs at baseline (n=31)
Transient transaminitis requiring corticosteroids	2/23	7/31
Infusion-related reactions	5/23	2/31
Headache	2/23	5/31
Influenza-like illness	4/23	3/31

Summary/Conclusion: This study demonstrates successful treatment of participants with generally prevalent titers of pre-existing NAbs to AAV5 with etranacogene dezaparvovec, supporting broad eligibility for AAV5-based therapies.

EP731 IMMUNOTHERAPY USING A 3RD GENERATION CD20 TARGETED CAR T-CELL (MB-106) FOR TREATMENT OF B-CELL NON-HODGKIN LYMPHOMA (B-NHL) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background: Immunotherapy with CD19 targeting CAR-T has become a standard treatment for patients (pts) with relapsed diffuse large cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) and clinical trials have shown high efficacy in other B-NHLs. However, long-term remissions for the approved indications are ~40%, and toxicities including cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) remain a challenge. CD20 is a proven target for treatment of B-NHLs/ CLL with demonstrated high clinical efficacy of unmodified, radiolabeled, and bispecific antibodies. CD20-targeted CAR-T represents a promising adoptive immunotherapy option that could be utilized to treat relapsed/refractory B-NHLs and CLL.
Aims: We present interim results of our ongoing phase I/II clinical trial investigating safety and efficacy CD20 CAR-T for high-risk B-NHLs and CLL (NCT03277729).
Methods: MB-106 is a fully human 3rd-generation CD20-targeted CAR-T with both 4-1BB and CD28 costimulatory domains. Lymphodepletion (LD) consists of cyclophosphamide (Cy) ± fludarabine (Flu). CAR-T cells are administered at one of 4 dose levels (DL): DL1: $3.3x10^5$, DL2: $1x10^6$, DL3: $3.3x10^6$, DL4: $1x10^7$ CAR T cells/kg. CAR-T is infused in the outpatient setting except for the first pt of each dose cohort (overnight observation). Pts with relapsed $CD20^+$ B-cell malignancies are eligible, including but not limited to DLBCL, follicular lymphoma (FL), MCL and CLL. Prior treatment with CD19 CAR-T is permitted. Treatment response is assessed on day 28. CRS and ICANS are graded per ASTCT consensus grading.
Results: The study underwent a major cell manufacturing modification after treating 7 pts with no objective responses as previously reported (Shadman, ASH 2020). This abstract includes pts who were treated under the modified process. Since December 2019, 12 pts (9 FL, 2 MCL, 1 CLL) were treated after LD with Cy-Flu. All DLs have been reached: DL0 (1 FL), DL1 (2 FL), DL2 (2 FL and 2 MCL), DL3 (3 FL, 1 CLL) and DL4 (1 FL), with no dose-liming toxicities. CRS occurred in 3 pts (25%): 2 pts with grade (Gr) 1 and 1 pt with Gr 2. Only 1 pt required tocilizumab and dexamethasone. No ICANS of any grade was observed. One pt developed Gr 3 neuropathic pain which, in the absence of other explanation, was attributed to the CAR-T. No pts had tumor lysis syndrome or Gr 3-4 infection. Clinical responses were observed at all dose levels. Overall response rate (ORR) was 92% (11/12) with a complete response (CR) rate of 58% (7/12). In FL pts (n=9), ORR and CR were 89% (8/9) and 67% (6/9), respectively. The CLL pt had a PET-negative CR and undetectable measurable residual disease in peripheral blood and bone marrow by flow cytometry (10^{-4}) (uMRD4) on day 28. Among pts who received DL3 (n=4) and DL4 (n=1), CR rate was 100% (5/5). All 7 pts who achieved a CR remain in remission at a median follow-up of 4 months (range 0 – 13 months). CAR-T expansion was robust, with median peak blood levels of CAR^+ T cells of 122 CAR^+ cells/µl (range 0.27-2024), corresponding to 19% (range 0.15 - 65%) of all $CD3^+$ cells.
Summary/Conclusion: The absence of significant toxicity at all dose levels, including no grade 3-4 CRS and no ICANS of any grade, suggests a highly favorable safety profile of MB-106 when compared to commercially available CAR-T cells targeting CD19. Treatment with MB-106 has also resulted in high ORR and CR rates with ongoing remissions in all patients who achieved a CR. Enrollment is currently ongoing and the data will be updated at the time of presentation.

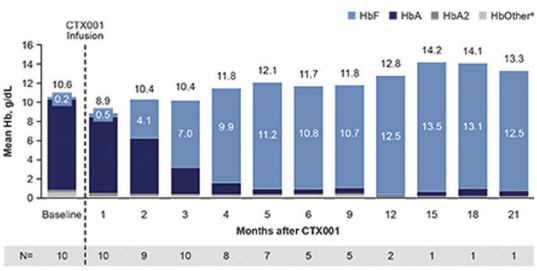
EP733 CTX001 FOR TRANSFUSION-DEPENDENT B-THALASSEMIA: SAFETY AND EFFICACY RESULTS FROM THE ONGOING CLIMB THAL-111 STUDY OF AUTOLOGOUS CRISPR-CAS9-MODIFIED CD34+ HEMATOPOIETIC STEM AND PROGENITOR CELLS

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Background: Elevated levels of fetal hemoglobin (HbF) are associated with improved clinical outcomes in patients (pts) with transfusion-dependent β-thalassemia (TDT). CTX001™ is a novel cell therapy that uses non-viral, ex vivo CRISPR-Cas9 gene editing in autologous hematopoietic stem and progenitor cells (HSPCs) at the erythroid enhancer region of the *BCL11A* gene to reduce expression of BCL11A, a repressor of γ-globin, and reactivate HbF production. Early data from pts with TDT infused with CTX001 showed increased levels of total hemoglobin (Hb), HbF, and F-cell pancellularity over time. All pts ceased packed red blood cell (pRBC) transfusions within 2 months (mo) after CTX001 infusion and remained transfusion-free through the reported period. The safety profile was generally consistent with myeloablative conditioning.
Aims: Here, we present additional patient data and follow-up (f/u) from an interim data cut on 21 January 2021. Included in the data set are all pts with TDT enrolled in the CLIMB THAL-111 trial (NCT03655678) infused with CTX001 who had ≥3 mo of f/u available at the time of analysis (N=10).
Methods: Pts (aged 12 to 35 years) with TDT receiving pRBC transfusions of ≥100 mL/kg/year or ≥10 units/year over the previous 2 years were eligible. After mobilization with G-CSF (filgrastim) and plerixafor, peripheral $CD34^+$ HSPCs were collected by apheresis and edited using a specific single-guide RNA and Cas9 nuclease. Prior to CTX001 infusion on Day 1, pts received myeloablation with busulfan. Pts were monitored for stem cell engraftment and hematopoietic recovery, adverse events (AEs), total Hb and HbF production, percentage of F-cells, and pRBC transfusion requirements during f/u.
Results: Mean duration of f/u was 9.8 mo (range: 4.3–23.8). Four of 10 pts had genotypes associated with more severe disease: β0/β0, n=1; [IVS-I-110]/β0, n=2; and β+[IVS-I-110]/β+[IVS-I-110], n=1. At baseline, pts had mean (SD) total Hb and HbF levels of 10.6 (2.2) g/dL and 0.2 (0.2) g/dL, respectively, and had received a mean of 14.7 pRBC transfusions annually. Following CTX001 infusion, median neutrophil engraftment occurred on Day 30 (range: 19–39) and median platelet engraftment occurred on Day 38.5 (range: 29–52).
All 10 pts reported AEs; most were mild or moderate in severity and the post-CTX001 safety profile was generally consistent with busulfan myeloablation. As previously reported, 1 patient had 4 serious AEs (SAEs) that the principal investigator considered related or possibly related to CTX001: headache, hemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome, all in the context of HLH and all of which have resolved. No other pts had a CTX001-related SAE.
All pts demonstrated increases in total Hb and HbF (Figure), and F-cell pancellularity over time. Pts stopped pRBC transfusions within 2 mo after CTX001 infusion and were transfusion-free at the time of this analysis (up to 23.8 mo total f/u).

Figure. Mean Hb fractionation and total Hb in patients with TDT (N=10)



Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; TDT, transfusion-dependent β-thalassemia
Mean HbF (g/dL) is indicated within the light blue bars and mean total Hb (g/dL) is shown above each bar
Number of patients (N) with data available at each time point is noted
*Hb adducts and other variants

Summary/Conclusion: The updated data reported here confirm previous reports showing CTX001 infusion increases total Hb and HbF with F-cell pancellularity in pts with TDT, and demonstrate the durability of this effect for up to 23.8 mo f/u. All 10 pts were transfusion-free within 2 mo after CTX001 infusion through the time of this analysis. The safety profile of CTX001 remained generally consistent with myeloablative conditioning and autologous hematopoietic stem cell transplantation. These results strongly support continued investigation of CTX001 as a potential functional cure for pts with TDT.
Submitted on behalf of the CLIMB THAL-111 Investigators.

EP734 FACTORS ASSOCIATED WITH PROGRESSION-FREE SURVIVAL (PFS) OF ADULT AND PEDIATRIC PATIENTS WITH RELAPSED / REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH ARI-0001 CART19 THERAPY.

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Background: Prognosis of relapsed/refractory (R/R) B-cell acute lymphoid leukemia (ALL) is poor, particularly in patients relapsing after allogeneic hematopoietic cell transplantation (alloHCT). In this setting, several chimeric antigen receptor products targeting CD19 have been capable of achieving complete response (CR) rates of 70 to 85%. Nevertheless, a significant proportion of patients relapse despite having achieved a minimal residual disease (MRD) negative CR.
Aims: To identify factors associated with progression-free survival (PFS) in patients with R/R B-ALL treated with ARI-0001 (Academic CART19 cells).
Methods: We report the outcome of all patients with R/R B-ALL consecutively treated with ARI-0001 cells in two centers (adult and pediatric) from Jul 2017 to Dec 2020, including patients treated in the CART19-BE-01 trial and the consecutive compassionate use program. All patients signed informed consent and all protocols were approved by the Ethics Committees and the Spanish Medicines Agency. Lymphodepletion was performed with fludarabine (90 mg/m2) and cyclophosphamide (900 mg/m2), followed by the infusion of 0.1-5 x10^6 ARI-0001 cells/kg in a single or fractionated manner. We analyzed the impact on PFS of the following variables: age (+/- 18 yr and +/- 25 yr), prior treatment lines (+/- 4), prior immunotherapy (blinatumomab and inotuzumab), prior alloHCT, tumor burden (+/- 5% blasts at bone marrow), type of dosage (single vs fractionated dosing), and loss of B-cell aplasia (BCA). The statistical analysis was performed using Kaplan Meier / log rank test for all variables except for B-cell aplasia, which was introduced as a time-dependent covariate in a Cox regression.
Results: A total of 53 patients with R/R B-ALL received ARI-0001 cells. Median age at infusion was 30 years (3-68), including 10 pediatric patients (19%), and 55% were men. Patients had a median of 4 prior treatment lines (2-8), including blinatumomab 23% (12/53), inotuzumab 53% (28/53) and alloHCT 79% (42/53). All patients received lymphodepletion before receiving ARI-0001 cells. Treatment was fractionated in 72% of patients. The median PFS for the entire series was 13.5 months (95% CI: 7.14-not available), with a median follow-up for survivors of 19 months (range: 2-40 months). PFS at 12 and 24 months was 50.9% (95% CI: 38.4-67.4%) and 32.9% (95% CI: 20.6-52.6%), respectively. The median overall-survival (OS) for the entire series was 29.2 months (95% CI: 15-not available). OS at 12 and 24 months was 70.2% (95% CI: 58.1-84.8%) and 53.9% (95% CI: 40.5-71.8%), respectively. By univariate analysis, only two variables had an impact on PFS (table 1): tumor burden (+/- 5% of blasts at screening), with a PFS at 24 months of 52.5% (36.4-75.7%) vs. 10.7% (2.1-54.4%) and a hazard ratio (HR) of 2.14 (95% 1.04-4.42) for patients with 5% or more blasts at screening (p = 0.0386). On the other hand, loss of BCA had a HR of 4.41 (95% CI: 1.59-12.2), p = 0.0043. Both variables (tumor burden and loss of BCA) were also confirmed in the multivariate model, with a HR of 2.05 (1.004-4.17) for patients with 5% or more blasts at screening (p = 0.0484) and a HR of 4.32 (1.57-11.86) for patients with loss of BCA (p = 0.0045).

Factors associated with PFS	
Tumor burden	
PFS at 24 months <5% blasts	52.5% (36.4-75.7%)
PFS at 24 months ≥5% blasts	10.7% (2.1-54.4%)
Univariate Hazard ratio (≥5% blasts)	2.14 (95% CI: 1.04-4.42) (p = 0.0386)
Multivariate Hazard ratio (≥5% blasts)	2.05 (95% CI: 1.004-4.17) (p = 0.0484)
Loss of absolute B-cell aplasia	
Univariate Hazard ratio	4.41 (95% CI: 1.59-12.2) (p = 0.0043)
Multivariate Hazard ratio	4.32 (95% CI: 1.57-11.86) (p = 0.0045)

Summary/Conclusion: ARI-0001 therapy was able to achieve long term remissions in this population of R/R B-ALL patients across all patient subgroups. Nevertheless, patients referred for ARI-0001 cell therapy with 5% or more of bone marrow blasts and those who lost B-cell aplasia after ARI-0001 cell therapy had a shorter PFS.

EP736 CTX001 FOR SICKLE CELL DISEASE: SAFETY AND EFFICACY RESULTS FROM THE ONGOING CLIMB SCD-121 STUDY OF AUTOLOGOUS CRISPR-CAS9-MODIFIED CD34+ HEMATOPOIETIC STEM AND PROGENITOR CELLS

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Background: Elevated levels of fetal hemoglobin (HbF) are associated with improved clinical outcomes in patients with sickle cell disease (SCD). CTX001™ is a novel cell therapy that uses non-viral, ex vivo CRISPR-Cas9 gene editing in autologous hematopoietic stem and progenitor cells at the erythroid enhancer region of the *BCL11A* gene to reduce expression of BCL11A, a repressor of γ-globin, and reactivate HbF production. Early data from patients with SCD infused with CTX001 showed increased levels of total hemoglobin (Hb), HbF, and

F-cell pancellularity over time. No vaso-occlusive crises (VOCs) were reported for any patient after CTX001 infusion. The safety profile was generally consistent with myeloablative conditioning.

Aims: Here, we present additional patient data and follow-up from an interim data cut on 28 January 2021. Included in the data set are all patients with SCD enrolled in the CLIMB SCD-121 trial (NCT03745287) infused with CTX001 who had at least 3 months of follow-up available at the time of analysis (N=4).

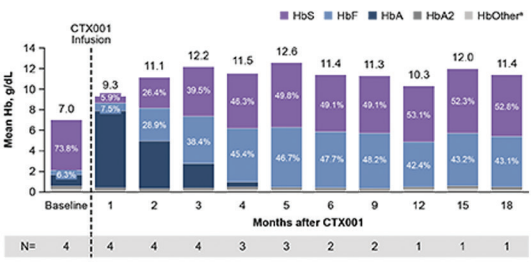
Methods: Patients (aged 12 to 35 years) with severe SCD, defined as ≥2 VOCs/year requiring medical care over the previous 2 years, were eligible. After mobilization with plerixafor, peripheral CD34+ hematopoietic stem and progenitor cells were collected by apheresis and edited using a specific single-guide RNA and Cas9 nuclease. Prior to CTX001 infusion on Day 1, patients received myeloablation with busulfan. Patients were monitored for stem cell engraftment and hematopoietic recovery, adverse events, total Hb and HbF production, hemolysis, percentage of F-cells, and VOCs during follow-up.

Results: Mean duration of follow-up was 10.1 months (range: 4.3 to 19.2). At baseline, patients had mean (SD) total Hb of 7.0 (1.6) g/dL and mean (SD) HbF of 6.3% (2.2%) of total Hb. Patients had a mean of 5.3 severe VOCs annually in the previous 2 years. Following CTX001 infusion, median neutrophil engraftment occurred on Day 25.5 (range: 17 to 30) and median platelet engraftment occurred on Day 31.5 (range: 30 to 40).

All 4 patients reported adverse events; most were mild or moderate in severity and the post-CTX001 safety profile was generally consistent with busulfan myeloablation. No serious adverse events considered by the principal investigator to be related or possibly related to CTX001 were reported.

All patients demonstrated increases in total Hb and HbF (Figure), as well as F-cell pancellularity over time. Mean %HbF rose to >30% by month 3 and all patients had %HbF >30% as of the last visit before data cut. No patients experienced VOCs during the time of this analysis (up to 19.2 months). Markers of hemolysis, including haptoglobin, lactate dehydrogenase, and total bilirubin, improved in all patients and normalized by month 6.

Figure. Mean Hb fractionation and total Hb in patients with SCD (N=4)



Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; SCD, sickle cell disease
Mean %HbF and %HbS of total mean Hb at each visit is indicated within the bars and mean total Hb (g/dL) is shown above each bar
Number of patients (N) with data available at each time point is noted
*Hb adducts and other variants

Summary/Conclusion: The updated data presented here confirm previous reports showing CTX001 infusion increases total Hb and %HbF with F-cell pancellularity in patients with SCD, and demonstrate the durability of efficacy up to 19.2 months of follow-up. All 4 patients were free of VOCs from CTX001 infusion through the time of this analysis. The safety profile of CTX001 remained generally consistent with myeloablative conditioning and autologous hematopoietic stem cell transplantation. These results strongly support continued investigation of CTX001 as a potential functional cure for patients with SCD.

Submitted on behalf of the CLIMB SCD-121 Investigators.

EP737 REAL-WORLD TREATMENT WITH CAR T-CELL THERAPY OF UNITED STATES (US) PATIENTS WITH LARGE B CELL LYMPHOMA (LBCL)

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Background: The advent of chimeric antigen receptor (CAR) T-cell therapy has represented one of the most innovative therapeutic advances in oncology in recent years. Impressive clinical responses to CAR T-cell therapy observed in patients with relapsed and refractory B-cell lymphoid malignancies have led to the Food and Drug Administration (FDA) approval of four CAR T-cell therapies in the US since 2017. Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) have now been on the US market for the treatment of patients with LBCL since 2017 and 2018, respectively, hence allowing for assessment of their use in real-world clinical practice.

Aims: This real-world claims-based study aimed to describe characteristics and treatment outcomes of patients with DLBCL treated with the CAR T-cell therapies tisa-cel or axi-cel.

Methods: Patients with at least 1 claim for tisa-cel or axi-cel and a diagnosis code of DLBCL were identified from the Symphony Integrated Dataverse (IDV), a large US claims database containing linked longitudinal prescription, medical, and hospital claims. The IDV contains claims for 280 million active unique patients representing over 73% of specialty prescriptions, 58% of medical claims, and 30% of hospital claims volume in the US. Patient characteristics and treatment patterns were summarized using descriptive statistics.

Results: Among a total of 93 patients with DLBCL identified in this study, 58% (n=54) received axi-cel and 42% (n=39) received tisa-cel. The majority (n=60, 65%) of patients were male, and the median age at time of tisa-cel or axi-cel was 64 years (range, 20-78 years). Commercial insurance was the primary payer at the time of tisa-cel or axi-cel therapy for most patients with DLBCL included in the study (n=77, 83%). Patients with DLBCL treated with tisa-cel or axi-cel were distributed across each of the 4 US census regions. The majority (n=55, 59%) of patients received tisa-cel or axi-cel in the outpatient setting. Tisa-cel or axi-cel was received a median of 12.9 months following patients' initial diagnosis of DLBCL. Less than half (n=42, 45%) of patients received 2 or more lines of systemic therapy prior to tisa-cel or axi-cel and 17% (n=16) received systemic therapy after tisa-cel or axi-cel during a median follow-up period of 6.3 months.

Summary/Conclusion: In the first few years of market availability in the US, the CAR T therapies tisa-cel or axi-cel have been used to treat patients with LBCL outside of the clinical trial setting mostly in the outpatient setting. Findings from this real-world study suggest that patients may be receiving tisa-cel or axi-cel prior to the failure of prior lines of therapy. Despite short follow up, one in 6 patients appear to have relapsed disease based on need for additional systemic therapy. Updated follow-up and outcomes will be presented at time of congress. Further research is warranted to understand real-world clinical outcomes among patients treated with CAR T therapy outside the trial setting.

EP738 T CELL LINEAGE MIXED CHIMERISM IN ACUTE LEUKAEMIA/MDS- IS IT PROGNOSTIC - A SINGLE CENTRE RETROSPECTIVE STUDY

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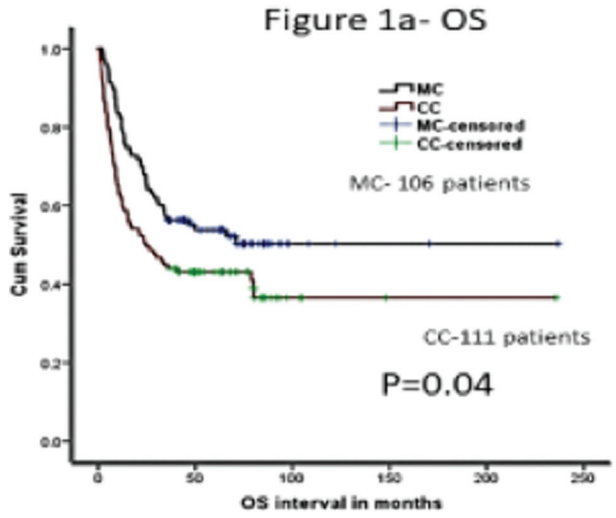
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Background: T-cell depletion, especially alemtuzumab, reduces the risk of graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) using unrelated donor peripheral stem cell graft (PBSC-matched/mismatched), but has been associated with an increased frequency of mixed t cell chimerism (MC) and subsequent relapse. In adult patients receiving alemtuzumab and having MC (T cell), early pre-emptive donor lymphocyte infusion (pDLI) has been safe and effective in reducing relapses, without increasing risk of graft vs host disease (GVHD). Among responders in paediatric cohort having lineage specific MC(CD34/33), pDLI could achieve outcomes nearly similar to patients having complete chimerism (CC). However, many patients having MC actually fail to receive timely pDLI, and their outcomes remain particularly dismal, which is not considered. Thus, we compared long term outcomes of patients with T cell MC (including patients not receiving pDLI) to patients having complete chimerism CC

Aims: Thus, we compared long term outcomes of patients with T cell MC (including patients not receiving pDLI) to patients having complete chimerism CC for overall survival, disease free survival and other outcomes

Methods: One-hundred six adult patients with CD3 MC after day 60, in patients undergoing HSCT for acute leukaemia/myelodysplastic syndrome (MDS) from an unrelated donor (UD), using alemtuzumab and predominantly PBSC grafts, between 2007-2016, were compared with 111 patients having CC. CD33 chimerism was >98%. In patients with

MC intention was to start pDLI (by day 100) after rapid withdrawal of immunosuppressants (chimerism <50%).
Results: Both groups were comparable for age, mismatches, graft source, and disease risk. MC group had more patients receiving reduced intensity (RIC) regimen (62% vs 52% in CC, p=0.15). The median follow-up was 33 (0.6-150 months). Fifty- three (56%) patients received pDLI. The median dose of pDLI was 1 x10^6/kg and median time to pDLI was 5 months from transplantation. Out of 56 patients, 36 patients (67%) had a response (RR) (85% achieving CC) and 17 (33%) patients had no response (NR). Fifty patients (44%) did not receive any pDLI (ND). pDLI was well tolerated with no difference in GVHD (p=0.65), infections (p=0.37) or NRM (P=0.37) between pDLI and ND. Overall survival (OS) was significantly better in MC group as compared to CC (52.4% vs 42%, p=0.04), mainly due to reduction in non- relapse mortality NRM (14% vs 26%, p=0.05) and all grade acute and chronic GVHD (38% vs 68%, p=0.001, and 37% vs 51%, p=0.025). Relapses and disease-free survival were comparable between the two groups (32% vs 38%, p=0.99 and 38.5% vs 45%, p=0.12, for CC and MC, respectively). After multivariate analysis, MC still had significantly better OS (p=0.02, HR-1.53, CI-1.0-2.2) and NRM (p=0.02, HR-2.44, CI-1.3-5.2, ref MC). Within MC group, response to pDLI was the only significant factor predicting OS, DFS and relapses with NR and ND having unfavourable outcomes as compared to RR (p=0.0001, HR=5.45, and p=0.001, HR-5.95, respectively).



Summary/Conclusion: In this large single centre study, we have shown that T cell MC in patients undergoing UD allografts with alemtuzumab is no longer an adverse prognostic factor, with timely initiation of pre-emptive pDLI, and their OS is in fact better than CC, mainly due to reduction in NRM and early onset aggressive GVHD. This strategy is safe and well tolerated. Response to pDLI is the main independent predictor of overall outcomes in patients with MC.

EP739 OBJECTIVE RESPONSE AT LOW DOSE IN THE FIRST-IN-HUMAN IMMUNICY-1 TRIAL EVALUATING NON-GENE EDITED ALLOGENEIC CYAD-211 ANTI-BCMA CAR-T PRODUCT IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA

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CYAD-211 is administered after a non-myeloablative preconditioning chemotherapy consisting of cyclophosphamide (300mg/m^2/day) and fludarabine (30mg/m^2/day) for 3 days. Three CYAD-211 dose-levels (DLs; 30, 100 and 300x10^6 cells per infusion), are evaluated, according to a 3+3 design. The lowest DL was implemented as a safety-run for this first-in-human trial.

Background: Autologous chimeric antigen receptor (CAR) T-cells targeting B-cell maturation antigen (BCMA) have shown impressive objective response rates in patients with advanced multiple myeloma (MM).
CYAD-211 is a first-in-class, non-gene edited allogeneic anti-BCMA CAR T-cell product that uses an "all-in-one" vector approach to co-express, in addition to the CAR, a single optimized short hairpin RNA (shRNA) to down-regulate the expression of the T-cell receptor (TCR) CD3ζ subunit thus reducing the risk of graft-versus-host disease (GvHD). This non-gene editing technology does not permanently alter the genome integrity, therefore decreasing the potential safety risk associated with "off-target" genome modifications. Preclinical experiments demonstrated that persistence of allogeneic T-cells produced with shRNA technology is superior to cells engineered with gene-editing technologies.
Aims: The objective of the open-label Phase I IMMUNICY-1 (NCT04613557) trial is to evaluate the safety and clinical activity of a single infusion of CYAD-211 in relapsed or refractory MM patients.
Methods: A bank of clinical- grade CYAD-211 cells was generated through a single production run using a portion of a single donor apheresis. The bank generated >10^{10} CYAD-211 cells suitable for the entire dose escalation segment and expansion cohort of the trial.
Patients with relapsed or refractory MM with measurable disease as per the International Myeloma Working Group (IMWG) response criteria are eligible for the trial.
Results: As of the data cutoff of February 24, 2021, enrollment in the DL1 was completed (Table). Clinical activity evaluation was performed on Day (D) 22 and D36 for the first two patients with one confirmed partial response (PR) and one stable disease (SD). No dose-limiting toxicity nor Grade ≥ 3 treatment-related adverse events (AE) were reported. No immune effector cell-associated neurotoxicity syndrome (ICANS) nor GvHD were observed. One cytokine release syndrome (CRS) grade 1 was observed in the patient presenting the PR. CYAD-211 cells were detected by PCR-based method in the peripheral blood of the PR patient.

Clinical data from patients at DL1 as of 25-Feb-2021

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	57	72	78
Gender	M	F	M
ECOG PS	0	0	1
MM subtype	λ light chain	IgG, λ light chain	IgG, λ light chain
Time since diagnosis (years)	7	7.5	6.4
R-ISS Stage at diagnosis	I	II	II
mSMART risk	Standard	Intermediate	-
Extramedullary disease	N	N	N
Bone marrow plasma cells (%)	15	65	5
Prior lines of therapy (number)	4	4	2
Prior autologous transplant	Y	Y	N
AE of clinical interest			
CRS	Grade 1 (fever)	-	-
ICANS	-	-	-
GvHD	-	-	-
Infection	-	-	-
Best response	**PR**	**SD**	***Not available yet***

ECOG PS: Eastern Cooperative Oncology Group performance status; F: Female; Ig: Immunoglobulin; M: Male; mSMART: Mayo Stratification of Myeloma and Risk-Adapted Therapy; N: No; R-ISS: Revised International Staging System; Y: Yes

Summary/Conclusion: The IMMUNICY-1 clinical trial seeks to provide the proof-of-principle that single shRNA-mediated knockdown can generate safe and functional allogeneic CAR T-cells in humans. The observed clinical activity at such low DL of 30x10^6 cells is encouraging in the allogeneic setting. Clinical and cell kinetics data from the completed first DLs will be presented at the time of the congress.The early stages of this trial continue to support the development of allogeneic CAR T-cell therapy as a feasible approach that may overcome many of the hurdles associated with autologous CAR-T cells.

EP740 PRELIMINARY ANALYSIS OF A PHASE 1 STUDY OF NEXI-002 AUTOLOGOUS MULTI-AGENT-SPECIFIC CD8+ T CELLS FOR THE TREATMENT OF RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

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Background: MM is an incurable malignancy that occurs predominately in older patients and is characterized by the growth of malignant plasma cells in the bone marrow. The median age of patients at diagnosis is 69 years and MM accounts for approximately 17% of all hematologic cancers. Despite substantial advances in therapy, virtually all patients relapse, emphasizing the need for additional effective treatments.
Aims: To characterize the safety and preliminary efficacy of NEXI-002, an HLA-restricted adoptive non-genetically modified and autologous cell product. The NEXI-002 product contains CD8+ T-cell memory subtypes that combine tumor potency with the potential for long-term immune persistence.
Methods: First-In-Human open-label phase 1/2 clinical trial. Safety, activity and correlative exploratory endpoints are evaluated and followed in patients during the study. HLA 02:01 patients underwent leukapheresis and artificial antigen presenting cells (aAPCs) were employed to isolate and expand CD8+ T-cell clonotypes expressing T cell receptors specific for HLA-restricted peptides from the WT1, CD138, CS1, and NY-ESO antigens. After expansion, the NEXI-002 product consists of γδ and CD8+ lymphocytes that are infused into the patient.
Results: Three patients were treated with single infusions of 80 to 100 million cells of NEXI-002 following lymphodepleting chemotherapy (fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 on Days -5 to -3). All three patients have completed the dose-limiting toxicity (DLT) period. No cytokine release syndrome, neurotoxicity, infusion-related reaction, or other NEXI-002-related serious adverse events were observed. At the time of analysis, correlative studies demonstrate the NEXI-002 product is comprised mostly of CD8+ antigen-specific T cells that include stem-like central memory, central memory, and effector T cells. The infused CD8+ antigen-specific T cells were detectable by multimer staining in peripheral blood and the product phenotype was maintained over time. Flow cytometry studies of cells stained for antigen specificity determined that infused NEXI-002 cells contain T cell clones that were undetectable in the peripheral blood of patients at baseline but were detected in blood and persist over the current 3-4 weeks of follow-up. A robust lymphocyte recovery occurred quickly after the infusion of NEXI-002, demonstrating CD3 (CD4/CD8) reconstitution following lymphodepletion chemotherapy.
Summary/Conclusion: Early results indicate that NEXI-002 infusion is safe and well tolerated and is capable of proliferation and persistence within peripheral blood. NEXI-002 may have the potential to provide clinical benefit for patients with RRMM. Due to these encouraging findings, the trial will be expanded to gain greater safety and activity experience with NEXI-002. Updated data will be available.

EP741 A 10 YEAR RETROSPECTIVE SERIES OF PERIPHERAL BLOOD STEM AND PROGENITOR CELL COLLECTION IN PEDIATRIC CANDIDATES FOR AUTOLOGOUS EX-VIVO GENE THERAPY

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Background: Collection targets for autologous hematopoietic stem and progenitor cell (HSPC) gene therapy (GT) should ideally account for the cell manipulation process and for unmanipulated backup storage. Therefore higher amounts of HSPCs in comparison to conventional autologous and allogenic HSPC transplantation harvests are required.
While pediatric donors have historically undergone bone marrow (BM) harvest, HSPC mobilization and apheresis may be safer and more suitable for the purpose of autologous GT.
Aims: To analyze the safety and collection yields of peripheral blood stem and progenitor cells (PBSCs) collection in pediatric candidates for GT.
Methods: We retrospectively analyzed the mobilization and apheresis procedures of all consecutive pediatric (<18 years) patients treated at IRCCS Ospedale San Raffaele (OSR) between April 1st 2010 and March 31st 2020, candidate to GT for for adenosine deaminase deficiency (ADA-SCID), b-thalassemia, metachromatic leukodystrophy (MLD), mucopolysaccharidosis 1 Hurler (MPSIH), or Wiskott-Aldrich syndrome (WAS).
Results: We included 45 consecutive patients (ADA-SCID = 4, b-thalassemia = 7, MLD = 10, MPSIH = 8, WAS = 16), who underwent mobilization with lenograstim, with (n=41) or without (n = 4) plerixafor, and 1-3 cycles of leukapheresis. Median weight was 15.8 kg (range 7-54.1); median age was 3.7 years (0.4-14.4). Forty patients were enrolled upfront to mobilization and leukapheresis, for collection of both the drug product (DP) starting material and an unmanipulated backup, while five for potential or actual limitations of BM harvest. HSPCs were used as a starting material for the manufacture of the DP (n = 2), cryopreserved for backup (n = 2), or both (n = 41). We recorded 108 adverse events within 14 days following the last apheresis, mostly of grade 1-2 (87%).
Minimum collection targets were usually 7-13 x10^6 CD34$^+$/kg. Overall, patients collected a median of 37.0 x10^6 CD34$^+$ cells/kg (range of 3.3-63.8 x10^6); male gender, underlying disease (b-thalassemia) and lower drug dose were found to be positive predictors of yield. Only three patients among those that underwent mobilization upfront (n = 40) required an additional HSPC collection.
42/43 backups were >2 x 10^6 CD34+ cells/kg; 41/42 patients received a drug product dose in the reference infusion range (from 4 to 30.9 x10^6 CD34+ cells/kg), and all patients that received the drug product engrafted.
As compared to our historical cohort of BM harvests, mobilization and leukapheresis allowed the collection of a higher number of cells in a short period of time. Shorter duration of anesthesia – required to place a central venous catheter – lower fluctuations in intravascular volume and reduced pain are additional advantages of PBSC collection.
Summary/Conclusion: Mobilization and leukapheresis allow the collection of a large number of HSPCs, even in pediatric donors of low weight, with a favorable safety profile, satisfying GT requirements. Beyond GT, the collection of large number of HSPCs by mobilization and leukapheresis may overcome significant weight discrepancies between a pediatric donor and a familial HSCT recipient, and prospectively allow to implement HSPC selection strategies.

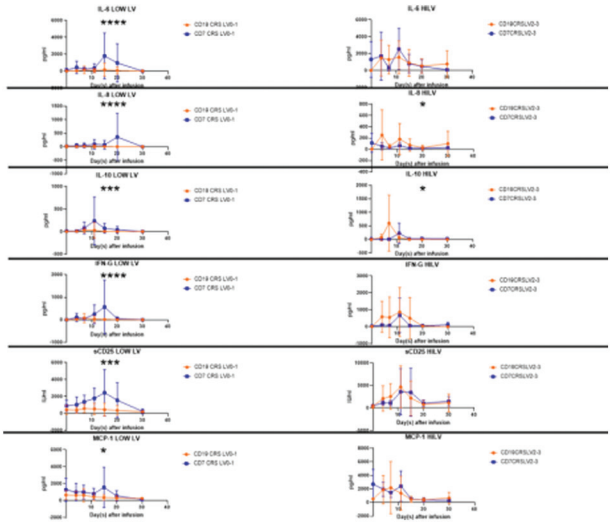
EP742 DIFFERENCES IN SERUM CYTOKINE LEVELS AND PEAK TIMES BETWEEN CD19 AND CD7 CAR-T TREATMENT

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Background: In the past few years, Chimeric Antigen Recepter T-cell(CAR-T) immunotherapy played as a superstar treating acute lymphocytic leukemia(ALL). CD19 CAR-T has been widely used on refractory or relapse B-ALL patients with exciting outcomes. CD7 has been pointed out as a potential target for treating T-ALL. According to our unpublished data, the manifestation of patients treated with CD7 CAR-T is different from the patients treated with CD19 CAR-T. In this experiment, we tried to figure out the difference between CD19 CAR-T and CD7 CAR-T in serum cytokine levels and peak time for guiding clinical practice.
Aims: To figure out the differences in serum cytokine level and peak time between samples of CD19 CAR-T treated and CD7 CAR-T treated.
Methods: peripheral blood sample were collected from 86 patients treated with CD19 CAR-T and 10 patients treated with CD7 CAR-T. According to CRS severity grading, 79/86 were classified as CD19 CRS low grades (0-2 grade), 7/86 as CD19 CRS high grades (higher than 3 grade), and 7/10 as CD7 CRS low grades, 3/10 as CD7 CRS high grades. 24 cytokines QBplex microbeads kits for cytokine monitoring were bought from Beijing Quantobio Company. Cytokine samples were analyzed by flow cytometry on day0, 4, 7, 11, 15, 20, and 30 after CAR-T infusion. ScFV positive CAR-T cells and T cells percentage and counts were detected at the same time by flow cytometry.
Results: Two group had similar ScFV positive CAR-T cells with median peak percentage 53% in CD7 CAR-T and 57% in CD19 CAR-T group, and median counts in peak time were 1.55X10e8/L in CD7 group and 2X10e8/L in CD19 group. Firstly, most cytokines from patients treated

with CD7 CAR-T were obviously higher than those from the patients with CD19 CAR-T treatment in CRS low grades. Secondly, in CRS high grades, most of the cytokines were secreted and reached a peak value in both of CD7 and CD19 CAR-T group. On the other hand, the peak time was earlier in CD19 group than CD7 group. Many main cytokines reached peak value between day7 and day 10 in CD19 group, and in CD7 group were between day 11 and day 15, even on day 20 in some cases. Besides, in CRS low grades, the expression levels were fairly low in CD19 CAR-T group, but those were much higher in CD7 group. In most cases, there were clinical CRS manifestations corresponding to cytokine levels in CD7 group and none or mild symptoms in CD19 group. In other words, most patients treated with CD7 CAR-T had higher cytokine levels and showed more intense symptoms than patients with CD19 CAR-T, even with CRS low grade. Meanwhile, in many cases, side-effects showed up later in CD7 CAR-T group than that in CD19 CAR-T group which corresponding to later peak time in CD7 group.



Summary/Conclusion: Most cytokine levels were higher in CD7 CAR-T group than CD19 CAR-T cases in CRS low grade, and reached peak time later in CD7 group. Clinical symptoms showed corresponding to cytokine levels in most cases. Although different technique and activated cell number might result these, serum cytokines played an important role in CAR-T therapy and study.

EP743 INTENTION TO TREAT VERSUS MODIFIED INTENTION-TO-TREAT ANALYSIS IN BCMA AND CD-19 CHIMERIC ANTIGEN RECEPTOR TRIALS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Chimeric antigen receptor T-cell therapy (CART) has revolutionized the treatment of hematological malignancies but is associated with logistical challenges. Current reporting of trials uses a modified intention-to-treat analysis (mITT) which may over-estimate efficacy and limit external validity.
Aims: We assessed what proportion of CD-19 and BCMA CART trials report the number of patients not receiving CART after being enrolled. We performed a meta-analysis of both the mITT and intention-to-treat (iTT) overall response rate (ORR) for CART.
Methods: Four databases were searched (Web of Science/MEDLINE/PubMed, Embase, and Cochrane Registry of Controlled Trials). All prospective clinical trials of CD-19 and BCMA-targeting CART enrolling two or greater patients from January 1st 2013 to November 1st 2020 were included. PRISMA guidelines were used for abstracting data and assessing the quality and validity of the data. Two independent reviewers verified the data and resolved any conflicts. Data was pooled using random effects model. The primary outcome was the proportion of trials reporting number of patients enrolled and those that actually received CART therapy. Secondary outcomes were calculated for trials that reported on the number of patients that dropped out of the study after enrollment and prior to CART administration. Secondary outcomes included ORR on an intention-to-treat analysis incorporating all enrolled patients.
Results: A total of 28 BCMA CART and 100 CD-19 CART trials were identified. Amongst 28 BCMA CART and 100 CD-19 CART trials, only 10 BCMA and 63 CD-19 trials clearly reported on how many patients were enrolled, and how many actually got CART. For this cohort of trials, the mITT ORR for BCMA CART was 78.0% (95% CI= 67.0-89.0%) and iTT ORR was 70.0% (95% CI=59.0-80.0%). For the CD-19 CART, the mITT and iTT ORR were 80.7% (95% CI= 77.0-84.3%) and 69.6% (95% CI=63.7-75.6%), respectively.
Amongst the 10 BCMA trials reporting on the number of patients enrolled but not receiving CART, a total of 395 patients were enrolled and received CART with results of their efficacy reported. An additional 46 patients did not receive CART after enrolling. For six of these patients, the reason for not receiving CART was rapid disease progression necessitating alternate therapy, however, for the remainder of the 40 patients (86.9%), the reasons were not reported.
Amongst the 63 CD-19 trials that reported on the total number of patients enrolled, 32 trials enrolled patients that did not subsequently receive CART, whereas in the other 31 studies all enrolled patients went on to receive CART. In these 63 studies, a total of 2559 patients were enrolled and received CART with efficacy results reported. An additional 286 patients did not receive CART after enrolling. The most common reasons listed were: not reported or other (80, 28%), death (49, 17%), difficulties with manufacturing CART (46, 16%), adverse events (17, 6%), progression of disease or disease-related complications (17, 6%), and infection (11, 4%).
Summary/Conclusion: Across BCMA and CD-19 CART trials, there is a difference of 8 – 11% in the overall response rate between modified and intention-to-treat analyses and a paucity of information regarding reasons why patients did not receive the intended study treatment.

EP744 LONG TERM CYTOPENIA AND INFECTIONS IN PATIENTS TREATED WITH ANTI-CD19 CAR T-CELLS: AN ANALYSIS OF BONE MARROW AND CLINICAL RISK FACTORS

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Background: Chimeric antigen receptor (CAR) T-cells therapy targeting CD19 is emerging as a promising treatment for patients affected by relapsed/refractory Diffuse Large B Cell Lymphoma (DLBCL) and Primary Mediastinal B Cell Lymphoma (PMBCL). Cytokine Release Syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) have been described as the most common toxicities in the first 14 days after CAR T-cells infusion. During follow-up, patients are often suffering from long-lasting cytopenia and infections, the causes of long-term toxicity have not yet been clearly explained.
Aims: To investigate the frequency of infections and cytopenia after CAR T-cells infusion and whether clinical characteristics, laboratory data and bone marrow (BM) function could be associated to the risk of long term toxicity
Methods: Consecutive patients receiving CAR T-cells at Fondazione IRCCS Istituto Nazionale dei Tumori in Milano between 2019 and 2020 with at least 3 months of follow-up were included in the study. Clinical and laboratory data were collected from electronic medical records; patients with persistent severe cytopenia (i.e. ANC < 1000/µl and/or PLT < 50000/µl) at 3 months of follow-up were investigated with BM biopsy, cytogenetic, FISH analysis and NGS studies.
Results: Forty-six patients receiving anti-CD19 CAR T-cells affected by DLBCL (n=34) and PMBCL (n=12) were included in this analysis. Median age was 49 years (range, 21-72) and median follow-up was 9 months (range, 1-21). Four patients died before 3 months of follow-up. All patients received anti Peumocystis jiroveci, antiviral and antifungal prophylaxis starting at lymphodepletion (LD) and continued until CD4 count > 200/µl. Overall in the first 3 months we observed 21 infectious events in 15/42 patients (33%), including bacterial (n=14), fungal (n=5) and viral (n=2) infections. CRS of any grade after CAR T-cells infusion,

the use of steroids and tocilizumab were significantly associated with an increased risk of infections at 3 months.
Severe cytopenia was observed in 11/42 (26%) of patients at 3 months and in 9/31 (29%) at 6 months. Neutropenia pre CAR T-cells infusion, a peak of ferritin > 5 times upper value (i.e > 1375 ng/ml) and female sex were significantly associated with a higher incidence of cytopenia at 3 months whereas neutropenia before LD was associated with cytopenia at 6 months
Three months after CAR T-cells BM examination was performed in 6/11 of patients with severe cytopenia and in 10 relapsed/refractory patients without cytopenia during work-up for a new treatment. In cytopenic patients, BM histologic examination showed dysmyelopoiesis (n=1), hypocellular marrow (n=3) and normal morphology (n=2), cytogenetic analysis was normal and FISH analysis for del5q and -7 were negative. NGS study was performed in 4 patients showing a clonal hematopoiesis of indeterminate potential (CHIP) due to DNMT3A mutations with a VAF of 2% and 9% in two of them. BM of 10 relapsed patients without cytopenia were histologically normal.
Summary/Conclusion: Three months after CAR T-cells infusion almost a third of patients experienced one or more infectious events and cytopenia was present in a quarter of patients. CRS and consequent treatment seemed to be factors predisposing to infections whereas cytopenia seemed to be associated to neutropenia pre CAR T-cells or high ferritin peak. At 3 months a limited occurrence of myelodysplastic features were observed in BM analyzed. A larger cohort of patients and a longer follow-up is required to confirm these data.

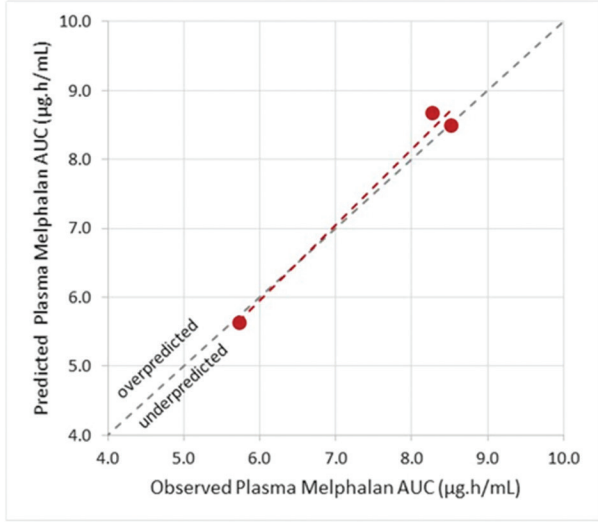
EP745 TOWARDS PATIENT-SPECIFIC DOSING OF MELPHALAN CONDITIONING FOR ARU-1801, A NOVEL GENE THERAPY FOR TREATMENT OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a severe genetic disease for which the only cure is allogeneic hematopoietic stem cell transplant (HSCT), but this procedure requires myeloablative conditioning (usually with busulfan) to allow donor cell engraftment at the risk of chemotherapy-related toxicities, including short-term (e.g. neutropenia, veno-occlusive disease) and long-term (e.g. ovarian failure, secondary leukemia) effects. Reduced-intensity conditioning (RIC) regimens may reduce toxicities, thus expanding access to gene therapy for SCD. ARU-1801 gene therapy (autologous CD34+ hematopoietic stem cells and progenitors [HSPCs] transduced with a lentiviral vector [LV] encoding a modified γ-globin^{G16D} gene) is being investigated with a melphalan RIC regimen (140 mg/m^2). We previously reported data on 3 patients; while two had stable engraftment, one patient had a gradual decline in VCN over time, potentially linked to sub-target melphalan exposure due to rapid clearance from renal hyperfiltration (GFR = 200 mL/min/1.73m2). Melphalan plasma exposure may be a key variable to efficacy of ARU-1801 gene therapy. Melphalan clearance is dependent on renal function and SCD is often associated with renal injury. Pharmacokinetic (PK) model-based dose adjustment may lead to reduced variability and optimized melphalan exposure.
Aims: To evaluate the potential of a model-based, individualized melphalan dosing strategy for ARU-1801 in SCD.
Methods: Three patients with SCD in the ongoing Phase 1/2 MOMENTUM study received a single IV dose of melphalan 140 mg/m^2 conditioning off-label prior to infusion of ARU-1801 gene therapy. PK samples were collected for 6 hours post-end of infusion (dried blood spots for first 2 subjects, plasma for third subject, assayed by direct ionization or liquid chromatography/mass spectroscopy, respectively). Blood-to-plasma ratio and hematocrit were used to convert data from blood PK samples to plasma concentration. Plasma PK parameters were determined using non-compartmental methods and the observed area under the plasma concentration-time curve (AUC) was compared to predicted values based on a population PK model of melphalan from 100 patients with multiple myeloma undergoing HSCT (Nath et al, BJCP 2010). Predicted AUCs were calculated based on melphalan dose and model-predicted plasma melphalan clearance, based on patient covariate values collected prior to melphalan infusion: fat-free-mass (FFM), hematocrit, and eGFR (based on Cystatin-C).
Results: Covariate values showed large variability across the 3 patients (2 female, FFM: 38.8 to 53.0 kg, BMI: 18.7 to 28.9 kg/m^2, hematocrit: 31.0 to 38.3, Cystatin-C eGFR 78 to 200 mL/min/1.73m^2). Preliminary geometric mean (and coefficient of variation) plasma melphalan AUC from 3 patients with SCD was 7.39 µg.h/mL (22.4%). The observed AUC agreed well with predicted values from the PK model, with r^2 = 0.98 (Figure 1). Notably, the model accurately predicted a low melphalan AUC in the patient with eGFR of 200 mL/min/1.73m^2 (predicted: 5.62, observed: 5.73 µg.h/mL).

Figure 1. Individual predicted vs observed melphalan AUC



Summary/Conclusion: Model-based predictions of melphalan AUC in patients with SCD appear to be accurate across a wide range of covariate values. These data suggest individualized melphalan dosing prior to ARU-1801 infusion may be feasible; additional data will be used to refine the PK model for patients with SCD. A simple melphalan dose adjustment algorithm based on few covariate values has the potential to reduce variability and optimize melphalan exposure, which may result in improved patient outcomes after treatment with ARU-1801.

EP746 FACILITY READINESS ASSESSMENT FOR CAR-T TREATMENT IN AUSTRALIA: NHL PERSPECTIVE

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Background: Chimeric antigen receptor T-cell (CAR-T) therapies have demonstrated the potential to treat relapsed/refractory hematological malignancies[1]. First CAR-T therapy (Kymriah) was launched in 2017 and up to this day there are 3 approved therapies in the US for DLBCL, MCL and ALL.[2] Kymriah and Yescarta, both are approved in the US, EU, Japan, and Australia.[3-8] Despite having demonstrated strong efficacy data in clinical trials in multiple indications[3-8], the commercial pick-up of these drugs hasn't been great. As per some studies, there are two key challenges affecting the commercialization of CAR-Ts:[9]
- **complex manufacturing and supply chain** Reprogramming/CAR-T creation and expansion and Infusion
- **high-touch commercial model:** High cost to set up, certify, and scale sites
These challenges make it difficult for healthcare facilities to utilize CAR-T treatment for eligible patients. It is crucial to find out the facilities which has the potential infrastructure to make the treatment available. In this study, we have come up with solutions to address those challenges by identifying the eligible facilities and their referrals. The target of our study is Australia, as it has an untapped capacity to make the CAR-T treatment available for patients due to its improved healthcare system and high healthcare spending.
Aims: - Identify potential healthcare facilities which are eligible for CAR-T treatments and clinical research, using:
- Site/ Facility Identification;
- Accreditations for different CAR-T processes (leukapheresis, manufacturing, infusion)
Methods: Due to complexities involved in manufacturing and supply chain, having a centralized manufacturing facility becomes critical for CAR-T therapies. Many strategic decisions around marketing and clinical trials can be taken by identifying eligible healthcare facilities considering factors like capability to perform complex processes, patient potential,

and clinical trial experience. To achieve this objective of identifying key facilities, we have used a proprietary approach as explained below:
- Site Identification was performed using top down drug consumption approach to obtain Relapsed/refractory Non-Hodgkin's lymphoma (NHL) treating hospitals and their estimated patient potential
- A Referral network was established for the hospitals which have accreditations for all 3 processes, considering them the most eligible sites for treatment or clinical research

Results: There are a total of 82 hospitals in Australia, from which:
- Eight Hospitals are fully accredited for CAR-T and could potentially treat 17% of eligible R/R NHL patients;
- · 62% of hospitals are without any accreditation for CAR-T processes;
- · 28% of partially accredited (1 or 2 processes) hospitals could benefit from additional certification to grant them autonomy to perform CAR-T;
- · Around 18% of hospitals have experience in conducting CAR-T clinical trials

Summary/Conclusion: A limited number of hospitals in Australia are equipped with adequate facilities to process and provide the CAR-T treatment. Hospitals with 1 or 2 processes accreditation could benefit to further 50% of patients from additional certification to grant them autonomy to perform the treatment. Utilizing the referral network data, patients can be referred to fully accredited facilities expanding treatment access.

EP747 ANAKINRA PROPHYLAXIS IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA RECEIVING ORVACABTAGENE AUTOLEUCEL (ORVA-CEL)

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Background: Orva-cel is a B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T cell therapy being evaluated in the phase 1/2 EVOLVE study (NCT03430011) in patients with relapsed/refractory multiple myeloma (RRMM) who had at least 3 prior lines of therapy. We previously reported safety and efficacy in the EVOLVE phase 1 study and established the recommended dose (RD) of orva-cel as 600×10^6 CAR$^+$ T cells (Mailankody S, et al. *J Clin Oncol*. 2020;38(suppl):abstr 8504).
Aims: Cytokine release syndrome (CRS), a dominant toxicity of CAR T cell therapy, is mediated in part by interleukin-1 (IL-1). Here, we report clinical outcomes of a cohort of phase 1 patients treated prophylactically with anakinra, an IL-1 signaling inhibitor, with the objective of assessing any reduction in the incidence of grade ≥2 CRS after orva-cel treatment at the RD.
Methods: Fourteen patients were enrolled sequentially for anakinra prophylaxis and treated with orva-cel at the RD. The non–anakinra prophylaxis control group comprised the remainder of the phase 1 patients receiving orva-cel at the RD (n = 19). The median follow-up (range) was 3.0 months (1.8–6.2) for the anakinra prophylaxis group and 8.8 months (5.3–12.2) for the non–anakinra prophylaxis group. Anakinra 100 mg was administered subcutaneously the night before orva-cel infusion, 3 hours before the infusion (Day 1), and every 24 hours on Days 2–5. Dosing was increased to every 12 hours if CRS developed. CRS was graded by Lee (2014) criteria. Tocilizumab and corticosteroids were used per protocol-specified treatment management guidelines.
Results: Disease characteristics and outcomes are shown in the **Table**. In the anakinra prophylaxis and non–anakinra prophylaxis groups, the median number of prior regimens was 6 and 5, and bridging therapy was used in 57% and 68% of patients, respectively. The total frequency of CRS was similar in the 2 groups, but with less grade 2 events in the anakinra prophylaxis patients (relative risk, 0.54 [95% CI, 0.21–1.38]). No grade ≥3 CRS was observed in either group. The incidence of neurological events (NEs), grade ≥3 infection, and macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) was similar. Tocilizumab and corticosteroid use was numerically lower with anakinra prophylaxis. Orva-cel expansion kinetics were similar in the 2 groups. All patients had a 2-month efficacy assessment, with an ORR of 100% in anakinra prophylaxis and 95% in non–anakinra prophylaxis patients.

Table. Disease characteristics and safety outcomes in the phase 1 EVOLVE study

	Anakinra prophylaxis, n = 14	Non–anakinra prophylaxis, n = 19
International staging system, %		
Stage I	43	47
Stage II	36	37
Stage III	21	16
Measurable serum and/or urine M-protein, %	93	74
LDH >ULN, %	21	0
CRS, %		
Grade 1	64	37
Grade 2	29	53
Grade ≥3	0	0
CRS time to onset, median (range), days	2 (1–11)	2 (1–2)
CRS duration, median (range), days	3 (2–8)	3 (1–7)
NEs, %		
Grade 1	7	5
Grade 2	7	5
Grade ≥3	7	0
Infection, %		
Grade 1	0	16
Grade 2	0	11
Grade ≥3	14	11
MAS/HLH, %		
Grade 1	0	5
Grade 2	7	0
Grade ≥3	0	5
Tocilizumab and/or corticosteroid use, %		
Any tocilizumab use	79	90
Multiple instances of tocilizumab use	29	37
Any corticosteroid use	43	63
Tocilizumab + corticosteroid use	43	63

LDH, lactate dehydrogenase; ULN, upper limit of normal.

Summary/Conclusion: In this nonrandomized evaluation of anakinra prophylaxis with orva-cel treatment, the incidence of grade ≥2 CRS was lower in patients receiving anakinra prophylaxis. The use of anakinra prophylaxis had no adverse effect on the incidence of NEs, infection, or MAS/HLH, nor on orva-cel expansion or disease response. These results warrant further study of anakinra prophylaxis in CAR T cell therapy.

EP748 A PROSPECTIVE PHASE I/IIA TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF GTA002, AN OFF-THE-SHELF, EX VIVO-CULTURED ALLOGENEIC NK CELL PREPARATION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (WINK TRIAL)

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Background: Although many patients with acute myeloid leukemia (AML) achieve morphological complete remission (CR) due to improved treatment modalities, the majority of them still relapse leading to poor long-term prognosis. These relapses are due to residual leukemic stem cells that can be identified as minimal/measurable residual disease (MRD), with MRD serving as a predictive factor for relapse and mortality. Elimination of MRD in patients having reached CR is seen as essential for optimal and persistent clinical responses.
Aims: A promising approach is the development of adoptive immunotherapies aimed at directly eradicating residual tumor cells using natural killer (NK) cells. NK cells can be applied clinically in an allogeneic setting, enabling the supply of high numbers of immune effector cells, which were not exposed to cytotoxic chemotherapeutics. A proprietary *ex vivo* expansion and differentiation method in a fully closed, automated manufacturing platform was developed to generate GTA002, an "off-the-shelf" (allogeneic), cryopreserved NK cell preparation, generated from CD34+ hematopoietic stem and progenitor cells derived from umbilical cord blood. The safety and tolerability of the product was demonstrated in a Phase I trial in elderly patients with AML (Dolstra et al. 2017).
Methods: We are currently conducting a prospective 2-stage, open-label, single arm, multicenter Phase I/IIa trial to evaluate the safety and efficacy of GTA002 in 33 adults with AML who are in CR with MRD and who are

not proceeding to allogeneic HSCT (ClinicalTrials.gov NCT04632316). After providing informed consent, patients enrolled in the clinical trial receive a lymphodepleting conditioning regimen consisting of cyclophosphamide and fludarabine followed by up to 3 NK cell infusions 4 days apart and will be followed up for 12 months. The dose escalation stage will assess the safety and tolerability of repeat NK cell infusions in a 3+3 design with 3 cohorts and a cumulative dose range of 325 to 3,000 x10^6 viable NK cells. The expansion stage will evaluate the safety, tolerability and efficacy of NK cell infusions in 24 additional subjects.
Results: Enrollment in the first cohort (one single NK cell infusion) started in December 2020. Preliminary safety data from the first cohort will be discussed at the meeting.
Summary/Conclusion: The overall objective of the trial is to evaluate whether GTA002 is safe and if it can eradicate MRD, thereby reducing the relapse risk and mortality in subjects with AML who are in CR with MRD and who do not proceed to allogeneic HSCT.

EP749 "MYTCELL": A SMARTPHONE APPLICATION GUIDES MANAGEMENT OF CAR T-CELL & BITE RELATED TOXICITIES

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Background: The Bispecific T-cell engager (BiTE) Blinatumomab and the CD19-specific Chimeric Antigen Receptor (CAR) T-cell products Axicabtagene-Ciloleucel and Tisagenlecleucel are approved Immunotherapies for relapsed and refractory B-cell neoplasms. However, they are accompanied by potentially lethal T-cell associated immune related adverse events that significantly differ from toxicities known from chemotherapy or even checkpoint blockade. Patients require comprehensive monitoring and a well educated interdisciplinary team of health care professionals.
Aims: To support the optimal management of these patients, we developed the interactive smartphone application "myTcell", which guides and educates physicians in the assessment and treatment of CAR & BiTE related toxicities.
Methods: We initiated a multi step content development process with an extensive literature research of toxicity guidelines consented by the ASTCT, EBMT and NCCN as well as of officially released drug information. Findings were translated into an information platform with diagnostic and therapeutic recommendations as well as algorithms for interactive toxicity grading tools. A prototype is currently being validated at three Geman treatment centers before becoming available in Europe. App development has been funded through educational grants by Celgene, Gilead Sciences and Novartis.
Results: "myTcell" guides disease and product specific in a step by step process through the clinical workflow of cell therapy including indication, leukapheresis, bridging therapy and application of CAR T cells and BiTEs. Upon entering relevant clinical data for grading of CRS, ICANS and HLH interactive tools display toxicity grade or likelihood of toxicity as well as grade-specific management recommendations. Further, "myTcell" assists with the diagnosis and treatment of so far underreported adverse events such as pancytopenia. Besides, "myTcell" includes an overview of the key literature and most recent publications in the field of CAR T-cells and BiTEs.
Summary/Conclusion: "myTcell" has the potential to become a highly usable smartphone app supporting the application of T-cell recruiting immunotherapies and the education of health care professionals. Thus, "myTcell" can increase guideline adherence, accelerate the broader and safer application of CARs and BiTEs and ultimately improve patient outcomes.

Hematopoiesis, stem cells and microenvironment

EP750 DIFFERENTIAL HEMATOPOIETIC SUPPORT ACROSS THE ADIPOCYTIC DIFFERENTIATION AXIS: PHARMACOLOGICAL MODULATION TO ACCELERATE HEMATOPOIETIC RECOVERY

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Background: The hematopoietic stem cell (HSC) niche constitutes a complex bone marrow (BM) microenvironment that tightly controls HSC proliferation. Adipocytes have been shown to inhibit hematopoietic progenitor proliferation, but adiponectin-expressing cells are required for full HSC support and pre-adipocytes can efficiently support the growth of hematopoietic cells in culture. Given that specific bone marrow stromal cell (BMSC) subpopulations, preadipocytes, and adipocytes are part of the same differentiation axis, this apparently contradictory data suggests that the same precursor can generate cells with divergent hematopoietic-supportive capacity.
Aims: We thus hypothesized that pharmacological modulation of the adipocytic differentiation axis could inhibit bone marrow-derived adipocyte maturation and predict hematopoietic progenitor support.
Methods: To test this hypothesis, we performed devised high content phenotypic screening pipeline to identify modulators of adipocytic differentiation with increased hematopoietic support in the absence of exogenous cytokines. For *in vivo* validation of the screen, compounds were tested for their capacity to shorten aplasia post lethal irradiation and bone marrow transplantation. Specifically, the Prestwick Chemical Library of FDA-approved drugs, a library containing natural products and the library of chemicals generated from swiss academic laboratories were screened for their potential to prevent lipidation.
Results: After confirmation screen and dose-response determination, 49 inhibitors were selected. RNA-seq further classified compounds inhibiting adipocyte-specific gene expression as well as maintaining expression of hematopoiesis-supportive cytokines. Functional *in vitro* assays further identified a specific vitamin D analog as the strongest niche modulator, and transcriptome analysis revealed a CAR-like phenotype. *In vivo* administration significantly decreased both the adipocyte size and content of bones at day 18 post BM transplantation, increased platelet recovery and increased total number of CFU per leg.
Summary/Conclusion: Our pipeline allowed for the screening of more than 4000 compounds and identified a vitamin D derivative as a first candidate to induce a CAR-like phenotype and accelerate hematopoietic recovery in radio/chemotherapy-induced aplasia.

EP751 INTEGRATED SINGLE CELL ANALYSIS IDENTIFIES UNIQUE MOLECULAR AND FUNCTIONAL FEATURES OF EXTRAMEDULLARY HAEMATOPOIESIS IN HUMANS

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Background: In adults, most hematopoietic stem and progenitor cells (HSPCs) reside within the bone marrow (BM), giving rise to all mature blood cells. Yet at any given time, a small proportion of HSPCs circulates in peripheral blood (PB), and under severe stress and disease, also the spleen can significantly contribute to blood production. However, the cellular, molecular and functional composition of circulating and extramedullary HSPC pools remains unexplored.
Aims: Here I will discuss the single cell characterisation of the adult human HSPC pool found in the two main extramedullary haematopoietic tissues, spleen and PB, comparing and contrasting it to BM.
Methods: Using matched and unmatched samples from deceased and living donors, we profiled more than 115,000 single CD34+ HSPCs by scRNA-seq and/or CITE-Seq and 3,900 single phenotypic haematopoietic stem cells / multipotent progenitors (HSC/MPPs) in functional assays.
Results: We find largely distinct HSPC compositions in extramedullary tissues and BM. The topography of the hematopoietic hierarchy in BM supports continuous HSPC proliferation and blood production. In contrast, modelling active differentiation using scRNA-seq data and flow cytometry analysis detect few to no proliferating progenitor cells in extramedullary tissues. Together with a balance of early to late progenitors heavily shifted to early progenitors in spleen and PB, this indicates a cellular configuration in extramedullary tissues positioned for lineage-primed demand-adapted haematopoiesis. Importantly, the vast majority of HSC/MPPs in spleen and non-mobilised PB are molecularly distinct from those found in BM, differing in adhesion molecules and lineage priming properties. Finally, single cell functional assays demonstrate that steady-state non-mobilised PB is dominated by quiescent HSC-like cells functionally restricted to erythrocyte and megakaryocyte production. The functional bias of PB HSC/MPPs towards a largely erythro-megakaryocyte skewed lineage output becomes imbalanced with age and in haematological conditions.

Summary/Conclusion: In summary, the cellular and functional composition of HSPC circulating in PB is uniquely different from that of BM. We show that alterations in this composition faithfully report impairments of haematopoiesis. Our study thus identifies extramedullary cellular reservoirs for demand-adapted haematopoiesis and provides a framework of clinical relevance.

EP752 A STAT5B-CD9 AXIS DETERMINES SELF-RENEWAL IN HEMATOPOIETIC AND LEUKEMIC STEM CELLS

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Background: Leukemic stem cells (LSCs) share characteristics of hematopoietic stem cells (HSCs) and represent the major therapeutic hurdle in leukemia patients. Many leukemic entities depend on an activated JAK/STAT signaling pathway, with STAT5 being critical in hematopoiesis and leukemia. As specific STAT5 inhibitors have not entered the clinics yet, alternative drug targets are needed. STAT5 is actually two distinct transcription factors, STAT5A and STAT5B which share more than 96% protein identity. It is widely believed that STAT5A and STAT5B are functionally redundant in the hematopoietic system. This dogma is challenged by the recent finding that activating STAT5 mutations in leukemia are restricted to *STAT5B*.
Aims: We aimed at understanding the distinct and individual roles of STAT5A and STAT5B in HSC and LSC self-renewal to identify downstream druggable targets.
Methods: We characterized the HSC compartment of mice lacking STAT5A or STAT5B via flow cytometry, single cell RNA-Seq and *in vitro* assays. We analysed *Stat5a*$^{-/-}$ or *Stat5b*$^{-/-}$ HSC and LSC potency in *in vivo* settings including serial transplantation and 5-FU treatment. We validated the potential downstream target CD9 in primary STAT5-dependent leukemia patient samples.
Results: We identified distinct functions for STAT5A and STAT5B in HSCs and in LSCs and define STAT5B as the driving force behind the maintenance and self-renewal of these cell types. We identify CD9 as a novel STAT5B target gene and show that the levels of CD9 correlate positively with STAT5 phosphorylation and negatively with the survival of STAT5-dependent leukemia patients. The elevated CD9 surface levels on LSCs render the cells particularly sensitive towards CD9-blocking, which we show to induce differentiation and apoptosis.
Summary/Conclusion: We suggest that CD9 may serve in prognosis and therapy of STAT5-dependent leukemia. We show that it is vital to consider STAT5A and STAT5B as distinct entities in normal and malignant hematopoiesis.

EP753 DENATONIUM AS BITTER TASTE RECEPTOR AGONIST AFFECTS THE CLONOGENIC CAPACITY AND DIFFERENTIATION OF HEMATOPOIETIC STEM CELLS

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Background: The ability of cells to detect changes in the microenvironment is important in cell signaling and responsiveness to environmental fluctuations. There are a variety of receptor types through which cells respond to changes in their microenvironment including those for cytokines, hormones, mechanical tension, and there are thousands of different receptors expressed on any given cell type. Among these, the largest group belongs to the family of G protein-couple receptors (GPCRs). Bitter taste receptors (T2Rs) comprise 25 distinct members of the GPCR family. Initially described in the oral cavity, T2Rs are actually widely expressed in different tissues and the increasing amount of evidence about their extra-oral localization has suggested a wider function in sensing microenvironment, also in cancer settings. We recently reported that Acute Myeloid Leukemia cells express fully functional T2R subtypes which are involved in the regulation of leukemia cell functions.
Aims: In this study, for the first time, we investigate the activity of bitter taste agonist Denatonium on HSCs biology.
Methods: Highly purified cord blood-derived CD34^{+} cells were used for this study. T2R expression was analyzed by RealTimePCR and IF. We investigated molecular profiling by GEP assay, viability by colorimetric assay, apoptosis and HSC subset frequency by FACS analysis. In vitro assays for primitive hematopoietic cells (CFU-C, LTC-IC) were performed. For *in vivo* engraftment studies, NSG mice were used.
Results: In the present work, we show that HSCs expressed several T2R subtypes at molecular and protein levels. Stimulation of HSCs with a T2R agonist, Denatonium (DEN), induced intracellular Ca^{2+} concentration increase, thus demonstrating T2Rs functionality. GEP analysis identified a number of genes significantly modulated by DEN treatment. Specifically, genes involved in the stem cell population maintenance and regulation of cell-matrix adhesion are deregulated. Functional assays demonstrated that DEN exposure does not affect HSC viability and not induce apoptosis. Nevertheless, depending on the extent of stimulation, DEN modulates the frequency of stem cell progenitors in the culture. In particular, acute stimulation increases the frequency of lineage restricted progenitors (CLP, CMP, GMP) and their clonogenic capacity. On the other hand, chronic exposure to DEN supported the depletion of the more primitive stem cell compartment, reducing the frequency of the LTC-IC. These results are supported by *in vivo* experiments. NSG mice transplanted with DEN-treated HSC showed an increased engraftment in BM and spleen matched by an increased frequency of more differentiated progenitors.
Summary/Conclusion: Our results expand the observation of T2R expression to the hematological setting and shed light on a role of T2Rs in the extrinsic regulation of HSC functions. Moreover, our data may suggest a role for microenvironment "bitter" molecules in regulating normal hematopoiesis. Notably, many common drugs, such as antibiotics, chloroquine, haloperidol, procainamide, are bitter tasting and are thus effective ligands for T2Rs. For this reason, they could exhibit off-target effect in T2R expressing cells, including normal hematopoietic cells. Our results may have implications in understanding the off-target actions of diverse drugs.

EP754 CLONAL HAEMATOPOIESIS: USING LONGITUDINAL COHORT DATA TO STUDY THE AGEING HUMAN HAEMATOPOIETIC SYSTEM

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Background: Clonal haematopoiesis (CH) is apparent in the general population from age 60 with a steady increase to 18-20% over age 90 driven by somatic mutations in leukaemic driver genes, leading to reduced diversity of the blood pool. CH carries an increased risk for leukaemia.
Aims: We investigated CH in the Lothian Birth Cohort through targeted error-corrected sequencing of blood samples taken from aged participants every 3 years for 15 years.
Methods: *Study Cohorts*
The Lothian Birth Cohorts (LBCs) of 1921 and 1936 are two longitudinal studies of ageing. Participants have been followed up every ~3 years, each for five waves, from the age of 70 (LBC1936) and 79 (LBC1921). MPN patient material was derived from the Cambridge Stem Cell Bank.
Error corrected sequencing
Genomic variants were determined in 1,148 LBC participants with error corrected sequencing. CH variants were classified as per Jaiswal et al.
Results: We identified 73 participants with CH (6.2%). The gene-specific prevalence ranged between 1-37 cases with CH-variant allele frequencies ranging from 0.034-0.677. Mathematical modelling of the population dynamics of clones shows that, at old age, the commonly used threshold to diagnose CH can be reached as the result of neutral drift in synonymous mutations. This clinically implemented detection method therefore leads to a ~50% false discovery rate of fit mutations. Using our longitudinal data, we can better detect clones whose growth cannot be explained by neutral drift by considering the measured distribution of fluctuations of neutral mutations. This method allows us to uncover fitness-inducing mutations with high sensitivity as well as uncover highly fit variants before they achieve the threshold-based definition of CH.
Summary/Conclusion: Longitudinal data allow for more accurate modelling and detection of fitness effects of CH in an aged population.

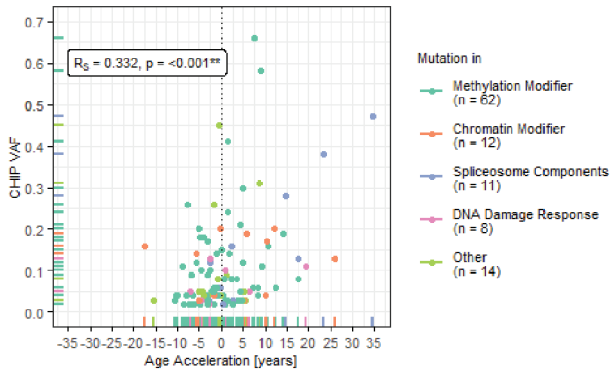
EP755 CHIP CLONE SIZE CORRELATES WITH EPIGENETIC AGE ACCELERATION

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) occurs in the peripheral blood of approximately 20% of people > 60 years of age without history of hematologic disorders. CHIP is associated with age related conditions such as cardiovascular diseases and increased all-cause mortality. DNA-methylation at various CpG loci is known to reliably correlate with chronological age and mortality. Different epigenetic clocks have been developed based on these methylation sites and their potential to reflect biological age is a research topic of great interest.
Aims: Aim of the current study was to investigate the relationship between CHIP status, epigenetic age, and epigenetic age acceleration in 382 elderly individuals.
Methods: Epigenetic age was determined using DNA extracted from peripheral blood of elderly individuals (median 74.8; range 55-98 years) without hematologic malignancy and with previously determined CHIP status (Arends et al., Leukemia, 2018). Methylation fractions were determined using methylation-sensitive single nucleotide primer extension. DNA methylation age (DNAm age) was calculated using an adapted version of an 8-CpG clock (Vidal Bralo et al., Front Genet, 2016), implementing a previously established regression model from the Berlin Aging Study II cohort. Age acceleration (AA) was determined as the residual that results from DNAm age regression on chronological age. Intrinsic epigenetic age acceleration (IEAA) was determined likewise with regression on chronological age and blood cell counts.
Results: Median DNAm age was 76.15 (SD ± 9.67) years. As determined previously, 107 (28%) of the 382 individuals had evidence of CHIP with a median VAF of 6%. In line with previous publications, sex was significantly associated with AA (female -1.18 years; male 0.96 years; p = .007). When looking at all cases, CHIP was not significantly associated with epigenetic age acceleration (CHIP pos. 1.07 years; CHIP neg. -0.41 years; p = .201). On the contrary, presence of CHIP clones with large VAF (≥ 20%, n = 15) significantly correlated with increased AA when compared to CHIP negative individuals (contrast analysis following ANOVA, p = .022). Mean difference in AA between these groups was 6.04 years. To further analyze the impact of clone size and to account for the continuous character of VAF, a Spearman correlation was performed for AA and VAF of individuals with CHIP (n = 107). Here, we observed a significant, positive correlation between age acceleration and clone size (R_s = .332; p = <.001; Figure 1), which remained significant after adjustment for sex and chronological age (R_s = .326; p = <.001). Comparable results were obtained when correlating IEAA and CHIP clone size (n = 84; R_s = .411; p = <.001 after adjustment for sex and chronological age). When looking at individual functional groups of CHIP genes [methylation modifiers (*DNMT3A*, *TET2*), chromatin modifiers (*ASXL1*, *EZH2*), spliceosome components (*SF3B1, SRSF2, U2AF1, ZRSR2*), DNA damage response (*TP53, PPM1D*), other], no significant correlations could be observed with respect to age acceleration. However, small group sizes preclude final conclusions and warrant further investigation.

Figure 1: Spearman Correlation for VAF and Epigenetic Age Acceleration



Summary/Conclusion: In our study investigating the correlation of epigenetic age and CHIP, clone size was significantly associated with epigenetic age acceleration, indicating premature aging in this population. Though cause and consequence relations require further study, these results provide a new perspective on the critical role of CHIP clone size.

EP756 CHANGES IN BONE MARROW STROMAL MICROENVIRONMENT PROGENITOR CELLS IN PATIENTS WITH HEMOBLASTOSIS

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Background: In patients with hemoblastosis, the stromal microenvironment of the bone marrow (BM) is changed, and there is convincing evidence supporting the role of multipotent mesenchymal stromal cells (MSCs) in the transformation of the bone marrow niche, which, as a result, promotes the survival of leukemic cells. MSCs regulate both normal and malignant hematopoiesis. The preservation of leukemia stem cells (LSC) in the body even after high-dose chemotherapy is the main difficulty in the treatment of hemoblastosis, which determines the development of relapses. Since LSCs are located in their niche and are regulated by various non-hematopoietic cells, including MSCs, studying the mechanisms of interaction between LSCs and MSCs can increase the effectiveness of treatment.
Aims: The aim of this work was to study general changes and differences in the characteristics of MSCs in patients with myeloid leukemia and patients with lymphoproliferative diseases.
Methods: The study included MSCs and colony-forming units fibroblast (CFU-F) obtained from the BM of 114 patients in the onset of the disease: 32 with AML (13 male and 20 female, age 39.2±2.3) 20-ALL (7 male and 13 female, age 26.4±1.9), 20-CML (11 male and 9 female, age 44.6±3.8) and 41-DLBCL (15 male and 26 female, age 54.9±2,0). MSCs and CFU-F from the BM of donors of appropriate age were used as control. All donors and patients signed informed consent. MSCs and CFU-F were cultured by standard methods. Relative expression level (REL) of several genes were investigated by real time PCR.
Results: The concentration of CFU-F in the BM of patients of all studied hemoblastosis at the onset of the disease is reduced in comparison with the values in donors of the corresponding age (Table). At the same time, concentration of CFU-F in the BM of ALL patients was most pronounced and reliably reduced by almost 4 times. A decrease in the concentration of these stromal progenitor cells may reflect systemic damage to the BM stroma. The revealed changes in DLBCL patients without bone marrow involvement indicate that there is not only a direct effect of leukemic cells on the stroma due to intercellular contacts, but also an indirect one, through factors secreted by the tumor. In patients with DLBCL total MSCs production is significantly higher than in donors. In other patients cumulative MSCs production does not differ from donors. In stromal cells of patients with hemoblastosis, there are both general changes associated with proliferation, differentiation and maintenance of hematopoiesis, as well as fundamental differences presented in Table. In all patients MSCs REL of *SPP1, ICAM1, TGFb1*, and *TGFb2* genes did not differ from donors' ones. In the MSCs of patients with leukemia, the REL of *IL6, JAG1, LIF* genes were increased, and REL of *IL8, SDF1* were not changed compared to the MSCs of the donors. MSCs from patients with acute leukemia were characterized by a decrease in *SOX9* and an increase in *CSF1, IL1b*, and *IL1bR1* expression. In MSCs of patients with myeloid leukemia, the *PPARG* and *PDGFRA* were increased. Gene expression in MSCs from DLBCL patients was significantly different from that in patients with leukemia.

Table. Concentration of CFU-F in bone marrow, total cellular production of MSCs, time to P0 and gene expression differences in patients with hemoblastosis and donors of the corresponding age.

REL of genes presented by the ratio to in MSCs of healthy donors. ↑-Higher than in donor MSCs, ↓ - lower than donor MSC

		AML	ALL	CML	DLBCL
CFU-F concentration per 106 BM cells	Patients	11,5±4,7	8,7±3,8*	15,8±4,2	11,5±2,1
	Healthy donors	22,3±2,7	30,6±3,4	21,7±2,4	18,3±4,9
Cumulative MSCs production for 4 passages, x106 cells	Patients	4,8±0,8	5,5±1,5	7,5±1,6	9,6±1,1*
	Healthy donors	5,2±0,4	8,8±1,2	5,2±0,5	7,2±1,1
Time to P0, days	Patients	17,6±0,6*	19,8±1,4*	17,7±0,8*	13,1±0,4
	Healthy donors	14,0±0,3	13,5±0,3	13,7±0,3	13,7±0,7
Inflammation	IL6	↑	↑	↑	Normal
	IL 8	Normal	Normal	Normal	↑
	CSF1	↑	↑	Normal	ND
	IL1B	↑	↑	Normal	ND
	IL1BR1	↑	↑	Normal	ND
HSC regulation	JAG1	↑	↑	↑	ND
	SDF1	↑	Normal	Normal	↑
	LIF	↑	↑	↑	ND
Differentiation	SOX9	↓	↓	Normal	Normal
	PPARG	↑	Normal	↑	Normal
Proliferation	FGF2	Normal	Normal	Normal	↑
	FGFR1	↑	Normal	Normal	↓
	FGFR2	Normal	Normal	↑	↑
	PDGFRA	↑	Normal	↑	ND
	PDGFRB	↑	Normal	Normal	Normal

*Significant differences between MSCs from the BM of healthy donors and patients at the onset of the disease, p<0.05

Summary/Conclusion: Altered functions of the stromal microenvironment in patients indicate its role in the maintenance and proliferation of tumor cells. The findings could pave the way for new therapies that target the altered stromal niche for hematopoietic cells.
The materials supported by grants from the Russian Foundation for Basic Research project 17-00-00170 and 19-29-04023 were used.

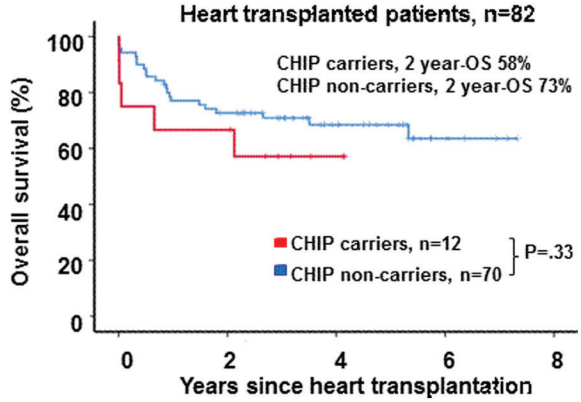
EP757 PREVALENCE AND CLINICAL IMPACT OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP) IN PATIENTS UNDERGOING HEART TRANSPLANTATION.

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is driven by leukemia-associated somatic variants, primarily affecting the genes *DNMT3A, TET2, ASXL1 and JAK2* and rises steadily with age. While CHIP occurs among the healthy elderly population, CHIP is associated with several pathogenic states, including an elevated risk for hematologic neoplasms, ischemic stroke and overall mortality. Experimental evidence suggests that CHIP is a novel emerging causal cardiovascular risk factor that contributes to the development of atherosclerosis and cardiac dysfunction and exacerbates cardiovascular diseases. Recent studies report an association of CHIP with ischemic heart failure as well as degenerative aortic valve stenosis resulting in increased mortality.
Aims: The goal of our study is to characterize the prevalence and clinical impact of CHIP in patients undergoing heart transplantation.
Methods: We investigated 82 patients who underwent heart transplantation between 2013 and 2018 in the Department of Cardiac, Thoracic, Transplant and Vascular Surgery of Hannover Medical School, and for whom DNA from peripheral blood before heart transplantation and follow up information was available. The study was approved by the institutional review board of Hannover Medical School and written informed consent was obtained according to the Declaration of Helsinki. DNA from whole blood was evaluated for CHIP with a custom TruSight myeloid sequencing panel and next generation sequencing (NGS), including 46 entire genes or hotspots. Variants were validated by an established NGS-MRD method with a sensitivity of 0.02%.
Results: Of 82 patients with a median age of 55.5 years, 39 (47.6%) were diagnosed with a dilated cardiomyopathy (DCM), 24 (29.3%) with coronary artery disease (CAD), 7 (8.5%) with restrictive cardiomyopathy (RCM) and 12 (14.6%) with other heart diseases. Fifty-six patients were male (68.3%). Twelve of 82 (14.6%) patients carried CHIP-associated variants. The median variant allele frequency was 9.76% (range 3.06-32.7%). One of the 12 patients carried 3 and one patient carried 2 concurrent CHIP-associated variants. Mutations in *DNMT3A* were the most frequently detected and were observed in 6 of 12 patients (50%). The prevalence of CHIP in DCM, CAD, RCM and other patients was 25.5, 12.5, 0 and 9.1%, respectively (P=.46). CHIP carriers were numerically older compared to non-carriers (59 vs 53.5 years, P=0.4) and had numerically less cardiovascular risk factors (CVRFs) at the time of HTx (>1 CVRF 75% vs 90%, P=.16; >2 CVRFs 16.7 vs 35.7%, P=.09). All other investigated baseline characteristics (hemoglobin, platelet count, leukocytes, donor/recipient characteristics) for HTx did not differ between the groups. Day-90 mortality was 25% vs 5.7% in CHIP carriers vs non-carriers (P.27). CHIP carriers had a similar 2-year overall survival (OS) after HTx when compared to non-carriers (58% vs 73%, P=.33, HR 1.62, 95%CI 0.61-4.3, Figure). CHIP-associated variants had no impact on the risk of allograft rejection (77.1% vs 58.3%, P=.28) or malignancy development after HTx (11.4% vs 16.7%, P=.64) compared to CHIP non-carriers.

Figure



Summary/Conclusion: Acquired somatic mutations in the CHIP-driver genes occur with a prevalence of 14.6% in patients undergoing HTx. Patients with CHIP had fewer traditional cardiovascular risk factors, suggesting that CHIP may contribute to their cardiovascular risk. CHIP was associated with a higher early mortality rate but did not affect long-term survival in patients undergoing HTx.
Axel Haverich and Michael Heuser share the senior authorship.

EP758 KER-050, AN INHIBITOR OF TGF-B SUPERFAMILY SIGNALING, OBSERVED TO HAVE A RAPID, DYNAMIC, AND DURABLE EFFECT ON ERYTHROPOIESIS.

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Background: Erythropoiesis, the multi-stage differentiation process of hematopoietic stem cells to red blood cells (RBCs), is a tightly regulated process required for adequate blood supply. Ineffective erythropoiesis causing anemia, such as in myelodysplastic syndromes (MDS) or myelofibrosis (MF), can result from defects at any stage in the pathway. However, current treatments target distinct stages of erythropoiesis, resulting in some patients being unresponsive to treatment; targeting multiple stages of erythropoiesis may provide a better treatment option. The TGF-β superfamily regulates erythropoiesis by maintaining a balance between progenitor quiescence and differentiation. KER-050, a modified ActRIIA ligand trap, is designed to promote erythropoiesis through inhibition of TGF-β ligands that signal though SMAD2/3, including activins and GDFs. In a Phase 1 clinical study, administration of KER-050 to healthy volunteers led to a robust, rapid, and sustained increase in RBCs and hemoglobin (HGB) as well as an increase in platelets, potentially suggesting a broader effect of KER-050 on hematopoiesis.
Aims: Determine the durability of effect and mechanism of action of KER-050 on erythropoiesis.

Methods: C57BL/6 male mice (12-week-old) were treated with a single dose of either vehicle or a research form of KER-050 (RKER-050). Peripheral blood was evaluated for reticulocytes (RET), RBCs, and HGB, and bone marrow (BM) erythroblasts were analyzed by flow cytometry, at multiple time points from 12 hours (hr) through day 51. Erythropoietin (Epo) levels were measured in serum.
Results: Treatment with RKER-050 resulted in rapid and sustained increases in RBCs and HGB, observed from 12hr through day 51. Within 12hr, RBCs (+8%) and HGB (+9%) were significantly increased. This response corresponded to a 20% reduction in BM proerythroblasts and erythroblasts (TER119+ cells) and a concomitant 18% increase (compared to vehicle) in circulating RETs, supporting that the maturation of these late-stage precursors contributed to the rapid RBC effect. Indeed, analysis of specific BM populations showed a general shift in the TER119+ cells from early to late erythroblast populations.
Within 48hr, the number of BM TER119+ cells increased by 37% compared to vehicle, demonstrating that precursor pools reduced at 12hr were quickly restored. In parallel, the initial increase in RETs observed at 12hr were transiently reduced (-15%), implying continued late-stage maturation of RETs to RBCs. This continued movement of earlier stage erythroid precursors into later stages of the pathway continued, with RET levels again replenished and TER119+ cells reduced by 48hr, likely supporting that the robust and sustained response in RBCs was due to administration of KER-050.
In addition to RKER-050 promoting differentiation of erythroid precursors to elicit its effect on RBCs, a RKER-050-mediated upregulation of Epo may also be contributing to the sustained increase in RBCs. Epo does not appear to play a role in the initial rapid RBC increase since Epo upregulation was not observed until day 4; however, Epo was increased from day 4 through day 37 which could indicate a role in sustaining the RKER-050-mediated increase in RET (+4%), RBCs (+8%), and HGB (+3%) to at least day 51.
Summary/Conclusion: In these studies, we observed that RKER-050 had a rapid and durable effect on erythropoiesis. The observed effects of RKER-050 on multiple stages of erythroblast maturation (both early- and late-stage) and increase in circulating EPO provide a strong rationale for investigating KER-050 as a treatment for ineffective hematopoiesis in MDS and MF.

EP759 CROSSTALK BETWEEN NITRIC OXIDE AND GLUCOCORTICOID RECEPTOR IS DISPENSABLE FOR INITIAL STRESS-INDUCED ERYTHROID PROGENITOR CELL EXPANSION

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Background: Nitric oxide (NO) is an ubiquitous signaling molecule that interacts with glucocortiocids in response to perturbed tissue homeostasis under hypoxic or inflammatory conditions. Using a mouse model of psychological stress, we have recently shown that chronic stress induces initial erythroid progenitor cell expansion by modulating the production of NO in the bone marrow. However, it remains unknown whether this stress-induced effect requires a NO-glucocorticoid receptor (GR) crosstalk.
Aims: This study was aimed to examine 1) a role of GR in initial stress-induced erythroid progenitor cell response and 2) a possible interaction between GR and NO in the bone marrow during chronic stress.
Methods: Adult male mice were subjected to 2h daily restraint stress for 7 consecutive days. The role of GR was assessed by subcutaneous administration of the GR antagonist mifepristone (RU486), 60 min prior to each restraint procedure. The number of bone marrow erythroid progenitors burst forming units-erythroid (BFU-E) and colony-forming unit-erythroid (CFU-E) was determined using colony assays. In order to examine a possible GR/NO interplay in the bone marrow during chronic stress, we used a blockade of NO biosynthesis, and mice were randomly assigned to following groups: (1) R - restraint group, exposed to daily restraint stress for 7 consecutive days; (2) L-NAME + R group, received a subcutaneous injection of L-NAME (non-selective nitric oxide synthase inhibitor) 30 min prior daily restraint; (3) L-NAME group, treated with L-NAME only; or (4) control group. To analyze GR activation, we assessed the nuclear translocation of GR by examining the level of GR expression in bone marrow nuclear cell fraction, using Western blot technique, and compared the protein expression levels among experimental groups. Plasma corticosterone levels were determined using a ^{125}I-coupled double antibody radioimmunoassay.
Results: Chronic stress induced a marked increase in the number of BFU-E (two-way ANOVA; $F(1,12)=29.996$; Bonferroni adjustment, $p<0.001$) and CFU-E (two-way ANOVA; $F(1,12)=28.946$; Bonferroni adjustment, $p<0.001$) progenitors in the bone marrow. Blockade of GR with RU486 prior to daily stress completely abolished the effect of repeated stress on both BFU-E (two-way ANOVA; $F(1,12)=27.301$; Bonferroni adjustment, $p<0.001$) and CFU-E cells (two-way ANOVA; $F(1,12)=28.168$; Bonferroni adjustment, $p<0.001$). Exposure to chronic stress significantly increased the expression of GR in bone marrow nuclear cell fraction (two-way ANOVA $F(1,12)=13.036$, $P<0.01$), and blockade of NO biosynthesis prior to each restraint did not alter stress-induced incresae in nuclear GR protein expression (two-way ANOVA; $F(1,12)=0.132$; $p>0.05$). In accordance, analysis of corticosterone levels among experimental groups revealed a highly significant difference in corticosterone concentration regarding the main effect for stress (two-way ANOVA; $F(1,12)=159.436$, $p<0.001$), while there was no significant main effect for the blockade of NO biosynthesis (two-way ANOVA; $F(1,12) =0.775$, $p>0.05$).
Summary/Conclusion: These findings suggest a crucial role for GR in the expansion of bone marrow erythroid progenitors under conditions of chronic stress. Although both GR and NO are required for stress-induced initial erythroid progenitor cell expansion, their interaction within bone marrow microenvironment is not essential for observed effect during chronic stress.

EP760 STUDY OF THE MACROPHAGE POLARISATION CONTINUUM WITH RELEVANCE TO COVID19

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Background: Macrophages are immune cells known for the detection and destruction of bacteria and viruses. In addition, macrophages are vital for a more generalised inflammatory response, providing cell-cell contacts and producing a cocktail of cytokines that stimulate a variety of other immunopathology's; including wound healing. Importantly, macrophages exhibit plasticity in their specific phenotypes, able to transiently convert between pro or anti-inflammatory subsets of cells along a continuum. For example, the pro-inflammatory M1 subset are heavily involved in immune modulation and the anti-inflammatory M2c subset is central to the erythroblastic island in the bone marrow.
Aims: The aim of our work was to further understand and characterise human macrophages and their polarity using a well characterised in vitro culture model. A multipronged approach of mass spectrometry, flow cytometry and a previously described2 imaging pipeline was utilised to interrogate the cell surface expression and behaviour of cultured cells.
Methods: We compared three populations against our control unstimulated macrophage (MØ) population, including the classically activated "inflammatory" M1 stimulated with interferon-g (IFNg) against the non-classically activated M2a macrophage subset stimulated with interleukin-4 (IL-4) and finally M2c macrophages stimulated with dexamethasone. The glucocorticoid dexamethasone was also applied as a treatment of the inflammatory M1 subset to better understand the specific effects of this steroid on macrophage polarisation to mimic anti-inflammatory steroid treatment for diseases such as COVID19.
Results: In doing this we demonstrate an increase in CD163 and CD206, markers synonymous with anti-inflammatory M2 macrophages when compared with untreated M1 macrophages. We detected specific alterations in cell surface markers and behaviour between the subsets of *in vitro*produced macrophages associated with the known phenotypes.
Summary/Conclusion: This provides a detailed dissection of the macrophage polarity continuum that is relevant to the macrophage field as a whole and to the current situation with COVID-19. This *ex vivo* method of recapitulating an aspect of the inflammatory response to disease has the prospect to be a test bed for future drugs and therapeutics.

EP761 NICHE HEALTH MAINTAINS SURVIVAL

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Background: Life is stressful. Stressors like chronic infections or inflammation can alter both the composition and the function of hematopoietic niche cells, which affects blood cell formation.
Aims: We aim to identify cellular maintenance processes which ensure hematopoietic niche health upon stress.
Methods: For this purpose, we use mice in which the hematopoiesis maintenance factor *Wnt5a* is specifically deleted in Osterix+ mesenchymal progenitor and stem cells (MPSCs). These mice show normal steady state hematopoiesis, but progressive damage of hematopoietic stem cells upon stress.
Results: Mice lacking *Wnt5a* in MPSCs suffer from stress-related bone marrow failure and increased mortality. Niche cells devoid of *Wnt5a* show defective actin stress fiber orientation due to an elevated activity of the small Rho GTPase Cdc42. This results in incorrect positioning of autophagosomes and lysosomes, thus reducing autophagy and increasing oxidative stress. Strikingly, a short pharmacological intervention to attenuate elevated Cdc42 activation in vivo restored actin-anchored autophagy in MPSCs salvages hematopoiesis and as a consequence improves survival upon stress.
Summary/Conclusion: In summary, our study identifies *Wnt5a*, by affecting Cdc42 regulated actin stress fiber orientation and autophagy in niche cells, as a restriction factor for niche health upon stress. Our data further imply a critical role for autophagy in MPSCs for adequate support of hematopoiesis by the niche upon stress.

EP762 IMMUNE STATUS IN HEMATOLOGICAL CANCER PATIENTS AFTER COVID19

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Background: Patients with immunosuppression, including those with hematologic cancers, are at greater risk of developing SARS-CoV infection. The virus is capable of infecting monocytes, macrophages and dendritic cells in order to promote the secretion of cytokines, and IL-6 can contribute to the excessive activation of the effects of the acquired immune system (usually lymphocytes) and innate immunity (neutrophils, monocytes, NK cells, etc.).
Aims: The purpose of the study was an assessment of the immune status of patients with hematological cancers after multi-course chemotherapy, therapy with anti-CD20+ antibodies and PCR-confirmed COVID19.
Methods: The study included 12 adult patients with lymphoproliferative diseases with a history of PCR-confirmed COVID-19. All patients underwent 4 to 6 chemotherapy cycles. The BD FACSCanto II flow cytometer with Becton Dickinson reagents were used to assess the immune status of patients. The research group consisted of patients with non-Hodgkin's large B-cell lymphomas. The blood plasma taken into a vacuum system with K2EDTA as an anticoagulant was used. The relative and absolute numbers of the main populations of T- and B-lymphocytes, the immunoregulatory index, and subpopulations of T-lymphocytes were assessed.
Results: Most patients showed a decrease in the relative number of lymphocytes, on average by 73%. The absolute and relative numbers of monocytes in half of the cases exceeded the norm or were similar to it. The immunoregulatory index in most cases (N=7) was decreased on average by 42%, compared to the norm. The absolute number of T-lymphocytes (CD3+) in 6 patients decreased on average by 42%±0.6. The population of T-helpers (CD3+CD4+) in 5 patients was reduced by an average of 44%±0.8. The number of double-positive (CD3+CD4+CD8+) T-lymphocytes in most cases (N=10) was reduced by 80%±0.8. At the same time, the number of double-negative (CD3+CD4-CD8-) T-lymphocytes increased by 177% in 7 patients. All patients showed a decrease in the B-cell immunity component. The relative number of B-lymphocytes (CD19+) was decreased on average by 78%, absolute number by 61%. The increase in all types of memory cells, both helper-inducer and cytotoxic populations, was registered.
Summary/Conclusion: Conclusions. Elevated numbers of various memory cells, together with a decrease in T-lymphocytes, could indicate the activation of the cellular adaptive immunity. A decrease in B-lymphocytes could indicate a decrease in the activity of the humoral component of adaptive immunity. The latter could also be a result of multi-course chemotherapy with anti-CD20+ monoclonal antibodies.

EP763 RING CHROMOSOMES IN HEMATOLOGICAL MALIGNANCIES

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Background: Ring chromosomes are uncommon and poorly investigated cytogenetic abnormalities in hematological malignancies.
Aims: The aim of the study was to shed light to the nature of ring chromosomes in bone marrow samples from patients with hematological malignancies and to identify the spectrum of chromosomal abnormalities in addition to ring chromosomes, by conventional and molecular cytogenetic analysis.
Methods: This study includes 40 patients with ring chromosomes identified among 28.821 patients with hematological malignancies from 1998 until 2019. The cytogenetic analysis was performed on 24h and 48h unstimulated bone marrow cultures using GTG-banding. Karyotypes were described according to the international system for human cytogenomic nomenclature (ISCN) 2016. Molecular cytogenetic analysis was performed by fluorescence in situ hybridization (FISH) using probes for the centromere of chromosomes (CEP) 1, 3, 7, 8, 9, 11 and for chromosomal regions 8q24.21 (MYC gene), 11q23 (MLL gene) and 17p13 (p53 gene) chosen each time according to karyotype and diagnosis. For each sample, 10 metaphases (mFISH) at least were analyzed.
Results: The frequency of ring chromosomes in hematological malignancies was ~ 0,14%. Among our patients with ring chromosomes, 48,5% had AML, 33,5% MDS, 6% MPD, 9% LPD and 3% ALL. The sex ratio was 1.1 (21 males/19 females) and the mean age was 67.6 years (range 12-91). Ring chromosomes were found as a sole abnormality in 2 patients (5%), with one more abnormality in 4 (10%) and in complex karyotypes in 34 patients (85%). The most frequent additional abnormality was marker chromosomes (51.2%), followed by -5/del(5q) (43,8%), -7/del(7q) (34,1%), -11 (26.8%), +8 (24.3%), -21 (19.5%), -17 (17.1%), -18 (14.6%). The nature of ring chromosomes was identified in 16 cases by mFISH and revealed: a) CEP 11 accompanied by MLL amplification in 9/16 (56.3%) all in complex karyotypes in AML or MDS cases. b) MYC amplification without CEP 8 in 2/16 (12.5%) as a sole abnormality. c) CEP 7 in 2/16 (12.5%) cases without additional abnormality in the karyotype except -7. d) CEP 1, 3 and 9 and TP53 gene in 1/16 (6.3%) each.
Summary/Conclusion: Ring chromosomes are very rare aberrations in hematological malignancies. They are observed mainly in AML and MDS, in elderly patients and in complex karyotypes. The most frequent additional abnormalities are marker chromosomes, -5/del(5q) and -7/del(7q). The most common origin of ring chromosome was that of chromosome 11, accompanied simultaneously by MLL amplification.

Hodgkin lymphoma - Clinical

EP764 CLINICAL OUTCOMES OF RELAPSED HODGKIN LYMPHOMA PATIENTS AFTER CONTEMPORARY FIRST-LINE TREATMENT: RESULTS FROM THE GERMAN HODGKIN STUDY GROUP

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Background: The relative benefit of targeted agents increasingly investigated and applied in relapsed or refractory Hodgkin lymphoma (rrHL) is difficult to estimate due to a lack of randomized trials.
Aims: This retrospective study thus aimed at evaluating disease characteristics, treatment patterns and associated outcomes at first occurrence of rrHL after contemporary first-line treatment.
Methods: We retrospectively identified patients with sufficiently documented first rrHL initially receiving standard of care 1st-line treatment in the GHSG HD13 (early-stage favorable), HD14 (early-stage unfavorable) and HD15 (advanced-stage) trials. We additionally evaluated rrHL patients enrolled in the placebo-controlled randomized GHSG HDR3i trial comparing conventional DHAP vs. everolimus + DHAP salvage therapy prior planned autologous stem-cell transplantation (ASCT). We assessed overall survival (OS) starting with date of 1st rrHL and ending with date of death for any reason and progression free survival (PFS) measured from date of rrHL to second rrHL or death from any reason. Patient, disease and treatment characteristics were analyzed with descriptive statistics and survival endpoints with Kaplan-Meier estimates.
Results: A total of 437 patients with first rrHL (HD13: n=87, HD14: n= 118, HD15: n=188, HDR3i: n=44) were identified. Of these, 402 patients with sufficient documentation and follow-up were assessed with a median age of 37.5 years (18.4-76.8). Time to relapse was ≤12 months in 49% and stage III/IV rrHL present in 52% of patients. High-dose chemotherapy and autologous stem-cell transplantation (ASCT) with and without consolidation was administered in 20% and 52% of patients, respectively. The remaining 111 patients (27%) did not receive ASCT mostly due to insufficient response to salvage chemotherapy, advanced age, localized disease or patients' preference. Overall, 10-year PFS and OS after first relapse were 48.2% (95% confidence interval CI: 42.0%>54.4%) and 59.3% (95%CI: 53.2%>65.4%), respectively (**Figure 1**). Patients unsuitable for ASCT had less favorable 10-year PFS (32.5%, 95%CI: 19.1%>45.9%) and OS (41.9%, 95%CI: 28.1%>55.6%). Significantly inferior PFS and OS was also observed in primary refractory patients (10-year PFS 36.0%, 95%CI: 24.2%>47.9%; 10-year OS 44.5%, 95%CI: 31.6%>56.6%) and those with stage IV disease at rrHL (10-year PFS 29.3%, 95%CI: 18.5%>40.9%; 10-year OS 39.6%, 95%CI: 27.9%>51.1%). Outcomes in these higher risk patients appeared more favorable with ASCT than without ASCT.

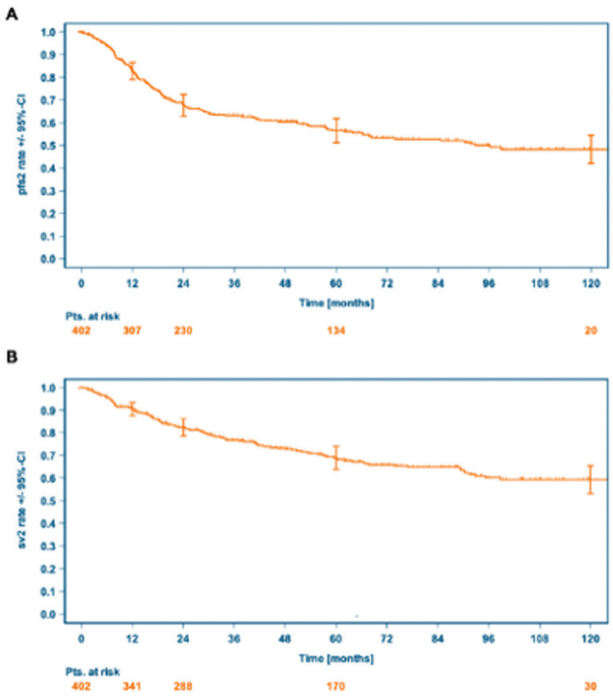


Figure 1 PFS (Panel A) and OS (B) after rrHL in patients treated in HD13, HD14, HD15 and HDR3i

Summary/Conclusion: Our analysis of relapse and treatment patterns after contemporary HL therapy provides a robust benchmark to evaluate novel therapeutic strategies in rrHL. We confirm the curative potential of current rrHL treatments including non-ASCT approaches and roughly 50% of rrHL patients do not experience a consecutive relapse after 2nd-line treatment.

EP765 MODIFICATION OF ESCALATED BEACOPP WITH DACARBAZINE SUBSTITUTION REDUCES TOXICITY WHILE MAINTAINING EFFICACY FOR THE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA.

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Background: In the treatment of advanced Hodgkin lymphoma, it is increasingly common practice to modify escalated BEACOPP (eBPP) by removing oral procarbazine and replacing it with intravenous dacarbazine (250mg/m2 D2-3) to reduce haematopoietic stem cell and gonadal toxicity. However, published data of the "escalated BEACOPDac (eBP-Dac)" regimen are very limited.
Aims: The aims are to compare efficacy and toxicity outcomes of patients treated with eBPDac versus eBPP.
Methods: This is a retrospective study of 147 patients from 16 centres in the UK, Ireland and France who were treated with eBPDac first line for advanced stage Hodgkin lymphoma. Outcomes were compared with 58 matched patients treated with eBPP at 4 UK centres. Most patients were treated as per HD15 or HD18 protocol. 28 patients in Paris and two in Truro followed the AHL2011 protocol with 2 courses of eBPDac given upfront and if iPET2 negative were deescalated to 4 cycles of ABVD.
Results: From 2009, 205 patients were treated first line with either eBPP (n=58) or eBPDac (n=147) with median follow-up 51.3 months and 22.9 months respectively. Patients were well matched with no significant differences in age (median: 23 y vs 27 y), sex, stage (stage 3/4: 81% vs 83%) and international prognostic score (IPS3+: 74% vs 65%).
51% of eBPDac patients received only 4 cycles (vs 12% of eBPP patients; p<0.001) reflecting publication of HD18 trial data. In total, 74% patients achieved iPET2 Deauville score ≤3 and 90% patients achieved PET negative remission by end of treatment. 77% of eBPDac patients achieved iPET2 Deauville ≤3 which was statistically similar to the eBPP cohort (67%; p=0.181) and matched the 76% iPET D2/3 reported in HD18. Of 205 patients, 202 are alive and 197 continue in first remission. Two eBPP patients have relapsed at 13 and 41 months and the latter died of refractory disease. One eBPDac patient had primary refractory disease, and three have relapsed at 2, 7 and 24 months. One 56-year-old eBPDac patient with high IPS died with bowel perforation during cycle 1 and one 34-year-old with alcoholic liver disease died 8 months after treatment while still in remission.
Toxicity was compared over the first 4 cycles. Mean day 8 (D8) ALT was similar between the two regimens. Mean D8 neutrophil count was lower in eBPDac than eBPP patients (1.81 vs 2.45; p=0.067; G-CSF given day 9), however it increased to 5.61 in eBPDac patients given GCSF from day 4. There is a trend toward fewer non-elective days of inpatient care

for eBPDac compared with eBPP (mean: 3.74 vs 5.83; p=0.118), and eBPDac patients received fewer red cell transfusions compared with eBPP patients (mean 1.93 units vs 4.16 units; p<0.001). Women aged < 35, who completed ≥4 cycles of eBPDac/eBPP had a similar rate of return of menstrual cycles (eBPP: 22/25; eBPDac: 29/29), although eBPDac patients appeared to restart menstruation earlier post chemotherapy (mean: 4.48 months vs 9.12 months, p=0.0026). However, this could also reflect the higher mean chemotherapy cycle number completed by the eBPP women (5.86 vs 4.60; p<0.001). The use of Goserelin to suppress ovulation varied between centres.

Baseline Characteristics	eBEACOPP N=58	eBEACOPDac N=147	p-value
Median Age (range)	23 (16-54)	27 (16-62)	U=4665, p=0.293
Male sex (%)	29 (50%)	88 (60%)	Fisher, p=0.213
Stage 2B / 2X / 2XB	11 (19%)	25 (17%)	
3	9 (16%)	27 (18%)	Fisher, p=0.879
4	38 (65%)	95 (65%)	
IPS 0-2	15 (26%)	51 (35%)	
3-4	32 (55%)	72 (49%)	
5-7	11 (19%)	24 (16%)	Fisher, p=0.474
IPS ≥3	43 (74%)	96 (65%)	
Treatment Outcomes			
Total cycle number 1	0	2 (1%)	
2	0	28 (20%)	
4	7 (12%)	73 (51%)	Fisher,
5	5 (9%)	2 (1%)	(4 vs 6)
6	45 (78%)	39 (27%)	p=3.93E-10
7	1 (2%)	0	
On treatment	0	3	
iPET Deauville score 1-2	10 (21%)	39 (27%)	
3	22 (46%)	72 (50%)	
4	16 (33%)	32 (22%)	
5	0	1 (1%)	Fisher, p=0.181
≤3	32 (67%)	111 (77%)	
No iPET	10	3	
Mean day 8 ALT (cycles 1-4) [SD]	40.2 (±32.7)	46.5 (±31.5)	t(96)=1.17, p=0.244
Mean day 8 neutrophils (cycles 1-4) [SD]	2.45 (±1.45)	1.81 (±1.09)	t(87)=2.77, p=0.0067
Mean no. days non-elective admission (cycles 1-4) [SD]	5.83 (±7.40)	3.74 (±5.47)	U=2762, p=0.118
Mean no. red cell units transfused (cycles 1-4) [SD]	4.16 (±4.12)	1.93 (±2.89)	U=1996, p=2.52E-5
Median follow-up from diagnosis in months (range)	51.3 (5.0-127)	22.9 (0.89-47.0)	U=1053, p=2.2E-16
Mean no. months for return of menstrual period post-chemotherapy [SD]	9.12 (±5.73)	4.48 (±2.06)	t(24)=3.55, p=0.0016
Mean no. cycles completed by women <35 years of age [SD]	5.86 (±0.35)	4.60 (±0.93)	U=113, p=5.20E-6

Summary/Conclusion: Accepting the limitations of a retrospective study, we suggest that substituting dacarbazine for procarbazine is unlikely to compromise the efficacy of eBPP and may have some toxicity benefits. Despite a predominance of high risk advanced stage patients, with nearly 2 years median follow-up we have observed only 2 deaths and 4 progression events from 147 patients treated with eBPDac, suggesting this regimen is highly efficacious for the treatment of Hodgkin lymphoma.

EP766 LONG-TERM FOLLOW-UP AND BIOMARKER ANALYSES OF RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENTS TREATED WITH BRENTUXIMAB VEDOTIN AND DHAP: THE HOVON/LLPC TRANSPLANT BRAVE STUDY

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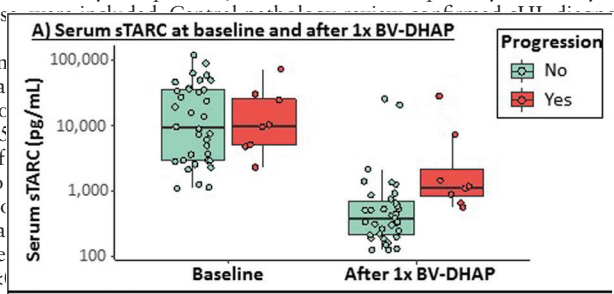
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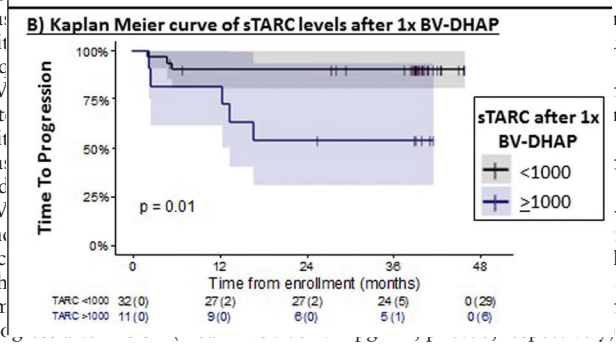
Background: Patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL) generally have a poor prognosis. We have shown that brentuximab vedotin (BV) in combination with DHAP (dexamethasone, cytarabine, cisplatin) is highly effective with manageable toxicity. Here we present the long-term follow-up, including thymus and activation regulated chemokine (TARC) and metabolic tumor volume (MTV) analyses.

Aims: The aim was to find predictive biomarkers for r/r cHL patients treated with BV-DHAP and to evaluate the long-term follow-up.

Methods: Patients were treated with 3 cycles of BV-DHAP followed by autologous stem-cell transplant (ASCT). Serum was collected at baseline, after each cycle, and during follow-up. Soluble (s)TARC was measured by ELISA. Based on levels in healthy controls, a baseline sTARC <1000 pg/mL was considered not elevated. Immunohistochemical (IHC) staining was done for TARC on the lymph node biopsy at baseline. Baseline ^{18}F-FDG-PET-CT scans were analyzed quantitatively for MTV using a fixed threshold of standard uptake value (SUV) ≥4.0. Predictive value of biomarkers for time to progression (TTP) was assessed by calculating the area under the curve (AUC) of the receiver operating characteristics curve and log-rank survival analysis. For biomarker evaluation, patients who died without progression (n=2) were censored at time of death.

Results: Sixty-five patients, of whom 46% had primary refractory dis-





Summary/Conclusion: Treatment with BV-DHAP in r/r cHL patients shows a high 3-year PFS and OS. Serum sTARC correlates with baseline MTV and can be used as an early response marker already after 1 cycle of BV-DHAP. InterimPET status is predictive for post-ASCT TTP and sTARC can complement interimPET response evaluation. In addition, we have identified low TARC expression in HRS cells as a possible poor prognostic factor. Risk assessment using different biomarkers could help guide treatment decisions in an era with new targeted treatment options for r/r cHL.

EP767 IMPACT OF THE FIRST COVID-19 LOCKDOWN IN GERMANY ON THE RATE OF ACUTE INFECTIONS DURING INTENSIVE CHEMOTHERAPY FOR HODGKIN LYMPHOMA

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Background: Acute infections and fever under chemotherapy are an important cause for morbidity and mortality in hematologic malignancies such as Hodgkin lymphoma (HL). Prophylactic anti-infective concomitant medication is prescribed frequently. Another protective measure could be self-protection via social distancing and wearing facemasks. However, evidence on the effect of self-protection on infections during chemotherapy is currently not available.
Aims: We asked if the frequency of acute infections during chemotherapy for advanced-stage HL decreased when Corona Virus Disease 2019 (COVID-19) protection measures were in effect.
Methods: We analyzed the occurrence of infections during all documented eBEACOPP cycles that started between 01 March and 30 June of 2017-2020 among patients treated within the GHSG HD21 study in Germany. We compared cycles starting between March and June 2020 with cycles starting between March and June of 2017-2019 regarding infection rates and infection characteristics by logistic regression models and means of descriptive statistics.
Results: We analyzed 911 cycles of 313 adult patients treated with 4 to 6 cycles of eBEACOPP. We found a significant decrease in the frequency of infections during chemotherapy for HL during COVID-19 lockdown from 131 (19.6%) of 670 cycles in the years 2017-2019 to 30 (12.6%) of 239 cycles during COVID-19 lockdown (OR 0.574 (95% CI 0.354-0.930), P = 0.024). Correspondingly, 20 (24.1%) of 83 patients had an infection during the COVID-19 lockdown versus 99 (43.2%) of 229 patients in the years 2017-2019 (P = 0.0023). The strongest effect was observed for unspecified infections (unknown type of etiologic agent), occurring in 39 cycles (5.8%) during 2017-2019 in comparison to 5 cycles (2.1%) during COVID-19 lockdown. There was also a strong trend towards fewer minor infections: during the COVID-19 lockdown period there were 8 cycles (3.3%) with a minor infection compared to 66 cycles (9.9%) with an infection during the reference period.
Summary/Conclusion: The significant and relevant decrease observed in acute infections while receiving chemotherapy for HL during the COVID-19 lockdown demonstrates the potential of protective measures to shield patients from transmissible pathogens. We conclude that these measures may be recommended for cancer patients at risk for infections during chemotherapy.

EP768 THYMUS AND ACTIVATION-REGULATE CHEMOKINE (TARC) IS A RELIABLE TUMOR MARKER FOR BOTH DIAGNOSIS AND MONITORING CLASSICAL HODGKIN LYMPHOMA

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Background: Classical Hodgkin lymphoma (cHL) accounts for 15% of all lymphoproliferative diseases, which is often presented with lymphadenopathy and B symptoms. The diagnosis of cHL is based on tissue sampling and histology, and the disease activity is monitored by serial PET/CT scans. cHL is considered to be highly curable, however substantial proportion of the patients suffer from refractory / relapsing disease. A reliable serum biomarker could support the management of these patients at the time of the diagnosis and later during the follow-up period. Thymus and Activation-Regulated Chemokine (TARC or CCL17) is highly expressed by Hodgkin and Reed-Sternberg cells and secreted into the serum, which raises the possibility to apply TARC as a tumor marker in cHL.
Aims: The aim of the study was to evaluate serum TARC as a reliable tumor marker in the course of treatment, and the follow up in patients with cHL.
Methods: Consecutive cases of cHL were enrolled in the study. In cohort 1 patients diagnosed between 2011 and 2018 were used to determine the cut off value of TARC. A second cohort of patients from 2019-2020 were used to validate the result. Serum TARC levels were determined with a quantitative sandwich enzyme immunoassay. Receiver Operating Characteristic (ROC) curve analysis was performed.
Results: In cohort 1, 613 patients diagnosed with cHL between 2011 and 2018 were enrolled. In 241 cases from this cohort, serum TARC concentrations were determined at baseline before therapy, as well. Receiver Operating Characteristic (ROC) curve analysis was performed for comparison with healthy controls (n=168). The cut-off value was found to be 637 pg/ml with 90.9% sensitivity and 98.2% specificity. During follow-ups measurements were carried out in 3 month intervals following diagnosis, and 6 month intervals after 3 years. The median serum TARC value was 14350 pg/ml in patients with active disease status. In cases with complete remission determined by PET/CT scans median TARC concentration was 401 pg/ml. ROC curve analysis of active versus complete remission groups showed 85.6% sensitivity and 93.7% specificity with a 936 pg/ml cut-off value. This result was used in the second half of the study: In cohort 2, 69 patients were enrolled who were consecutively diagnosed with cHL between 2019 and 2020. In this cohort 58 of 69 patients had TARC value above the cut off limit. In 2019 we treated 27 patients, and 23 of them had a positive TARC test result at baseline. At the end of the first line treatment 18 were in complete remission verified by PET/CT. More importantly all of these patient had a TARC value below 936 pg/ml.
Summary/Conclusion: Our results show that TARC is a robust and reliable tool in classical Hodgkin lymphoma both at diagnosis and for follow-up. The cut off values we found were similar to the previously published results. Measuring TARC can provide a sensitive method for treatment response assessment that can make the PET/CT based treatment protocols more effective.

EP769 BRENTUXIMAB VEDOTIN WITH CHEMOTHERAPY IN ADOLESCENTS AND YOUNG ADULTS (AYAS) WITH STAGE III OR IV HODGKIN LYMPHOMA: A SUBGROUP ANALYSIS FROM THE PHASE 3 ECHELON-1 STUDY

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Background: Classical hodgkin lymphoma (cHL) is a rare disease that commonly occurs in adolescents and young adults (AYAs), typically defined as 15 to 39 years. Given their young age at presentation, key factors in treatment selection include not only a high cure rate, but minimal long-term toxicities. Brentuximab vedotin (Adcetris®; A) is a CD30-directed ADC approved in combination with doxorubicin, vinblastine, and dacarbazine chemotherapy (A+AVD) for adults with previously untreated stage III/IV cHL based on results from the phase 3 ECHELON-1 trial. Recent 5-year data demonstrated a significantly improved PFS per investigator (INV) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (HR, 0.69; 95% CI, 0.54–0.9; P=0.003) (Straus 2020).
Aims: To describe key efficacy and safety results for AYA pts enrolled in ECHELON-1.
Methods: ECHELON-1 (N=1334) is a global, open-label, multicenter, randomized trial of pts with previously untreated stage III/IV cHL. A total of 771 AYAs (58%) received either A+AVD (n=396) or ABVD (n=375) with a PET scan after cycle 2 (PET2). An analysis of PFS (time from randomization to progression or death from any cause) per INV was conducted.
Results: These results refer to the AYA subset. After a median follow-up of 60.7 months (95% CI, 60.4-61.0), there was a 36% reduction in the risk of progression or death with A+AVD vs ABVD (HR 0.64; 95% CI, 0.45-0.92; P=0.013) with a 5-year PFS of 86.3% vs 79.4%, respectively, similar to the ITT population. The PFS benefit of A+AVD vs ABVD was independent of PET2 status; PET2 positivity (Deauville 4-5) was 6% and 8%, respectively.
On the A+AVD arm, 81 pts (20%) had at least one subsequent anticancer therapy (including radiotherapy) vs 96 pts (26%) on the ABVD arm; 26 pts (7%) received subsequent high dose chemotherapy and autologous stem cell transplant vs 32 pts (9%) on the A+AVD and ABVD arms, respectively.
Any-grade peripheral neuropathy (PN) occurred in 64% and 40% of pts on the A+AVD and ABVD arms, respectively. Resolution or improvement of PN occurred in 88-89% of pts on both arms. Ongoing PN was predominantly Grade 1 (62%) and Grade 2 (26%), with 8 pts (3% of

the total cohort) on the A+AVD arm and one pt (<1%) on the ABVD arm reporting ongoing Grade 3 PN. Seven pts (1.8%) and 5 pts (1.4%) on the A+AVD and ABVD arms, respectively, reported a secondary malignancy. Subsequent pregnancies were reported in female pts (44 A+AVD; 26 ABVD) and partners of male pts (31 A+AVD; 30 ABVD). No stillbirths were reported. All but one pt in each arm was <40.
Summary/Conclusion: Consistent with the ITT population, AYAs treated with A+AVD compared to ABVD had a durable PFS benefit at this significant 5-year milestone. No impact on the rate of secondary malignancies and a numerically greater number of pregnancies were observed, outcomes of interest to AYAs. Additionally, the majority of PN events improved or resolved over time. A+AVD should be considered a treatment option for AYAs with stage III/IV cHL.

EP770 BRENTUXIMAB VEDOTIN- CONTAINING REGIMENS FOR THE TREATMENT OF RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA IN CLINICAL PRACTICE: FOCUS ON SUBSEQUENT THERAPIES.

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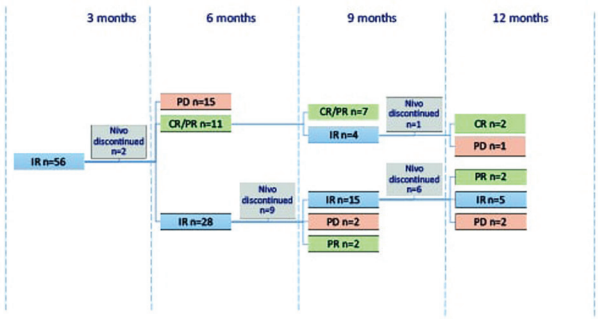
Background: Brentuximab vedotine (BV) has shown a high overall response rate in refractory/relapsed Hodgkin lymphoma (r/r cHL) with reported stable remissions achieved in pivotal clinical trial. However, only limited data is available regarding its role in role-term outcomes in real life clinical practice in light of recent treatment landscape shift due to the introduction of immune checkpoint inhibitors.
Aims: -
Methods: This retrospective analysis included patients with r/r cHL (n= 131) treated with BV – containing regimens in Pavlov University clinic from 2012 to 2020. Median age at BV- treatment was 28 year (range, 16-50). Seventy two percent of pts had advanced stages at BV- treatment. 61% of pts had primary refractory disease. ASCT was performed in 47,3% of patients prior BV- therapy. Median number of previous therapy lines was 4 (3-11). BV was used a monotherapy in 100 pts (76,3%) and in combination with bendamustine in 31 pts (23,6%). Median number of treatment cycles was 4 (range, 3-11). Dose of BV was 1,8mg/kg for all pts; dose of bendamustine was 90mg/m2 in day 1 and 2 of the 21 day cycle.
Results: At the time of analysis the median follow- up for alive pts (n=95) was 48,9 (3,0-104,6) months. Overall response rate was 61,0% (80 pts): CR in 38,9% (51 pts) and PR in 22,1% (29 pts). The duration of response for these pts was 11,1mo (1-101,4 months). Most of patients (93,1%, n=122) received additional therapy after BV-based treatment. The type of next therapy was BV-retreatment in 14,7% (18 pts), PD-1 inhibitors in 44,2% (54 pts), allogeneic stem cell transplantation (allo SCT) in 23,7% (29 pts), chemotherapy in 17,2% (21 pts). Overall, 58 pts were treated with anti PD-1 therapy at various time point after BV-based treatment.
The median overall survival (OS) was not reached and 5-year OS was 75,6%. The median progression free survival (PFS) was 6,0 mo (4,7-7,3 months) and 5- year PFS was 24,4%. At the moment of analysis, nine pts (6,8%) were in a remission after BV with no additional treatment.
Among factors significantly associated with favorable prognosis regarding the OS were PD-1 treatment after BV (5- year OS 89,7% vs 58,9%, p=<0,001) and consolidation by allo-SCT (5- year OS 82,8% vs 69,6%, p=0,049). Regarding PFS, the consolidation of remission by allo-SCT was significantly associated with favorable prognosis (5-year PFS 72,4% vs 10,8%, p=< 0,001)
Importantly, there was no benefit of combined regimens of BV+Bendamustine vs BV- monotherapy (5- year PFS of 30% vs 21,8%, p= 0,149), nor the overall response rate, p=0,881).
Summary/Conclusion: Brentuximab vedotin based regimens are highly active in inducing response in patients with r/r cHL with only modest potential achieve sustained remissions. There was no significant benefit of BV-benda combination regarding the PFS when compared to BVmonotherapy in the analyzed patient population. The outcomes of patients after BV treatment in the era of immunotherapy are more favorable than in registration studies, with significant advantage regarding OS in patients receiving anti-PD-1 treatment after BV failure. The alloHSCT represents an important approach for consolidation of response achieved with BV treatment, however the optimal strategy regarding the alloHSCT remains to be defined in prospective randomized trials.

EP771 OUTCOMES OF PATIENTS WITH INDETERMINATE RESPONSE DURING PD-1 INHIBITOR THERAPY FOR RELAPSED AND REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Background: Currently, the issue of adequate criteria for evaluation of response to immunotherapy of Hodgkin lymphoma is not resolved. LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC) introduced a new concept of indeterminate response (IR). However, only a limited number of studies have evaluated the efficacy of PD-1 inhibitors using LYRIC criteria. Thus, the prognosis of patients who develop IR warrants further analysis.
Aims: To assess the response evolution and prognosis of patients with relapsed and refractory classical Hodgkin lymphoma (r/r cHL) who demonstrated IR during nivolumab (Nivo) therapy.
Methods: We retrospective reviewed data on 160 patients with r/r cHL treated with Nivo 3 mg/kg as part of the Russian Named Patient Program or 40 mg as part of a clinical trial (NCT03343665). Response was evaluated using PET-CT every 6 cycles (3 months).
The analysis identified 56 (35%) patients who achieved IR at first response evaluation according to LYRIC criteria after 3 months of therapy. Nivo dose was 3 mg/kg in 39 (70%) patients, 40 mg in 17 (30%) pts. There were 25 (45%) male and 31 (55%) female patients. Median age was 36 (23-64). Median time from diagnosis to Nivo was 33 (10-200) months. Thirty-nine (70%) patients were resistant to first-line chemotherapy. Prior to Nivo treatment brentuximab vedotin was administered in 24 (43%) patients and 15 (27%) patients underwent autologous HSCT. Stable disease (SD), partial response (PR) and progressive disease (PD) were in 1 (2%), 9 (16%) and 46 (82%) pts respectively. Extranodal disease was detected in 41 (73%) pts and B-symptoms in 37 (66%) pts. Median number of therapy lines was 4 (2-10).
Results: Two out of 56 pts discontinued Nivo at 3 months of therapy due to patient's decision. After 6 months of Nivo therapy 28 pts maintained IR, other variants of response are demonstrated in Picture 1. Nine patients with IR at 6 months discontinued Nivo due to discretion of the treating physician and continued different type of therapy. Among 19 pts with IR who continued Nivo therapy, at 9 months of treatment 15 pts retained IR. After 9 months of therapy Nivo was discontinued in 6 pts with IR due to discretion of the treating physician in 4 pts, secondary MDS in 1 pt and Named Patient Program closure in 1 pt. At 12 months of therapy 5 pts maintained IR, 2 pts transformed to PR and 2 pts to PD [Pic.1].
It is worth noting that biopsy was performed at the time of IR in 3 pts and tumor cells were found in all specimens.
Median follow-up was 36 (6-53) months. Three-year overall survival (OS) and progression-free survival (PFS) was 93% and 20%, respectively. Nivo dose was not associated with OS (p=0.76) or PFS (p=0.11). Disease status at the Nivo initiation was significantly associated with PFS (p=0.04), but not with OS. Extranodal disease presence was significantly associated with PFS (p<0.0001), but not with OS.



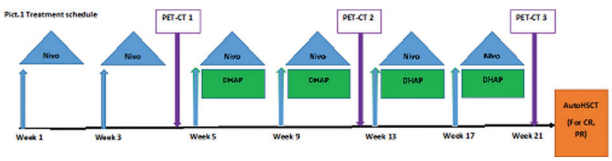
Summary/Conclusion: Patients with r/r cHL can maintain long-term stable clinical course during IR and Nivo therapy continuation despite the presence of tumor cells revealed in biopsy specimens. Thus, LYRIC criteria allow preventing early discontinuation of PD-1 inhibitor therapy in patients for which it could be potentially beneficial.

EP772 PRELIMINARY RESULTS OF THE COMBINATION OF NIVOLUMAB AND DHAP IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA (NIVO-DHAP) AS A SECOND-LINE THERAPY BEFORE AUTOLOGOUS HSCT

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Background: Immunotherapy with checkpoint inhibitors (anti-PD-1) is highly effective in relapsed/refractory (R/R) classical Hodgkin Lymphoma (cHL). Nivolumab, that was registered in Russia in december 2017, is widely used for this setting as a monotherapy. However, we have promising data about using Nivolumab in combination with different chemotherapy protocols as a bridge to autologous hematopoietic stem cell transplantation (autoHSCT), which remains the standard treatment for chemosensitive R/R cHL in the past decades.
Aims: To evaluate the safety and efficacy of Nivo-DHAP combination as a bridge to autoHSCT in patients with R/R cHL.
Methods: Study trial consisted of 2 cycles of Nivo as a monotherapy (fixed dose 240 mg every 14 days) with 4 subsequent cycles of Nivo-DHAP (fixed doses of Nivolumab 480 mg with standard doses of DHAP every 28 days). Response rate was assessed using PET-CT according to the Ligano and LYRIC criteria before Nivo-DHAP (PET-CT 1), after 2 cycles of Nivo-DHAP (PET-CT 2) and after 4 cycles of Nivo-DHAP (PET-CT 3). In case of chemosensitive disease at the end of the treatment, patients were proceeded to autoHSCT. Treatment schedule is represented at Picture 1. Cyclophosphamide+G-CSF, G-CSF alone or G-CSF+plerixafor were administered for stem cell mobilization. Safety assessment was carried out according to the toxicity criteria of the Common Terminology Criteria for Adverse Events (CTCAE) (v4.03). 20 patients treated from March 2020 until January 2021 were included in the preliminary analysis. All subjects provided written informed consent. Median age was 34 (21-55), male/female 12/8. 4 patients had more than 2 previous lines of therapy.
Results: The overall response rate was 75% (n=20, complete response (CR) 10%, partial response (PR) 65%, stabilization 20%, indeterminate response 5%) at PET-CT 1 (after 2 cycles of Nivo as a monotherapy). At PET-CT 2 (after 2 cycles of Nivo-DHAP) overall response rate reached 100% (n=20, CR 60%, PR 40%). At PET-CT 3 (after 4 cycles of Nivo-DHAP) it remains 100% (n=19, 1 patient is still on treatment). Hematological toxicity grade 3-4 was registered in 6 patients (30%), non-hematological toxicity were moderate (≤ grade 2): neurotoxicity – 3 (15%), nephrotoxicity – 2 (10%), skin toxicity – 1 (5%), endocrine disorders – 1(5%), infusion reactions – 1 (5%) patients respectively. Cytarabine and cisplatin doses were reduced in 5 patients (10-50% from baseline according to the standard approach). At the time of analysis, 13 patients underwent autoHSCT. In 2 patients stem cell mobilization failure was considered even with plerixafor administration.



Summary/Conclusion: Preliminary results of the combination of Nivolumab and DHAP showed high efficacy and relatively low toxicity in patients with R/R cHL before autoHSCT. We plan up to 40 patients in 2021 in order to obtain reliable data on the safety and efficacy of the regimen as well as to assess long-term survival and perform the retrospective comparative analysis with a group of patients who received the «traditional» DHAP without Nivolumab.

EP773 SUBCLINICAL COAGULATION DISORDERS IN NEWLY DIAGNOSED PATIENTS WITH HODGKIN LYMPHOMA (HL): A PHENOMENON RELATED TO THROMBOINFLAMMATION

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Background: Hodgkin lymphoma (HL) is characterized by an inflammatory syndrome, associated to advanced stages and B-symptoms and frequently manifested with increase in inflammation markers.
We observed in clinical practice, that HL patients frequently present at diagnosis with mild coagulation disorders, namely prolonged prothrombin time (PT) / INR and activated partial thromboplastin time (aPTT), which is not described as an established knowledge in textbooks.
Aims: We aimed to 1) analyze coagulation parameters [prothrombin time (PT), INR and activated partial thromboblastin time (aPTT)] in newly diagnosed HL patients in comparison to healthy individuals, 2) correlate them with clinical and laboratory parameters, and 3) investigate the possible underlying mechanisms.
Methods: Coagulation parameters (PT/INR, aPTT, fibrinogen, D-dimers) were determined and recorded in 80 consecutive patients with newly diagnosed HL before treatment initiation, compared to 225 healthy individuals and analyzed according to demographic data, clinical findings (histology, disease extent, IPS, B-symptoms) and laboratory parameters related to inflammation (hemoglobin, platelet and white blood cell count, ESR/CRP, albumin, α_2/γ-globulins, ferritin/haptoglobin). Coagulation factors (F)II, V, VII, X and TFPI were measured in plasma and serum with ELISA, respectively, in 35/80 patients.
Results: HL patients demonstrated increased median values of all parameters compared to controls: INR 1.12 vs 0.99 (p<0.001), aPTT 37.8 vs 33.9 (p<0.001) and fibrinogen 587.5 vs 303 (p<0.001). INR was elevated (>1.2) in 28.7% of patients, aPTT (>40 sec) in 32.9%, fibrinogen (>400 mg/dL) in 83.3% and D-Dimers (>0.5 μg/ml) in 54.4%. Elevated INR/PT, aPTT, and fibrinogen were observed more frequently in patients with advanced stages (IIB/III/V) and B-symptoms. INR and aPTT correlated strongly with all inflammation markers (Spearman's rho 0.25-0.53 and 0.26-0.38) except of leukocyte counts (and γ-globulins and ferritin for aPTT). Significantly increased levels of FII, FV and FX were observed in the majority of the patients (54.3%>88.6%), while FVII was found to be within normal limits and decreased in 1/35 patients. TFPI levels were also elevated in most cases (65.7%). A negative strong correlation between INR and FVII was noted (p<0.001). FII, FV, FX correlated with each other and with fibrinogen (p= 0.001-0.030), as well as with inflammation markers. No correlation was found between coagulation factor levels and clinical stage, B-symptoms or IPS, except the one of FX with high IPS (p=0.039).
Summary/Conclusion: Among HL patients 29-33% present with PT/INR and aPTT prolongation at diagnosis, which correlate with advanced stages, B-symptoms, and inflammation markers. This observation is of clinical importance because it prevents further unnecessary investigation. The observed negative correlation between INR and FVII, in combination with the increased levels of TFPI, suggests a possible role of TFPI in terms of excessive inhibition of TF/FVII complex. Notably, the increased levels of FII, FV, and FX correlate with inflammation markers. Taken together, the above data lead to the hypothesis that, prolonged PT/INR and aPTT are collateral findings related to disease activity and raised due to excessive activation of hemostasis in the context of thromboinflammation in HL. Similarly, the elevation of FII, FV, and FX is interpreted within thromboinflammation, which is seemingly in contrast

with the prolonged PT/aPTT, suggesting an underlying compensatory mechanism.

EP774 OUTCOME AND PROGNOSTIC FACTORS IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA WHO REMAIN PET/CT-POSITIVE AFTER 2 CYCLES OF ABVD: REAL-LIFE EXPERIENCE IN A MULTICENTER SETTING IN GREECE.

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Background: Positive PET/CT after 2 cycles of ABVD (interim PET, iPET) has a strong adverse prognostic significance in patients with advanced Hodgkin lymphoma (HL), who continue treatment with ABVD. These patients could be successfully salvaged by treatment escalation to BEACOPP, but more "real-life" data are needed in order to predict their outcome.
Aims: The aim of this study is the evaluation of treatment strategies, patient outcome and potential prognostic factors in iPET positive (iPET+) patients in 15 hematological departments of Greece.
Methods: This is a retrospective study of 282 patients with advanced HL according to GHSG (stages III/IV or IIB with bulky mediastinal and/or extranodal disease), who received 2 cycles of ABVD and underwent PET/CT. iPET was evaluated according to the Deauville 5-point scale score (D5PSS) and scores 4 and 5 were considered positive (residual uptake >liver). In case of PET positivity, further treatment strategy (intensification to BEACOPP or not) was at the treating physician's discretion, as this study reflects every-day clinical practice. However, consistent strategies have been followed within the same Department. Radiotherapy was also at physician's discretion.
Results: iPET was negative in 77% and positive in 23% of patients respectively. 62 out of 65 iPET(+) patients were ≤60 years old and consisted the study population, as they were eligible for treatment intensification. Of these patients, 37 received intensified treatment: 36 with BEACOPP (of whom 31 received BEACOPP-escalated, 2 BEACOPP-14 and 3 BEACOPP-baseline) and 1 with ESHAP. 25 patients continued with ABVD due to individual Department's treatment strategy (n=18), or, in 7 patients, because of treating physician's decision or due to misclassification as D5PSS 3. The 5-year progression free survival (PFS) was 53% in the whole population of iPET(+) patients. It was 59% vs 41% for patients who received intensified treatment or continued with ABVD respectively (p=0.09). In Departments which did not follow the treatment intensification strategy the 5-year PFS was 32% for patients who continued with ABVD. Patients who remained iPET(+) with D5PSS 4 had 5-year PFS 60% vs 37% for patients with D5PSS 5 (p=0.13). Apart from patient's age, no other potential prognostic factor associated with disease extent or aggressiveness affected the outcome of iPET(+) patients. Surprisingly, patients <45 years old had inferior outcome in univariate analysis. In multivariate analysis, D5PSS 5 (vs 4) was an independent adverse prognostic factor for PFS (HR: 2.789, 95% CI: 1.049-7.416, p=0.04), whereas continuation with ABVD vs treatment intensification was of borderline significance (HR: 2.434, 95% CI: 0.934-6.340, p=0.069).
Summary/Conclusion: Our study provides "real-life" data confirming the adverse outcome of iPET(+) patients as well as the remarkable efficacy of treatment intensification with BEACOPP-escalated. Of note, the 5-year PFS almost reached 60% despite the fact that the study included patients with "strictly" advanced-stage disease, without admixing early stages with adverse characteristics. Conventional prognostic factors may be replaced by different scores of iPET positivity. However, larger studies are needed in order to confirm and extend these results in order to draw safe conclusions.

EP775 TREATMENT OF HODGKIN DISEASE IN RELAPSE AFTER 3 LINES INCLUDING BRENTUXIMAB WITH DOSE DENSE PROTOCOL PLUS LENALIDOMIDE

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Background: Hodgkin disease, one of lymphoid malignancy that affects any age group with good results on standard chemotherapy. When relapse occurs, response rate decrease and survival becomes shorter. The introduction of anti-CD30 has improved results in relapsed patients; however, prognosis becomes very bad after further relapse.
Aims: to evaluate a new combination between dose-dense chemotherapy and lenalidomide in refractory Hodgkin lymphoma after at least 3 lines of chemotherapy and even after relapse on brentuximab
Methods: This is a prospective study conducted at Al Bairouni University Cancer Center in Damascus, Syria. We have included 75 patients with known HD in relapse after 3 lines of chemotherapy including Brentuximab. They received Cyclophosphamide 2gram/m^2 + Mesna uroprotection in day 1, Procarbazin 100mg/m^2 for 7 days, Gemcitabine 1000mg/m^2 on days 1 and 8, prednisolone 1mg/kg from day 1 through day 14 with G-csf support for 5 days from day 9 through day 13. Treatment is repeated every 21 days for 6 cycles. Lenalidomide at a dose of 10 mg daily was given upfront for 6 months.
Results: Complete response was documented in 52 patients (69.3%) and partial response in 12 patients (16%) while disease progressed in the remaining 11 patients. At 3 years of follow up, another 12 patients progressed with a progression free survival rate of 69.3% and 61 patients were found alive after 3 years with an overall survival rate of 81.3%. hematologic toxicities dominated the scene especially long term neutropenia and thrombocytopenia which decreased adherence to protocol to 85%. 10 out 75 patients received brentuximab as a 3rd line. 8 out of the 10 patients received brentuximab showed a complete response (p.value 0.05).among the 11 progressed patients, 6 had a pulmonary infiltration (p value 0.03)
Summary/Conclusion: In the light of good response rate and acceptable toxicity profile, we can recommend this combination as a 4th line treatment in relapsed HD patient and as a salvage in those candidates for peripheral stem cell transplant; however, larger number of patients is mandatory in order to generalize these results.

EP776 PET-STATUS AND PATIENTS WITH NEWLY HODGKIN LYMPHOMA (HL) PROGNOSIS: IS IT ALL THAT DEFINITIVE?

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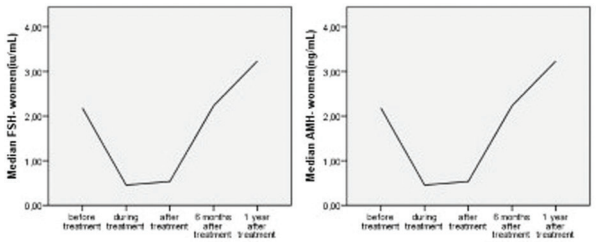
Background: Using PET in a metabolic response assessment has provided an opportunity of individualized treatment for patients with newly diagnosed HL. Current risk assessment systems cannot provide a reliable prediction of failure in an individual treatment. The main idea lying behind several PET protocol studies is identifying patients within a high-risk group and potential early relapse/refractory disease.
Aims: The primary endpoints were to assess a correlation between PET findings and response to therapy, type of regimen and clinical outcome, as well as whether there is a difference when patient treatment is intensified or not intensified depending on PET findings.
Methods: This sub-study was conducted in a scope of a broader prospective multicenter study on the predictive value of PET response assessment (205 patients with HL, up to 69 years of age). Patients received a treatment with ABVD or BEACOPP-14/esc or "switched-regimens" (ABVD+BEACOPP-esc/14, BEACOPP-esc/14+ABVD). Metabolic PET imaging was performed on routine protocols using Deauville criteria for response assessment.
Results: The ORR was 91.7%. The ORR for patients with stage I-II was 95.5% (106/111) vs 87.2% (82/94) for patients with stage III-IV.
In total, the disease progression occurred in 48.3% (15/31) of interim PET-positive (PET2+) patients and 11.5% (20/174) of interim PET-negative (PET2-) patients ($p<0.05$). We confirmed a significant difference between the 5-year event free survival (EFS) rate for patients with PET2+ vs PET2-. Thus, PET2- patients with early and advanced stages had an EFS level much higher than the PET2+ patient group (87% and 85% vs 55% and 15% respectively, Log-rank test, $p=0.0001$).
Using ABVD and "switched-regimens" for I-II-stage patients did not reveal a significant correlation to the 5-year EFS.However, a more intensified treatment for patients with stage III-IV of HL showed a significantly better level of EFS compared to the ABVD regimen, and it did not depend on PET2 status (Log-rank test, $p=0.0003$). Moreover, intermediate-risk group cohort (2B stage) tends to improve the EFS levels when the regimens was given BEACOPP-esc/14+ABVD vs ABVD+BEACOPP-esc/14 vs ABVD (80% vs 60% vs 55% respectively, $p=0.064$) and was independent of PET2 status.
End-of-treatment PET-negative (PET3-) status was found in 83.8% (130/155) of the study group patients and 16.1% (25/155) had the end-of-treatment PET-positive (PET3+), respectively ($p<0.05$). Using the Cox regression, we confirmed a significant correpatienlation between the EFS with PET3 status and ABVD regimen. 1-year EFS for this group of ts with PET3+ was worse than PET3-(15% vs 83% respectively, $p<0.0001$). Additionally, the combination of ABVD and radiotherapy for early stages has improved the EFS rate compared to sole ABVD treatment without radiation (86% compared 60%, $p=0.013$) based on PET3 status.
Summary/Conclusion: Our results of PET use with primary HL patients have demonstrated a high prognostic value of the interim and end-of-treatment PET. For intermediate-risk group and advanced stages in particular, the efficiency of treatment intensification improves regardless of their PET status.

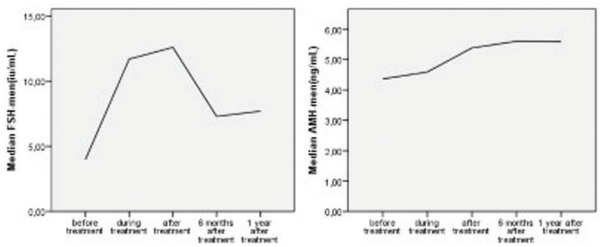
EP777 EVALUATION OF GONADAL FUNCTION IN YOUNG MEN AND WOMEN DIAGNOSED WITH HODGKIN LYMPHOMA

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Background: ABVD or escBEACOPP chemotherapy +/- radiation is the treatment approach for patients with Hodgkin lymphoma (HL). As a result of treatment improvement, there are many long-term survivors, in whom treatment-related complications are recognized. Among these, gonadal insufficiency plays a fundamental role, with major psychological/social consequences. This is more prevalent in female patients, in whom collection and cryopreservation of oocytes or ovarian tissue are usually not applied in everyday clinical practice. Evidence-based data are scarce on this subject. Moreover, little is known about the kinetics of gonadal function and sex hormones during chemotherapy to safely guide contraceptive measures.
Aims: The aim of this study is the prospective evaluation of gonadal function in young men and women with hematological malignancies receiving chemotherapy. We here present the preliminary results on 45 patients with Hodgkin lymphoma.
Methods: This is a prospective study of gonadal function in HL patients, with an age limit of ≤40 years in women and ≤45 years in men. Hormonal measurements were performed at pre-specified time points: before treatment, during chemotherapy, at the end of chemotherapy and every six months for the following three years. The following hormones were measured: follicle-stimulating hormone (FSH), lutenizing hormone (LH), progesterone (PG), estradiol (E_2), anti-Mullerian hormone (AMH) in women and FSH, LH, testosterone, AMH and inhibin–β in men. The study included: 19 women [median age: 27 years, 19 ABVD] and 26 men [median age: 30 years, 26 ABVD]. FSH reflects gonadal function in both men (Sertoli cells) and women (increased levels indicate gonadal dysfunction). AMH is considered as the most sensitive biomarker for gonadal reserve in women (decreasing values correlate with ovarian insufficiency), but its exact role in men is not clarified. E2 and testosterone are the major sex hormones.
Results: Women: FSH values increased between the beginning and the end of treatment (median value: 4.35IU/mL, 7.7IU/mL, $p=0.001$). FSH increased from the beginning, peaking in the middle and remaining high until the end, without reaching normal levels six months after the end. Consistently with FSH, AMH showed a decrease during treatment: [median values: 1,92IU/mL (start), 0,18IU/mL (middle), $p=0.000$], maintained low levels through the rest of the treatment and slowly reached normal values six months later. Estradiol was not affected.
Men: Spermatogenesis, reflected by the increase of FSH, was affected: [median values: 3,7IU/mL (start), 11IU/mL (middle), 15IU/mL (end), fsh0-1 $p=0.000$, fsh0-2 $p=0,000$]. FSH increased during treatment, reaching a peak towards the end. FSH did not reach normal values after six months ($p=0,017$), but only after one year. Contrary to women, AMH values gradually increased during treatment: [median values: 4,13IU/mL (start), 4,28IU/mL (middle), 5,61IU/mL (end), $p=0.001$] and remained high until six months after the end of treatment. Most surprisingly, testosterone increased (start, middle, end: 430ng.dl, 534ng/dl, 596ng/dl, 0-1 $p=0,003$, 0-2 $p=0,002$ respectively).





Summary/Conclusion: Gonadal function in patients with HL is affected during chemotherapy in both sexes. In women, both FSH and AMH indicate gonadal dysfunction for at least 6 months after chemotherapy; AMH proved as a more sensitive marker compared to FSH. In men, gonadal function returned to baseline levels at one year after chemotherapy. However, in men, unexpectedly, AMH and testosterone significantly

increased during treatment, possibly reflecting destruction of Leydig cells.

EP778 ENDOCRINE DISORDERS IN HODGKIN LYMPHOMA SURVIVORS

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Background: Current treatment options for Hodgkin's lymphoma are mostly effective, but may have a negative pronounced damaging effect on some organs. Long-term effects of antitumor therapy in HL survivors include secondary cancers, cardiovascular and pulmonary disorders, neurological complications, and endocrine and gonadal dysfunctions. Endocrine late effects with hormonal disturbances, could have many physical and social consequences for HL survivors.
Aims: To assess the prevalence and risk factors of endocrine disorders in HL survivors.
Methods: The study evaluated the functioning of the endocrine system in 160 patients with HL (55 male and 105 female) aged 18 to 65 years after chemoradiotherapy. The clinical examination included a biochemical analysis of blood, test of serum hormones (THS, T3, free T4, PTH, FSH, LH, free testosterone, DHEA-S, SHBG) by ELISA, BMD was assessed by dual-energy X-ray absorptiometry.
Results: The structure of endocrine pathology in patients with HL included primarily hypothyroidism (25%), hyperparathyroidism (15,6%) and hypogonadism (29% of male and 25.3% of female). Dysfunction of the hypothalamic-pituitary-thyroid axis occurred significantly more often in patients after combined chemoradiotherapy than in patients receiving chemotherapy only ($\chi 2=9,4$, p=0,002). We found that increased levels PTH was negatively correlated with BMD in the lumbar spine (r = -0,74, p = 0,00002) and in the femoral neck (r = -0,66, p = 0,0003). The men with HL had lower free testosterone than controls (p=0,04). However, LH and FSH levels in male with HL were elevated: p = 0,0004 and p = 0,04, respectively. Women of reproductive age with HL had higher levels of LH in the luteal phase (p = 0,05) and a higher levels of FSH in the follicular phase (p = 0,02) than controls.
Summary/Conclusion: The high prevalence of endocrine disorders in HL survivors demonstrates the necessity to develop screening programs for early treatment of endocrine pathology in patients with HL, as well as the participation of endocrinologists in the follow-up and treatment of this category of patients.

EP779 GERMAN EVIDENCE-BASED LIVING GUIDELINE ON DIAGNOSIS, THERAPY AND FOLLOW-UP OF ADULT PATIENTS WITH HODGKIN LYMPHOMA

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Background: The German guideline for diagnosis, treatment and follow-up of adult patients with Hodgkin Lymphoma is an evidence-based guideline that is updated according to the living guideline principle. The guideline was first published in February 2013, and updated in June 2018. The second update (presented here) was published in October 2020; a third update will follow in 2021.
Aims: To keep recommendations on diagnosis, treatment and follow-up up-to-date and in line with new clinical research evidence.
Methods: The guideline was developed and updated jointly by a number of different national clinical and methodological experts. In March 2019, the systematic literature search was updated and conducted in MEDLINE, Embase und CENTRAL. After independent screening by methodological experts, the newly identified evidence was presented to the clinical working groups of the guideline. Subsequently, data was extracted from all studies that contributed to the clinical research questions of the guideline, and evaluated according to GRADE principles. Based on these results, new recommendations were derived and existing recommendations updated. All unmodified, updated and new recommendations were revised, discussed and voted on in a formal consensus process by a clinical expert panel from the participating professional societies. The guideline was funded by the German Cancer Aid (funding number 113332).
Results: The updated guideline entails 168 recommendations in total; thereof 29 updated and 13 new recommendations. The new recommendations concern patients in the intermediate stages, pregnant patients and rehabilitation measures. In patients with intermediate risk, a PET/CT-guided radiotherapy approach can be applied, if treated with two cycles of $BEACOPP_{escalated}$ followed by two cycles of ABVD ("2+2"). Thus, after chemotherapy with "2+2", an interim PET/CT scan shall be performed. Only those patients with a positive (Deauville-Score ≥4) interim PET/CT scan-result shall receive consolidation radiotherapy. For pregnant patients who are diagnosed in their first trimester of pregnancy, start of chemotherapy should be delayed until the beginning of the second trimester, if justifiable. For pregnant patients who are diagnosed in their second or third trimester, chemotherapy can be administered. Whether or not awaiting delivery is an option, shall be decided individually. If chemotherapy is administered, it should be stopped at the latest between the 35th and 37th week of pregnancy, or two weeks before delivery. Radiotherapy should be avoided during pregnancy. Patients who receive chemotherapy during pregnancy, can receive consolidation radiotherapy after delivery, but there should not be more than 12 weeks between completion of chemotherapy and start of radiation therapy. Prematurity, particularly before the 32nd week of pregnancy, should be avoided. Furthermore, pregnant patients shall undergo close obstetric monitoring, in addition to standard examinations. After therapy, all patients shall be offered medical rehabilitation to enable social reintegration and participation in work life.
Summary/Conclusion: Living guideline in the sense of a regular, standardized process in a defined time frame provides current recommendations for the treatment of different patient groups, which should be translated into daily clinical practice. As far as possible, guideline implementation will be monitored by recommendation-based quality indicators measured by cancer registries or certification systems.

EP780 TREATMENT OUTCOMES OF HODGKIN LYMPHOMA: PET GUIDED DE-ESCALATION IN REAL WORLD

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Background: Acceptance of de-escalating therapy in the REAL world has been slow due to the limited access and cost of PET scans.
Aims: To audit Hodgkin Lymphoma (HL) characteristics and 5-year outcomes in a single tertiary cancer center.
To study the outcomes of patients who underwent PET directed therapy compared to patients who received standard 6 cycles of ABVD therapy
Methods: 1396 lymphomas (>18 years) were entered in the *Onco-Collect* data base of patients receiving 1st line treatment from May 2011 to December 2017. Demography, Clinical features, staging, prognostic stratification, and first line treatment response and outcomes of 280 HL patients treated at a tertiary center have been analyzed. A PET directed approach was followed for patients receiving ABVD therapy. Early stage (1 and 2) patients received 4 or 6 cycles and in Late stage (3 and 4) received ABVD x 6 cycles or ABVD followed by AVD in patients who were in complete remission after 2 cycles.
Overall Response (OR) rates, and DFS were evaluated for patients receiving 1st line treatment, and these patients were followed till September 2020.
Results: HL formed 20% of the lymphoma cohort receiving 1st line treatment at our Institute. The median age was 37 years at presentation and age distribution was 53%, 39% and 8% respectively for <40 years, between 40 to 65 years and ≥ 65 years of age. Gender ratio for male to

female was 2.18:1. 41% Patients presented in early stage [I & II], and 58% in late stage [III &IV].
Most common protocol used was standard ABVD in 90% patients. The OR rate (CR +PR+ SD) was 89.2%, and the progression on treatment 6.8%. With a median follow-up of 48 months, the DFS is 79.36%. DFS for the patients above 65 years was 62% at 5 years and for those below 65 years was 76% (p=0.052). The 5-year DFS for stage 1, 2, 3 and 4 was 94.73%, 85.57%, 78.81% and 67.78% respectively (p=0.017). Patients with early-stage disease receiving 6 cycles (#55) had similar outcomes at 5 years compared to patients receiving 4 cycles +/- radiotherapy (#34). Outcomes for late-stage disease, after the omission of bleomycin after 2 cycles in patients achieving PET CR was comparable to patients receiving 6 cycles of ABVD
Summary/Conclusion: HL presents at a median age of 37 years in the adults ≥18 years and the bimodal peak is not seen in our population. The OR to treatment is nearly 90%, with CR in 76% patients. Our initial experience with de-escalation of therapy have yielded encouraging results in the REAL world setting. Long term outcomes for Stage 3 & 4, can be improved with chemotherapy escalation strategies or use of targeted molecules and immune therapy.

EP781 THE PROGNOSTIC VALUE OF PD-L1 AND PD-L2 LOCI ALTERATIONS IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA TREATED WITH NIVOLUMAB

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Background: PD-1 inhibitors represent an effective option in the treatment of relapsed and refractory classical Hodgkin lymphoma (r/r cHL). The chromosomal alterations in 9p24.1 (PD-L1 and PD-L2) locus were shown to be a characteristic feature of malignant Reed-Sternberg (RS) cells, and considered as a potential predictive marker of immunotherapy efficiency in the limited number of reports.
Aims: The aim of the current study was to investigate the prevalence and the type of 9p24.1 alterations in severely the pretreated population of r/r cHL patients receiving nivolumab (nivo) during Russian named patient program, as well as to assess their influence on the efficiency of immunotherapy
Methods: This retrospective analysis included 46 patients with r/r cHL who were treated with nivo (26 female and 20 male). The median age was 30 (14-64). The histological types of cHL in this cohort were nodular sclerosis in 84,8% (n=39), mixed cellularity 8,7% (4), lymphocyte rich 4,3% (2), and lymphocyte depleted in 2,2% (1). An advanced disease at initial diagnosis was in 65,2 % (n= 30) of patients; 56,5% (n=26) of patients had primary resistant disease. The median number of previous lines of therapy was 5 (2-10). In 7 patients, the tumor biopsy was performed at the disease progression after immunotherapy with subsequent 9p24.1 locus analysis. Determination of the type of alteration in the biopsies was carried out according to the protocol presented in the previously published studies (Roemer MG, et.al. 2016).
Results: The alterations of the PD-L1 and PD-L2 loci were observed in all analyzed tumor specimens before and after nivo treatment. The type of alteration observed before immunotherapy was polysomy in 9% (n = 4), copy gain - in 69% (n = 32), amplification - in 22% (n = 10) of cases. The comparison of 9p24.1 alteration structure before and after immunotherapy showed an increase in the number of cases with 9p24.1 locus amplification (1/7 before vs. 4/7 after, p=0,14).
The analysis of the association of 9p24.1 alterations with the clinical outcomes was performed. There was a significant difference in progression-free survival among patients according to alteration type (p = 0.02): for 9p24.1 amplification, a 3-year PFS was 20% (95% CI 3.1- 47%) with median of 20.6 months (95% CI 6.6-35.6), for copy gain a 3-year PFS was 34% (95% CI 18-50%) with median PFS 23.8 months (95% CI 6.6- 35.6) and for polysomy, a 3-year PFS was 0% with a median PFS 7.2 months (95% CI 4.3-NE). However, the statistically significant influence of alteration type on best overall response was not observed (p = 0.2).
There was no significant dependences between alteration type and analyzed clinical factors, including initial disease stage (p = 0.86), the initial presence of B-symptoms (p = 0.78), and the primary refractory disease (p = 0.98). Despite the limited number of patients, a significant association (p = 0.03) of chromosomal alterations with the histological type of cHL was observed in the analyzed population: in all cases of 9p24.1 amplification, the nodular sclerosis type of cHL was confirmed during the histological investigation.
Summary/Conclusion: The polysomy of 9p24.1 may be considered as a negative prognostic factor regarding progression-free survival in a limited population of patients. The dynamics of 9p24.1 locus alterations before and after nivolumab therapy, as well as their association with the histological type of classical Hodgkin lymphoma were described.

Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

EP782 IBRUTINIB PLUS RITUXIMAB (IR) VS PLACEBO PLUS RITUXIMAB (R) FOR WALDENSTROM'S MACROGLOBULINEMIA (WM): FINAL ANALYSIS AFTER FIVE YEARS OF FOLLOW-UP FROM THE RANDOMIZED PHASE 3 INNOVATE STUDY

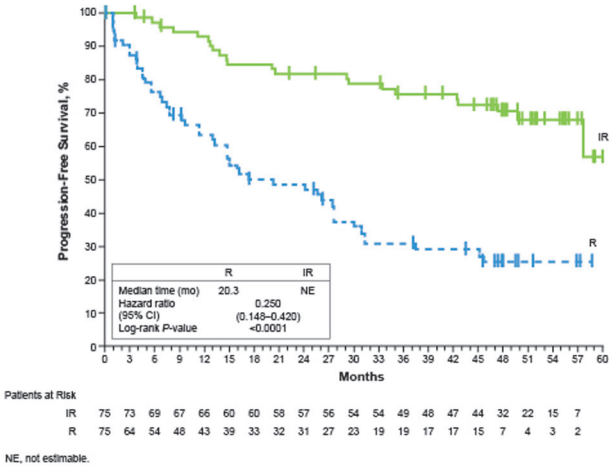
R. García-Sanz [1,*], C. Buske [2], A. Tedeschi [3], J. Trotman [4], D. MacDonald [5], V. Leblond [6], B. Mahe [7], C. Herbaux [8], J. V. Matous [9], C. S. Tam [10], L. T. Heffner [11], M. Varettoni [12], M. L. Palomba [13], C. Shustik [14], E. Kastritis [15], S. P. Treon [16], J. Ping [17], B. Hauns [17], I. Arango-Hisijara [17], M. A. Dimopoulos [15]

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Background: Ibrutinib is a once-daily Bruton's tyrosine kinase inhibitor approved as either a single agent or in combination with rituximab (R) for treatment of patients (pts) with WM across all lines of therapy. In the primary analysis of the phase 3 iNNOVATE™ study (NCT02165397; median follow-up 26.5 mo), IR demonstrated superior progression-free survival (PFS) vs placebo plus R in pts with WM.
Aims: We present results from the final analysis of the randomized arms of iNNOVATE.
Methods: Pts with confirmed symptomatic WM were randomized (75 pts per arm) to once-daily ibrutinib 420 mg or placebo plus R (375 mg/m^2/wk IV at weeks 1–4 and 17–20). Pts could receive first-line treatment or be previously treated; pts with prior R therapy had to have achieved at least a minor response (MR) to their last R-based regimen. Endpoints included PFS and response rates per Independent Review Committee, overall survival (OS), hemoglobin (Hgb) improvement, time to next treatment (TTNT), and safety. Change in serum IgM was also assessed.
Results: Pt characteristics were well balanced between arms. After a median follow-up of 50 mo (range 0.5+ to 63), median PFS had not been reached (NR; 95% CI 57.7 mo to not estimable) with IR vs 20.3 mo (95% CI 13.0–27.6) with R (hazard ratio [HR] 0.25 [0.15–0.42]; *P*<0.0001) (**Figure**); 54-mo PFS rates were 68% vs 25%. PFS benefit with IR vs R was independent of prior treatment status (HR [95% CI]: first-line, 0.32 [0.14–0.70]; previously treated, 0.22 [0.11–0.43]) or genotype (HR [95% CI]: MYD88^{L265P}/CXCR4^{WT},

0.18 [0.08–0.43]; MYD88^{L265P}/CXCR4^{WHIM}, 0.27 [0.12–0.62]; MYD88^{WT}/CXCR4^{WT}, 0.29 [0.07–1.19]). Improved PFS with IR was observed across prespecified subgroups, including age, serum IgM, Hgb, IPSSWM, and MYD88 mutation status. Major response rates (≥partial response) with IR increased and were sustained over time, reaching 76% vs 31% with R (P<0.0001); overall response rates (≥MR) were 92% vs 44% (P<0.0001). A greater proportion of pts achieved sustained Hgb improvement with IR vs R (77% vs 43%; P<0.0001). IgM decreased rapidly during the first year; maximum change was –33.5 g/L with IR (56 mo) vs –26.9 g/L with R (57 mo). Median OS was NR in either arm; 54-mo OS rates were 86% with IR vs 84% with R. Median TTNT was NR with IR and 18 mo with R; 87% of pts receiving IR and 29% receiving R had not received subsequent treatment at 54 mo. Thirty-five pts (47%) on R crossed over to single-agent ibrutinib after disease progression. The safety profile of IR was consistent with previous reports. The prevalence of grade ≥3 AEs of clinical interest with IR generally decreased over time. Of 12 pts with grade 3–4 atrial fibrillation, 9 (75%) remained on treatment; no other ibrutinib discontinuations due to common (≥10%) grade 3–4 AEs occurred. 88% of AEs that led to an ibrutinib dose reduction resolved following dose reduction. After study closure, 68 pts (45%) remained on treatment (32 in an extension study; 36 in a commercial setting).

Figure. PFS per IRC by treatment group



NE, not estimable.

Summary/Conclusion: With up to 5 years of follow-up, IR showed ongoing superiority across clinical outcomes in pts with WM regardless of genotype, prior treatment, and key pt characteristics. Similar patterns of response with IR were observed in pts receiving first-line treatment and in previously treated pts. No new safety signals were observed; IR maintained a manageable safety profile after an additional 24 months of follow-up.

EP783 PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (MAGNOLIA STUDY)

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Background: BCR signaling mediated through Bruton's tyrosine kinase (BTK) plays a critical role in the development and maintenance of marginal zone lymphoma (MZL). BTK inhibitors have established activity in relapsed/refractory (R/R) MZL with the phase 2 study of ibrutinib demonstrating an objective response rate (ORR) of 48% (Noy et al. *Blood*. 2017;129:2224-2232).

Zanubrutinib is a potent and highly specific next-generation BTK inhibitor designed with greater selectivity for BTK vs TEC- and EGFR-family kinases, which are thought to be related to off-target toxicities. Therapeutic activity of zanubrutinib was established in an early-phase study (BGB-3111-AU-003) of 20 patients (pts) with R/R MZL demonstrating an ORR of 80%, with a complete response (CR) rate of 15%, and partial response (PR) rate of 65% (Tedeschi et al. EHA 2020, abstract 2804).

Aims: To present initial efficacy and safety results in pts with R/R MZL enrolled in MAGNOLIA (BGB-3111-214).

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study of adults with R/R MZL who had received ≥1 line of therapy including ≥1 CD20-directed regimen. All were treated with zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Use of long-term antiplatelet and anticoagulation agents was permitted. The primary end point was ORR determined by an independent review committee in accordance with the Lugano classification. Secondary end points include ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), and safety.

Results: As of January 11, 2021, 68 pts were enrolled and treated. Median age was 70 years (range, 37-95), with 28% aged ≥75 years. Subtypes included extranodal (mucosa-associated lymphoid tissue; 38%), nodal (38%), splenic (18%), and indeterminate (6%) MZL. Median number of prior therapies was 2 (range, 1-6) and 32% of pts had disease that was refractory to last therapy.

Median duration of drug exposure was 59.1 weeks (range, 3.7-84.1). Sixty-six pts were evaluable for efficacy. At a median study follow-up of 15.5 months (range, 1.6-21.7), investigator-assessed ORR (CR + PR) was 74% (CR 24%, PR 50%, stable disease 17%). Responses were observed in all subtypes, with an ORR of 68%, 84%, 75%, and 50% in extranodal, nodal, splenic, and indeterminate subtypes, respectively. CR rate was 36% for extranodal MZL, 20% for nodal, 8% for splenic, and 25% for indeterminate subtype. Median DOR and PFS were not reached; 15-month PFS was 68% and 12-month DOR was 81%. IRC review is ongoing.

Twenty-eight (41%) pts discontinued treatment: 20 due to disease progression, 1 withdrew consent, 3 required prohibited medications, 4 due to adverse events (AEs; 2 due to COVID-19 pneumonia, 1 due to pyrexia attributed to disease transformation, and 1 due to myocardial infarction [MI]). The most common (≥10%) treatment-emergent AEs reported were diarrhea (22%), bruising (21%), constipation (15%), pyrexia (13%), abdominal pain (12%), upper respiratory tract infection (12%), back pain (10%), and nausea (10%). Most AEs were grade 1 or 2. Neutropenia was the most common grade ≥3 AE (10%). Two pts

died from COVID-19 pneumonia and 1 pt with pre-existing coronary artery disease died from MI. No fatal AEs were considered related to zanubrutinib. All-grade AEs of interest included neutropenia (13%), thrombocytopenia (13%), atrial fibrillation/flutter (3%), and hypertension (3%). No major/serious hemorrhage was reported. No AEs led to dose reductions.

Table: Baseline Characteristics, Efficacy, and Safety Outcomes

	R/R MZL (N = 68)[a]
Baseline Characteristics	
Male sex, n (%)	36 (52.9)
ECOG PS 0-1, n (%)	63 (92.6)
Bone marrow involvement, n (%)	29 (42.6)
Efficacy (investigator assessment)	**(N = 66)[b]**
ORR, n (%) [95% CI]	49 (74.2) [61.99, 84.22]
Best response, n (%)	
CR	16 (24.2)
PR	33 (50.0)
SD[c]	11 (16.7)
PD	5 (7.6)
Discontinued study before first assessment	1 (1.5)
Time to response (months), median (range)	2.8 (1.7, 8.5)
Safety[d]	**(N = 68)[a]**
Any AE	65 (95.6)
Grade ≥3 AE, n (%)	26 (38.2)
Serious AE, n (%)	25 (36.8)

AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease, PR, partial response; R/R, relapsed/refractory; SD, stable disease.
[a] Safety analysis set is defined as all patients who received at least one dose of study drug.
[b] Efficacy-evaluable set is defined as patients who received at least one dose of study drug and with centrally-confirmed diagnosis of MZL (2 patients were excluded due to MZL transformation to diffuse large B-cell lymphoma).
[c] Three patients with stable disease were continuing on study treatment.
[d] Treatment-emergent AEs including AEs that had an onset date or worsening of severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after study drug discontinuation or initiation of a new anticancer therapy. Worsening of an event to Grade 5 beyond day 30 after last dose of study of a treatment-emergent adverse event is also considered a treatment-emergent adverse event (if it is prior to new anticancer therapy start).

Summary/Conclusion: Zanubrutinib demonstrated high response rates and durable disease control with a favorable safety profile in pts with R/R MZL.

EP784 PRELIMINARY CLINICAL DATA FROM A PHASE 1B STUDY OF MAVORIXAFOR AND IBRUTINIB IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA WITH MYD88 AND CXCR4 MUTATIONS

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Background: Waldenström macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by increased clonal IgM-secreting cells. Though other covalent and noncovalent BTK inhibitors (BTKi) are in development for WM, ibrutinib is the only BTKi approved by the FDA and EMA for WM. Most patients with WM (>90%) have somatic mutations in *MYD88*, and a subset (≤40%) also have WHIM-like activating mutations in *CXCR4* (*CXCR4*^{WHIM}). The presence of *CXCR4*^{WHIM} impacts response to BTKi in WM, as manifested by delayed response, inferior depth of response, and/or shorter progression-free survival. Inhibition of CXCR4 has been shown to sensitize *CXCR4*^{WHIM}-expressing cells to ibrutinib. Mavorixafor, an oral small-molecule antagonist of CXCR4, has been shown to inhibit CXCL12 binding and ERK hyperactivation for many *CXCR4* mutations in vitro.
Aims: This study examines the safety and efficacy of mavorixafor in combination with ibrutinib in patients with WM with *MYD88* and *CXCR4* mutations.
Methods: This phase 1b, open-label, multicenter, single-arm study (NCT04274738) examines intra-patient dosing, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of mavorixafor in combination with ibrutinib. Eligibility includes age ≥18 years, clinicopathological WM diagnosis, consensus criteria indication for treatment, measurable disease, 0–3 prior therapies, confirmed *MYD88*^{L265P} and *CXCR4*^{WHIM} mutations, and ability to provide written informed consent. Patients are initiated on mavorixafor 200 mg and ibrutinib 420 mg, both oral and once-daily (QD). Mavorixafor escalation to 400 mg occurs after 28 days if no dose-limiting toxicities (DLTs) are observed and to 600 mg after 400 mg is deemed safe (<2/6 DLTs). Patients are followed for adverse events (AEs) and change from baseline in IgM, PK, and PD (peripheral white blood cell [WBC] counts).
Results: At data cutoff (January 22, 2021), 7 patients have enrolled; all continue on study. All 7 patients were escalated to 400 mg, with 6 remaining at 400 mg and 1 de-escalated to 200 mg (median exposure, 90 days). None have yet escalated to 600 mg. A total of 56 AEs were observed (84% grade 1 severity). Of 50 AEs with complete assessment for causal relationship to study drugs, 4 were deemed related to mavorixafor only, 7 to ibrutinib only, and 18 to the combination. A single patient experienced all events attributed to mavorixafor only (all grade ≤2 GI events). Only 1 DLT was observed, consisting of grade 3 hypertension with definitive attribution to ibrutinib and possible attribution to mavorixafor. No AEs led to study discontinuation, and no serious AEs were observed. Six out of 7 patients showed decrease in IgM after 1 cycle. Four patients were treated for ≥3 cycles; all had decrease in serum IgM, with 2 achieving a ≥50% decrease from baseline consistent with partial response after 3 cycles (median decrease, 51.0%; range, 4.4%–84.5%). Mavorixafor and ibrutinib exposures were consistent with previous reports, and combination treatment increased peripheral lymphocytes, neutrophils, and monocytes.
Summary/Conclusion: Our findings to date in patients with WM carrying both *MYD88* and *CXCR4* mutations show that mavorixafor in combination with ibrutinib is well tolerated at doses up to 400 mg QD. Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies, suggesting no drug–drug interactions, and mavorixafor exposures tracked with increases in key WBC counts. Combination of mavorixafor with ibrutinib led to rapid and clinically meaningful decrease in IgM levels, suggesting that mavorixafor may sensitize *CXCR4*^{WHIM}-expressing cells to BTKi.

EP785 ROLE OF MAINTENANCE RITUXIMAB (MR) AFTER FIRST-LINE (1L) BENDAMUSTINE + RITUXIMAB (BR) OR R-CHOP IN PATIENTS (PTS) WITH MANTLE CELL LYMPHOMA (MCL) FROM A LARGE US REAL-WORLD (RW) COHORT

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Background: Maintenance with rituximab (MR) after 1L R-CHOP improved overall survival (OS) in both young and elderly pts with MCL in clinical trials. How MR is used in routine clinical practice and the benefits of MR after 1L BR are less defined.
Aims: To evaluate the RW patterns and outcomes of MR after 1L BR or R-CHOP in a large US MCL cohort.
Methods: This retrospective study included adult pts with MCL diagnosed Jan 2011-Nov 2020 in the nationwide Flatiron Health EHR-derived deidentified database. MR is defined in pts who received 1L induction combination with R, and R was continued as monotherapy for ≥28 days. Pt characteristics, treatment patterns, RW time to next treatment (rwTTNT, defined as start of 1L treatment to subsequent treatment

or death), and rwOS were evaluated for pts treated with 1L BR or R-CHOP±MR ("entire cohort"). Considering the potential for selection biases in the application of MR, analyses were also performed in pts who were alive and did not initiate subsequent treatment within 8 months of starting 1L BR or within 6 months of 1L R-CHOP ("MR-eligible cohort"). Multivariate analyses (MVA) were performed for rwTTNT/OS on the effects of MR adjusting for age, ECOG PS, LDH, WBC, and blastoid/pleomorphic and bulky disease status.

Results: Among 2946 pts with documented 1L MCL treatment, 86.3% were from community oncology setting. In the entire cohort, 854 pts received BR alone (median duration of treatment [mDOT]: 4.1 months), 368 received BR+MR (mDOT: 25.7 months), 365 received R-CHOP alone (mDOT: 3.5 months), and 147 received R-CHOP+MR (mDOT: 26.9 months). Median age of pts starting 1L BR±MR (72.8 years) was older than pts starting 1L R-CHOP±MR (66.4 years). A lower proportion of pts receiving BR+MR had high-risk MCL international prognostic index (MIPI; 26.0% vs 38.0%) and blastoid/pleomorphic MCL (4.9% vs 7.5%) vs BR alone. With estimated median follow-up of 39.8 months (range 0.03-117.1) for BR±MR and 61.0 months (range 0.03-115.0) for R-CHOP±MR, the 36-month rwTTNT rate was the highest with BR+MR (72%), followed by R-CHOP+MR (68%). Median rwTTNT was reached at 17.0 and 7.8 months for BR and R-CHOP alone, respectively.

In the MR-eligible cohort, 590 pts received BR alone (mDOT: 4.67 months), 365 received BR+MR (mDOT: 25.8 months), 207 received R-CHOP alone (mDOT: 4.0 months), and 145 received R-CHOP+MR (mDOT: 26.9 months). Disease characteristics of intermediate/high MIPI or blastoid/pleomorphic biology were similar among those treated with BR/R-CHOP only vs those with BR/R-CHOP+MR (Table). MVA showed that MR was independently associated with longer rwTTNT (hazard ratio [HR] 0.45; 95% confidence interval [CI], 0.38-0.53; p <0.001) and rwOS (HR 0.56; 95% CI, 0.45-0.7; p <0.001). With estimated median follow-up of 38.9 months (range 0.03-117.1) for BR±MR and 64.3 months (range 0.03-115.0) for R-CHOP±MR, the 36-month rwTTNT rate was 73% for BR+MR and 69% for R-CHOP+MR. Estimated median rwTTNT was reached at 36 and 21.5 months for BR and R-CHOP alone, respectively. The 36-month rwOS rate was 84% for BR+MR, 76% for BR alone, 89% for R-CHOP+MR, and 76% for R-CHOP alone.

Table. Baseline characteristics and clinical outcomes in the MR-eligible cohort

	MR-eligible cohort			
	BR N = 590	BR+MR N = 365	R-CHOP N = 207	R-CHOP+MR N = 145
Baseline characteristics				
Median age at LOT 1, years	73.2	71.9	66.4	67.7
Bulky disease, n/N (%)	82/577 (14.2)	63/362 (17.4)	31/203 (15.3)	20/142 (14.1)
ECOG PS ≥ 2, n/N (%)	34/307 (11.1)	14/181 (7.7)	5/66 (7.6)	3/69 (4.3)
MIPI intermediate risk, n/N (%)	65/156 (41.7)	47/100 (47.0)	18/35 (51.4)	19/37 (51.4)
MIPI high risk, n/N (%)	51/156 (32.7)	26/100 (26.0)	12/35 (34.3)	12/37 (32.0)
Blastoid/pleomorphic MCL, n (%)	29 (4.9)	18 (5.0)	23 (11.1)	12 (8.3)
Clinical outcomes				
36-month rwTTNT rate, % (95% CI)	50 (45-55)	73 (68-78)	37 (30-45)	69 (62-78)
36-month rwOS rate, % (95% CI)	76 (72-81)	84 (80-89)	76 (69-82)	89 (84-95)

LOT, line of therapy.

Summary/Conclusion: This is the largest RW cohort of pts with MCL who were treated with 1L BR or R-CHOP followed by MR. MR was associated with improved rwTTNT and rwOS. The best rwTTNT rate was seen with 1L BR+MR. The phase 3 SHINE study (NCT01776840) is evaluating the potential benefit of adding ibrutinib to BR with R maintenance in pts with previously untreated MCL.

EP786 KTE-X19 VERSUS STANDARD OF CARE FOR RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA PREVIOUSLY TREATED WITH BRUTON TYROSINE KINASE INHIBITORS: REAL-WORLD EVIDENCE FROM EUROPE

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Background: Patients with mantle cell lymphoma (MCL) who progress after receiving a Bruton tyrosine kinase inhibitor (BTKi) have generally poor prognosis. KTE-X19, an autologous anti-CD19 chimeric antigen receptor T cell therapy, is being evaluated in patients with relapsed/refractory (R/R) MCL who received 1–5 prior therapies including a BTKi (phase II multicenter, single arm ZUMA-2 trial). Results for 60 efficacy-evaluable patients with ≥12 months of follow-up have been previously reported (Wang et al., ASH 2020, Abstract 1120). After a median follow-up of 17.5 months, the estimated overall survival (OS) rate at 15 months was 76%; median OS was not reached.

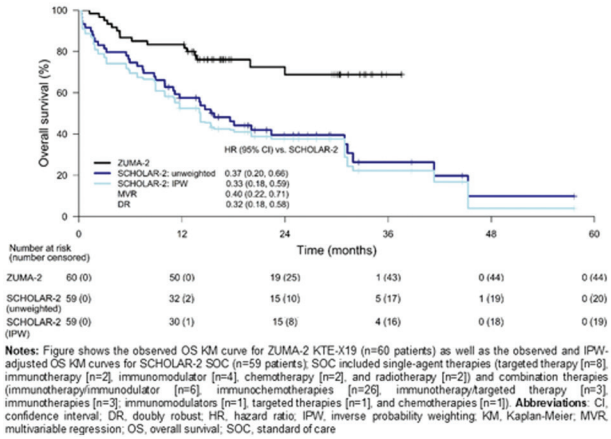
Aims: To estimate and compare effectiveness of treatment of R/R MCL post-BTKi with KTE-X19 versus active standard of care (SOC) in a real-world patient cohort in Europe, based on individual patient data.

Methods: The estimated clinical efficacy of KTE-X19 came from ZUMA-2, and real-world data on the effectiveness of SOC across Europe was collected in a retrospective, observational, multicenter chart review (SCHOLAR-2). An SOC cohort was constructed to closely match the patients enrolled in ZUMA-2 (patients with ECOG 0–1 and a minimum of 12-month potential follow-up from initiation of active therapy post-BTKi). A naïve (unadjusted) comparison was performed as a benchmark, followed by three separate comparisons using inverse probability weighting (IPW), multivariable regression (MVR), and doubly robust methods designed to adjust for imbalances in prognostic factors across the two non-randomized populations. Survival times were summarized using Kaplan-Meier curves. Cox proportional hazards models were used to estimate the effect of KTE-X19 relative to SOC with outcomes presented as hazard ratios (HRs) along with the 95% confidence intervals (CIs).

Results: Clinical data from 288 R/R MCL patients treated with a BTKi between July 2012–July 2018 were collected in SCHOLAR-2 across 24 centres in Denmark, France, Germany, Italy, Spain, Sweden, and the United Kingdom. The SOC cohort included 59 patients who received their first subsequent active treatment(s), referred to as SOC, prior to July 2019. Baseline characteristics were median age of 63 years, 73% male, 46%/54% ECOG 0/1, 82% stage III–IV disease, 36% with a prior autologous stem cell transplant (ASCT), and 95% with ≥2 prior lines of therapy. The median number of prior lines of therapy including BTKi was 3 (range: 1–6). Median duration on prior BTKi was 7.3 months, and the ORR to prior BTKi was 40%. In ZUMA-2, baseline characteristics were median age of 65 years, 85% male, 97% Stage III-IV, median of 3 prior lines of therapy, 43% prior ASCT, and median duration of 7 months on prior BTKi with ORR of 37%.

At a median follow-up of 27.6 months from initiation of SOC in SCHOLAR-2, the median OS was 15.7 (95% CI: 10.0–30.9) months; 15-month OS rate was 52%. Results of the naïve, unweighted, comparison showed that KTE-X19 was superior to SOC with an OS HR of 0.37 (95% CI: 0.20–0.66; p<0.001). The IPW-adjusted median OS in SCHOLAR-2 was 14.2 (95% CI: 8.8–30.9) months. With the IPW approach (base-case), the HR was 0.33 (95% CI: 0.18–0.59; p<0.001), consistent with the naïve analysis. The HR estimates were also consistent across sensitivity analyses using the MVR and doubly robust models (Figure 1).

Figure 1: Kaplan-Meier curves of overall survival in ZUMA-2 (KTE-X19) and SCHOLAR-2 (standard of care)



Notes: Figure shows the observed OS KM curve for ZUMA-2 KTE-X19 (n=60 patients) as well as the observed and IPW-adjusted OS KM curves for SCHOLAR-2 SOC (n=59 patients); SOC included single-agent therapies (targeted therapy [n=8], immunotherapy [n=2], immunomodulator [n=4], chemotherapy [n=2], and radiotherapy [n=2]) and combination therapies (immunotherapy/immunodulator [n=6], immunochemotherapies [n=26], immunotherapy/targeted therapy [n=3], immunotherapies [n=3]; immunomodulators [n=1], targeted therapies [n=1], and chemotherapies [n=1]). **Abbreviations**: CI, confidence interval; DR, doubly robust; HR, hazard ratio; IPW, inverse probability weighting; KM, Kaplan-Meier; MVR, multivariable regression; OS, overall survival; SOC, standard of care

Summary/Conclusion: This analysis suggests that KTE-X19 can improve survival over current active SOC in Europe for the treatment of R/R MCL in patients who have previously received BTKi therapy.

EP787 OUTCOMES WITH KTE-X19 IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA IN ZUMA-2 WHO HAD PROGRESSION OF DISEASE WITHIN 24 MONTHS OF DIAGNOSIS

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Background: KTE-X19 is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the United States and European Union for the treatment of relapsed/refractory mantle cell lymphoma (MCL). In the ZUMA-2 study in which KTE-X19 was evaluated in relapsed/refractory MCL, the objective response rate at a median 17.5-month follow-up period was 92% (67% complete response rate; *Blood*. 2020;136[suppl, abstr]:20-22).
Aims: To report results in patients with or without progression of disease within 24 months of diagnosis (POD24), an indicator of poor outcomes (*Br J Haematol*. 2019;185:940-944).
Methods: Eligible patients with relapsed/refractory MCL underwent leukapheresis and conditioning chemotherapy followed by a single infusion of KTE-X19. Efficacy results are reported for the 60 treated patients with ≥1 year of follow-up (median, 17.5 months), and safety results are presented for all 68 treated patients.
Results: High-risk disease characteristics were common in patients with (n=33) and without POD24 (n=35), although patients with POD24 had higher tumor burden and lactate dehydrogenase levels, and more had blastoid-type MCL (Table). The objective response rate in patients with (n=28) and without POD24 (n=32) was 93% and 91%, with complete response rates of 61% and 72%, respectively. In patients with and without POD24, median progression-free survival was 11.3 months (range, 0.9–30.3) and 29.3 months (range, 0–35.9), respectively. Medians for duration of response and overall survival were not reached in either group.
Most common Grade ≥3 adverse events in patients with versus without POD24 were neutropenia (91% vs 80%), thrombocytopenia (61% vs 46%), and anemia (55% vs 51%); Grade ≥3 cytokine release syndrome and neurologic events occurred in 9% versus 20% and 27% versus 34%, respectively. There were no cases of Grade 5 cytokine release syndrome, KTE-X19–related secondary cancers, or replication-competent retrovirus in either group.
In patients with versus without POD24, median peak CAR T-cell levels and median area under the curve were 53.4 cells/mL (range, 0.2–2566) and 583.4 cells/mL (range, 1.8–27,743.6) versus 112.4 cells/mL (range, 0.2–2589) and 1588.3 cells/mL (range, 3.8–27,238.7), respectively; by 12 months, B cells were detectable in 8/11 (73%) vs 7/15 patients (47%) in ongoing response.

Table

Characteristics	With POD24 (n=33)	Without POD24 (n=35)
Median age, year	65	66
Median prior therapies, n	3	3
Received ≥3 prior therapies, %	88	74
Ibrutinib	85	86
Acalabrutinib	21	26
Ibrutinib and acalabrutinib	6	11
Auto-SCT	36	49
Disease stage III/IV, %	97	97
Extranodal disease, %	52	60
LDH ≥1.5×ULN, %	24	9
Intermediate-/high-risk MIPI, %	48	63
MCL morphology, %		
Classical	48	69
Pleomorphic	6	6
Blastoid	33	17
Median tumor burden (SPD), mm² (range)	2254.6 (260–14,390)	1380.2 (293–16,878)
Ki-67 proliferation index, %	(n=23)	(n=20)
≥50%	74	65
≥30%	83	81
TP53 status	(n=20)	(n=16)
Mutated, %	15	19

LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; POD24, progression of disease within 24 months of diagnosis; SCT, stem cell transplant; SPD, sum of product diameters; *TP53*, tumor protein 53 gene; ULN, upper limit of normal.

Summary/Conclusion: KTE-X19 provided a high complete response rate across all patients, with the medians for duration of response and overall survival not reached. Patients with POD24 had more aggressive high-risk disease characteristics (tumor burden, lactate dehydrogenase levels, and blastoid-type MCL) and generally lower CAR T-cell expansion and progression-free survival versus patients without POD24. Earlier intervention with CD19-directed CAR T-cell therapy may benefit patients with MCL with known high-risk factors.

EP788 EARLY SAFETY AND EFFICACY FINDINGS OF AUTO1 (CAT19), A FAST-OFF RATE CD19 CAR, IN RELAPSED / REFRACTORY INDOLENT B CELL LYMPHOMAS

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Background: We have previously described AUTO1 (CAT19), a CD19 CAR with a fast off-rate CD19 binding domain, designed to reduce CAR T-cell immune toxicity and improve engraftment. Its clinical activity has been tested in r/r paediatric and adult B-ALL. Cumulatively, this data confirms the intended fucntion of the receptor, with low levels of CRS/ICANS and long-term engraftment of CAR T-cells observed in both patient groups. Recently, CAR therapy has been explored in indolent lymphomas such as follicluar (FL) and mantle cell lymphoma (MCL), but a high incidence of toxicity inluding Grade 3-4 ICANS has been reported.

Aims: We have initiated testing of AUTO1 (CAT19) in the setting of indolent B-cell lymphoma (NCT02935257).
Methods: Manufacturing: CAR T-cell products were generated using a semi-automated closed process from non-mobilised leucapheresate. **Study design:** subjects>/=16y underwent lymhpodepletion with fludarabine (30mg/m2 x3) and cyclophosphamide (60mg/kg x1) followed by a single CAR T-cell infusion of 200 x10^6 CD19 CAR T-cells. Study endpoints include feasibility of manufacture, grade 3-5 toxicity and remission rates at 1 and 3 months.
Results: As of 18 February 2021, we recruited 10 patients of median age 57 years (range 39-68y), 7 with FL and 3 with MCL. Patients had received a median of 3 prior lines (range 2-5) and all patients had stage III/IV disease at screening. Apheresis and product manufacture was successful in all 10 patients and 9 patients were infused: 7 with FL and 2 with MCL. Grade1 CRS was reported in 4/9 and Grade 2 CRS in 1/9. 1/9 developed MAS which resolved with anakinra/dexamethasone. No ICANS was observed on study. Excellent CAR engraftment was observed and 9/9 patients were in CMR by 18FDG PET-CT post-treatment. At a median of 3.1 months (range 1-5.6m), 8/9 patients are in ongoing remission. One patient died in CMR at month 5.6 of COVID-19.
Summary/Conclusion: AUTO1 (CAT19) has a tolerable safety profile in adult patients with r/r low grade B-cell lymphoma despite high disease burden. Early data shows 100% complete remission rates and excellent CAR engraftment/expansion. Additional patients, updated data and longer follow up will be presented.

EP789 ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL): LONG-TERM EFFICACY AND SAFETY RESULTS FROM A PHASE 2 STUDY

Y. Song [1,*], K. Zhou [2], D. Zou [3], J. Zhou [4], J. Hu [5], H. Yang [6], H. Zhang [7], J. Ji [8], W. Xu [9], J. Jin [10], F. Lv [11], R. Feng [12], S. Gao [13], H. Guo [14], L. Zhou [14], J. Huang [14], W. Novotny [14], R. Wei [14], J. Zhu [1]

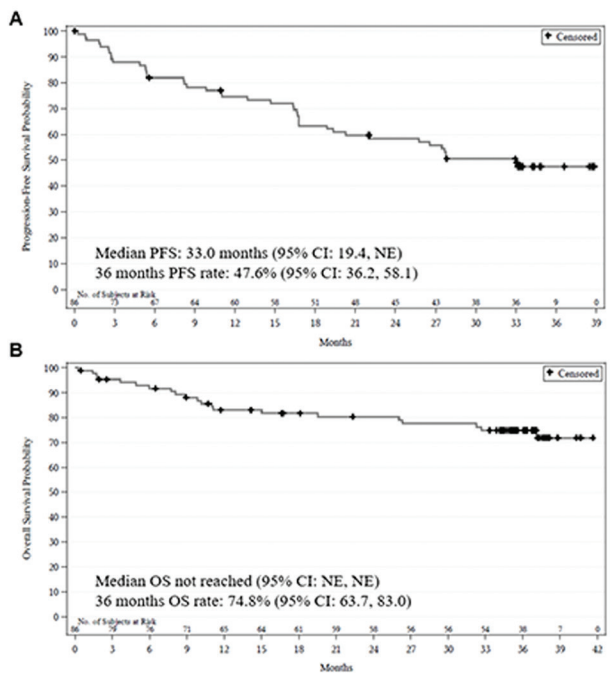
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Background: Zanu is a highly selective, potent and irreversible Bruton tyrosine kinase inhibitor approved in the United States and China for treatment of adult pts with R/R MCL. Phase 2 study results of zanu showing high activity in R/R MCL (median follow-up (mfu), 18.4 mo) were previously reported (*Clin Cancer Res*. 2020;26:4216). We present here long-term results of this study (mfu, 35.3 mo).
Aims: To evaluate the sustainability of efficacy and long-term safety of zanu in pts with R/R MCL.
Methods: In this single-arm, multicenter phase 2 study (NCT03206970), pts received oral zanu (160 mg twice a day) continuously until progressive disease (PD) or unacceptable toxicity. Response assessments per 2014 Lugano criteria were performed every 12 wk for 96 wk, and every 24 wk thereafter. ORR rate (investigator-assessed ≥ partial response), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety were assessed.

Results: Eighty-six pts were enrolled at 13 centers in China. Median age was 60.5 y, and 83.7% had an intermediate-/high-risk Combined MCL International Prognostic Index score (MIPI-b). Most pts had advanced MCL (90.7% stage III/IV); 45.3% had bone marrow involvement, and 70.9% had extranodal disease. Bulky disease >10 cm and >5 cm was found in 8.1% and 43.0% of pts, respectively. Median number of prior lines of therapy was 2 (range, 1-4), and 52.3% of pts had refractory disease.
As of Sep 8, 2020, mfu was 35.3 mo (range, 0.3-41.6); 45.3% of pts were on zanu, and 54.7% had discontinued zanu primarily due to PD (43.0%) and adverse events (AEs; 9.3%). ORR was 83.7%,and 67 (77.9%) pts achieved complete response. Median DOR was not reached; 57.3% (95% CI, 44.9-67.9) of responders were estimated event (PD/death)-free at 30 mo. Median PFS was 33.0 mo (**Fig A**); response was generally consistent across all subgroups analyzed (MIPI-b, prior therapy, refractory status, etc). Median OS was not reached (**Fig B**).
The safety profile was largely unchanged vs that of the previous mfu. The most common (≥20%) treatment-emergent AEs (TEAEs) were decreased neutrophil count (46.5%), upper respiratory tract infection (38.4%), rash (36.0%), decreased white blood cell count (33.7%), and decreased platelet count (32.6%); most were grade (gr) 1/2 events. Gr ≥3 TEAEs (≥5%) were decreased neutrophil count (18.6%), pneumonia (12.8%), platelet count decreased, white blood cell count decreased (7.0% each), and anemia (5.8%). Most AEs occurred during the early stage of zanu treatment and very few new events were reported during this follow-up period. Four new pts had gr ≥3 TEAEs of any infections (18.6% total, 65.1% all gr), and no new pt had gr ≥3 TEAEs of hypertension (3.5% total, 16.3% all gr) or major hemorrhage (serious/gr ≥3 bleeding or all gr central nervous system bleeding; 3.5% total). No cases of atrial fibrillation/flutter, gr ≥3 cardiac AEs, second primary malignancies, or tumor lysis syndrome were reported throughout this study. No new TEAEs led to death (8.1% total), treatment discontinuation (9.3% total), or dose reduction (2.3% total); 3 new pts had dose interruption during this follow-up period (18.6% total).

Figure

Figure: (A) Progression-Free Survival **(B)** Overall Survival



Summary/Conclusion: These data continued to show the deep response with zanu in pts with R/R MCL that was generally consistent across all subgroups, including high-risk pts. The long-term follow-up show that sustained PFS was achieved with zanu treatment, and about half of pts remained progression free at 36 mo. The new TEAEs reported during the follow-up period were limited; there were no new safety concerns.

EP790 HIGH-RISK MANTLE CELL LYMPHOMA IN THE LYMA TRIAL: A LYSA STUDY.

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Background: Around 5-10% of mantle cell lymphoma (MCL) patients are primary refractory to chemotherapy. They have an extremely dismal prognosis, similar to responsive patients that relapsed within 12 months. Despite better understanding of risk factors and evolving classifications, these scores could not predict all high-risk patients and were not designed to guide treatment strategy in newly diagnosed MCL.
Aims: We conducted an ancillary study in a prospective phase III trial randomizing observation versus Rituximab maintenance after R-DHAP followed by ASCT (NCI NCT00921414; LyMa Trial; Le Gouill et al, NEJM 2017). Herein, we report our study of high-risk MCL patients.
Methods: High-risk MCL patients were defined as being primary chemo-refractory or having relapsed within 12 months following randomization (Visco BJH 2018; Eskelund ICML 2019). Patient's characteristics at baseline, treatment at relapse and outcomes were assessed. Survivals of high-risk versus control MCL patients were compared.
Results: Among the 299 MCL patients included in the LyMa trial, 31 high-risk MCL patients were identified (10.4%). Their characteristics at baseline were similar to control patients (n=268), regarding age, performance status, Ann Arbor staging, presence of B symptoms (p = NS). High-risk patients had more often elevated LDH (65% vs. 38%, p=0.006), high-risk MIPI score (45% vs. 16%, p < 0.001), Ki-67 > 30% (71% vs. 31%, p < 0.001) and blastoid/pleomorphic histology (32% vs. 9%, p < 0.001). In multivariate analysis, high-risk MIPI score and Ki-67 > 30% were associated with high-risk MCL. There was no significant difference in terms of TP53 expression between high-risk and control MCL. Many high-risk MCL patients have been classified as low-risk at diagnosis, with 36% of them having a low-risk MIPI score, 68% having a classic histology and 29% having a Ki-67 ≤ 30%. High-risk patients had more often positive MRD pre-ASCT in blood (47.1% vs. 20.6%, p=0.029) but not in the BM (50% vs. 34.9%, p=0.26) and had more positive PET pre-ASCT (48% vs. 25.6%, p=0.032). Median OS was 17 months in high-risk MCL patients, compared to 68 months in late progressors ((95% CI, 12 to 26 months vs. 47 to not reached respectively, p < 0.001). At relapse, 11/31 (36%) had a CNS involvement. Salvage therapies consisted of chemotherapy in 26 patients (CHOP, MTX-AraC, bendamustine, VR-CAP), rituximab in 26, temsirolimus in five, lenalidomide and combination of ibrutinib and lenalidomide in two other patients, as second line therapy. Ibrutinib was also used in two other patients as third line. Overall response rate was 37%, with 27% of complete response. Seven patients received allogeneic stem cell transplantation, of whom four died, from toxicity in two and from lymphoma in two. Median PFS and OS were 19.2 months and not reached for responding patients compared to 3.2 and 8.2 months for stable/progressive disease respectively.
Summary/Conclusion: Known risk factors do not perfectly identify high-risk MCL patients at baseline. High-risk patients with early disease progression had an extremely dismal prognosis and should receive innovative strategies combined with systematic CNS prophylaxis as salvage therapy.

EP791 UPDATED OUTCOMES WITH AXICABTAGENE CILOLEUCEL (AXI-CEL) RETREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA IN ZUMA-5

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Background: ZUMA-5 is a Phase 2 study of axi-cel anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL; follicular lymphoma [FL]; marginal zone lymphoma [MZL]). In the primary analysis, 11 patients (9 FL; 2 MZL) were retreated with axi-cel, achieving an overall response rate (ORR) of 100% (91% complete response [CR] rate) at a median follow-up of 2.3 months post-retreatment, with no Grade ≥3 cytokine release syndrome (CRS) or neurologic events (Chavez et al. ASH 2020. #2036).
Aims: To report updated clinical and translational outcomes with longer follow-up of axi-cel retreatment in patients with R/R iNHL in ZUMA-5.
Methods: Eligible adults with FL or MZL had R/R disease after ≥2 lines of therapy. Patients were considered for retreatment if they progressed after a response at month 3, had no evidence of CD19-negative relapse in biopsy, had no axi-cel–neutralizing antibodies, and had no Grade 4 CRS or neurologic events with first treatment. Retreatment was per investigator discretion. At both treatments, patients received axi-cel (2×10^6 CAR T cells/kg) after conditioning chemotherapy.
Results: As of 9/14/2020, 13 patients with iNHL (11 FL; 2 MZL) received axi-cel retreatment, with 2 patients retreated after the primary analysis. Before their first treatment, patients had median 4 prior lines of therapy; 85% had stage 3–4 disease; 82% had FLIPI of ≥3; 46% were POD24, and 77% had refractory disease.
Among the 13 retreated patients, 85% had a CR to first treatment. Median first duration of response (DOR) was 8.2 months. Detectable CD19 was confirmed in all evaluable biopsies from retreated patients at relapse, and median time from first treatment to retreatment was 10.6 months. Following retreatment, the ORR was 100% (77% CR rate). After a median follow-up of 11.4 months, the median DOR had not yet been reached; 46% of retreated patients had ongoing responses at data cutoff.
At first treatment, CRS occurred in 9 patients (5 Grade 1, 4 Grade 2); neurologic events occurred in 5 (3 Grade 1, 1 Grade 2, 1 Grade 3). At retreatment, CRS occurred in 8 patients (6 Grade 1, 2 Grade 2); neurologic events occurred in 4 (3 Grade 1, 1 Grade 2). Median peak levels of biomarkers typically associated with severe CRS and neurologic events were similar at retreatment and first treatment (IL-6, 7.7 vs 5.7 pg/mL; IL-2, 1.8 vs 0.9 pg/mL; IFN-γ, 62.9 vs 64.2 pg/mL).
In the 11 retreated patients with FL, tumor burden (median sum of product diameters [SPD]) was lower before retreatment vs first treatment (1416 vs 4770 mm^2). Engraftment index (CAR T-cell expansion relative to sum of product diameters) is an indirect proxy for effector:target ratio and a key covariate of response to axi-cel (Locke et al. *Blood Adv*. 2020). Although median peak CAR T-cell levels appeared lower at retreatment vs first treatment (5.2 vs 14.3 CAR+ cells/μL blood), engraftment index was similar (0.003 vs 0.005 cells/μL×mm^2).
Summary/Conclusion: Axi-cel retreatment achieved deep and durable responses, with an acceptable safety profile. Tumor CD19 positivity was maintained at relapse, and engraftment index was similar at both treatments, comparing favorably to previous reports in aggressive lymphomas (Locke et al. ASCO 2020. #8012). These data suggest axi-cel retreatment is a promising option for patients with R/R iNHL.

EP792 A PHASE IISTUDY OF A SELECTIVE PI3KΔ INHIBITOR YY-20394 IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA.

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Background: Although many new therapies are being investigated for patients with relapsed/recurrent (/r) follicular lymphomas (FL), effective treatment options are very limited.The oral highly selective PI3Kd inhibitor YY-20394, was previously evaluated in a Phase1 dose escalation study, and demonstrated an acceptable safety profile and notable efficacy. In this study, we report on the topline data from an ongoing Phase 2 study of YY-20394 under investigation in patients with relapsed or refractory FL with at least 2 prior systemic treatments.
Aims: To evaluate the efficacy and safety of YY-20394 in FL patients.
Methods: Informed consent was obtained for all patients of the study. YY-20394 was given 80mg orally once daily (QD) with 28 days cycle until disease progression, unacceptable toxicity or withdrawal from the study. Adverse events (AEs) were graded by NCI-CTCAE v5.0. Efficacy was assessed according to IRWG criteria by the Independent Review Committee (IRC).
Results: As of a data cut-off of February 22, 2021, the study was fully enrolled (93 patients) with 89 patients evaluable for efficacy. For the 93 r/r FL patients, the median age is 50.4 years (range 29-78); 61.3% (57/93) are male and 38.7% (36/93) are female and all are Asian. At baseline, the majority of patients had an ECOG performance status of 0 (55.9%, 52/93) or 1 (40.9%, 38/93) and were classified as Ann Arbor-Cotswolds stage III (21.5%, 20/93) or IV (73.1%, 68/93). Nearly all patients (98.9%, 92/93) had grade 1, 2, or 3a FL; only 1 out of 93 patients had transformed to grade 3b high-grade lymphoma. Patients had received a median of three lines of prior treatment regimens (range 2-20), with 34 patients (34.6%) having received four or more lines of prior treatment regimens. Thirty-three percent of patients (31 out of 93 patients) had refractory disease after their last treatment regimen. All patients had received prior rituximab and alkylating agents. Three patients (3.2%) had undergone HSCT.
For the 89 evaluable patients, efficacy was determined by IRC. Complete response (CR) were achieved in 11 patients (12.4%), partial response (PR) in 60 (67.4%), stable disease (SD) in 15 (16.1%), and progressive disease (PD) in 3 (3.2%), for an Overall response rate (ORR) of 79.8% (95% confidence interval [CI] 58.5-83.0%) and a disease control rate (DCR) of 96.6%. The median time to response (TTR) is 1.87 months (range 1.66-5.60 months). All the patients have had at least 6 months of follow-up. The median time to disease progression has not been determined yet because 50.5% (47 out of 93) patients are still receiving YY-20394 treatment, and nearly two thirds of the 93 patients had a treatment duration of > 6 months at the cut-off date. The treatment duration for 29 subjects were more than 300 days, with the longest treatment duration of 637 days to date.
Among all 93 enrolled patients with r/r FL in the phase II study, the most common nonhematologic TEAEs (all grades /grade≥3) were pneumonia (24.7%/17.2%), ALT elevation (17.2%/2.2%), hypertriglyceridemia (23.7%/3.2%), hyperglycemia (18.3%/2.2%), rash (14.0%/2.2%), diarrhea (15.1%/1.1%), pneumonitis (0%/5.4%). Gr≥3 hematologic TEAEs were neutropenia (14.0%), thrombocytopenia 1.1%),) and leukopenia (5.4%).
Summary/Conclusion: YY-20394 is well tolerated with a promising objective response rates in patients with relapsed or refractory follicular lymphoma. Clinical trial information: NCT04370405

EP793 PREVALENCE OF SECOND CANCER DURING LONG TERM FOLLOW-UP IN HAIRY CELL LEUKEMIA PATIENTS TREATED WITH CLADRIBINE: A THIRTY-YEAR EXPERIENCE

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Background: Hairy cell leukemia (HCL) is a rare lymphoproliferative disease with an excellent prognosis after therapy with purine analogs. Conflicting results have been published concerning second cancer in these patients: several studies have showed an increase of second cancer during long term follow-up.
Aims: The aim of the study is to report on the prevalence of second cancer among HCL patients treated with cladribine (2CDA) in first line in the last 30 years.
Methods: We retrospectively reviewed data of patients treated with 2CDA between March 1991 and May 2019 at 18 Italian Hematological centers. All patients consented to the study.
Results: Among 553 patients reported, only 513 were evaluable because treated with 2CDA alone. M/F ratio was 4.5 with a median age of 54 years (range 24-88) and ECOG was 0 in 85% of cases. Twenty-seven (5%) patients were diagnosed with a previous cancer: no relapse was reported during follow-up.
At a median follow-up of 6.96 years (range 3.81-12.47), 19 second neoplasms were reported in 18 patients (3.5%), a percentage that is lower than what reported in the literature. No cases of relapse of a previous cancer were reported. Six patients had a cancer of urinary tract (4 prostate, 2 kidney, 1 bladder), 5 had a GI cancer (1 esofagus, 1 stomach, 3 colorectal), 4 had an hematological neoplasm (2 multiple myeloma, 1 mantle cell lymphoma and 1 diffuse large B cell lymphoma), 2 had breast cancer and 1 had lung cancer. Moreover, precancerous lesions were reported in 1.2% of patients: 4 presented with skin cancer (3 basocellular carcinoma and 1 dysplastic nevus), 1 with pleomorfic parotid adenoma and 1 with colorectal displastic adenoma. No therapy-related myeloid neoplasms were observed.

Surgical therapy alone was a curative option in 8 patients, while chemotherapy alone was reported in 5 cases. A combination of surgery and chemotherapy +/- hormone therapy was used in 5 cases.
Median OS of the population was not reached; 95.7%, 92.8% and 82.3% of patients are expected to be alive at 5, 10 and 15 years, respectively. Among 45 patients which died during follow-up, 6 cases (1.2%) were due to second cancer.
We compared our data with that reported by the Italian registries of cancer for the same period of observation. Among the general population, the cumulative standard incidence of cancer was 704.4 casesx100.000 inhabitants for males and 484.7 casesx100.000 inhabitants for females. In our population, the cumulative standard incidence of cancer other than HCL was 543.3 x 100,000 (IC 95%: 283.6-803.1) for males and 492.6 x 100,000 (IC 95%: 0.0-1099.0) for females. No statistically significant differences were identified between the two cohorts.
Summary/Conclusion: While 2CDA is greatly effective in treating HCL, the occurrence of second cancer is rare. The cumulative incidence of second neoplasms in our population did not significantly differ from that reported among the Italian population.

EP794 RISK FACTORS FOR POD24 IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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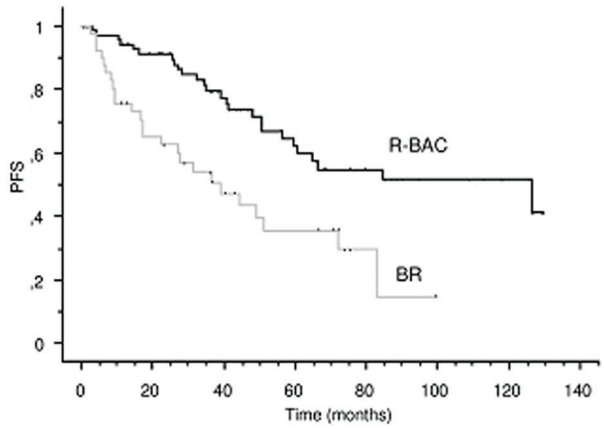
Background: Follicular lymphoma (FL) is an indolent non-Hodgkin's lymphoma with heterogeneous outcomes. Progression of disease within 24 months (POD24) is strongly associated with poor outcome. Therefore, prediction of POD24 at diagnosis is essential to support the precision medicine treatment strategies making in clinical practice. However, risk factors associated with POD24 remain uncertain in FL patients.
Aims: To perform a systematic review and meta-analysis to identify the potential risk factors for POD24 in FL patients.
Methods: Comprehensive literature search in Embase, Medline and the Cochrane Library was performed from database inception to 1 September, 2020 to identify prognostic studies in patients with newly diagnosed grade 1-3a FL. The interested outcome was POD24. For studies not reporting POD24, we attempted to synthesize the association between risk factors and any progression within 24 months that defined by original studies. This study protocol has been registered on PROSPERO with registration number PROSPERO CRD42021231824.
Results: A total of 96 studies reporting 81 prognostic factors were included, among which 11 factors were eligible for meta-analysis. Results showed that elevated sIL-2R (HR 2.48; 95% CI, 1.74-3.54; p< 0.0001 [7 studies]), total metabolic tumor volume (TMTV) >510mL (HR 2.17; 95% CI, 1.60-2.95; p<0.0001, [5 studies]), elevated β2m (HR 4.14; 95% CI, 2.07-8.28; p<0.0001 [4 studies]), elevated LDH (HR 3.05; 95% CI, 1.63-5.71; p=0.0005, [4 studies]), grade 3a (HR 2.22; 95% CI, 1.31-3.74; p=0.0030, [3 studies]), lymphoma-associated macrophages (LAM)/ high -power field(HPF) ≥15 (HR =4.13; 95% CI, 1.92-8.88; p=0.0003, [2studies]), Vitamin D insufficiency (<20 ng/ml) (HR=2.66; 95% CI, 1.44-4.92; p=0.0020, [2studies]) were significantly associated with an increased risk of POD24. Absolute lymphocyte count (ALC)/Absolute monocyte count (AMC) ratio (cutoff:4.7), sex, and EZH2 mutation status, effector T-cell gene expression (two studies for each factor) were found not to be significantly associated with POD24.
Summary/Conclusion: To our knowledge, this is the first study that comprehensively analyses the risk factors associated with POD24 in FL patients. Results from this meta-analysis confirmed significant association between 7 factors and POD24. Our findings may contribute to the development of an optimized risk stratification model of FL POD24 in the future.

EP795 RITUXIMAB, BENDAMUSTINE, AND CYTARABINE (R-BAC) COMPARED WITH RITUXIMAB AND BENDAMUSTINE (BR) IN PREVIOUSLY UNTREATED ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA (BE-VE-BAC STUDY)

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Background: Both rituximab plus bendamustine (BR), and rituximab, bendamustine, and cytarabine (R-BAC) are considered suitable induction therapies in elderly patients with mantle cell lymphoma (MCL), according to most recent ESMO and NCCN clinical practice guidelines. However, a direct comparison between the two regimens, either prospective or retrospective, has never been performed.
Aims: To compare the outcome and the safety features of patients with newly diagnosed MCL treated with BR or R-BAC between 2009 and 2020 in 7 Departments from north-east of Italy.
Methods: This is a multicenter retrospective observational study. The two regimens (BR and R-BAC) represented routinary induction regimens in the selected centers for patients with MCL not candidate to autologous transplant. Primary endpoint was 2-years progression-free survival (PFS). All patients treated with at least one cycle of either BR or R-BAC were included, provided they had a minimum follow-up of 12 months since start of treatment. Response was based on Lugano criteria. Due to the retrospective nature of the study, treatment assignement to one therapy instead of the other was based on local doctor decision. Inclusion bias were estimated by a propensity score stratified by gender, age, MCL morphology, and MIPI score.
Results: 137 patients with MCL with a median age of 72 years (range 53-90) were retrospectively analyzed. According to our propensity score calculation, the probability of receiving R-BAC was higher in younger patients (P<0.0001), but no other significant difference in the distribution of above mentioned prognostic variables was observed between the two groups. Therefore, we limited our survival analysis to patients with 80 years or less, which allowed us a fair comparison between the two groups (P=NS). This cohort included 115 patients (42 BR, 73 R-BAC) that represented the subjects for the present analysis. Of them, 76 (66%) were males, MIPI was elevated in 61%, 15% had blastoid or pleomorphic morphology, and median follow-up was 48 months (range 12-133). Patients treated with R-BAC achieved CR in 93% of cases, as compared with 55% for BR (P<0.0001). The 2-years PFS was 91%±3% and 63%±7% for R-BAC and BR, respectively (P=0.0007, Figure 1). Median overall survival (OS) was 125 months for R-BAC and 78 months for BR (P=0.07). MIPI score was the only predictive significant variable both in terms of PFS and OS. In terms of toxicity, R-BAC was associated with significantly more pronounced grade 3-4 thrombocytopenia than BR (32% versus 15%), although R-BAC doses were frequently reduced as compared to the original scheme.



Summary/Conclusion: The BE-ve-BAC study indicates that R-BAC, even when administered in the 2-days schedule or with attenuated dose, is associated with significantly prolonged PFS than BR in elderly patients with previously untreated MCL. As hypotesized hematological toxicity was significantly higher for the latter regimen as compared to BR. Further patients from more centers of our area are expected to be included, and long-term follow up of the R-BAC500

study is awaited to confirm our findings in an independent prospective setting.

EP796 PRIMARY THERAPY AND RELATIVE SURVIVAL IN PATIENTS WITH LYMPHOPLASMACYTIC LYMPHOMA/ WALDENSTRÖM'S MACROGLOBULINEMIA (LPL/WM): A POPULATION-BASED STUDY IN THE NETHERLANDS, 1989-2018

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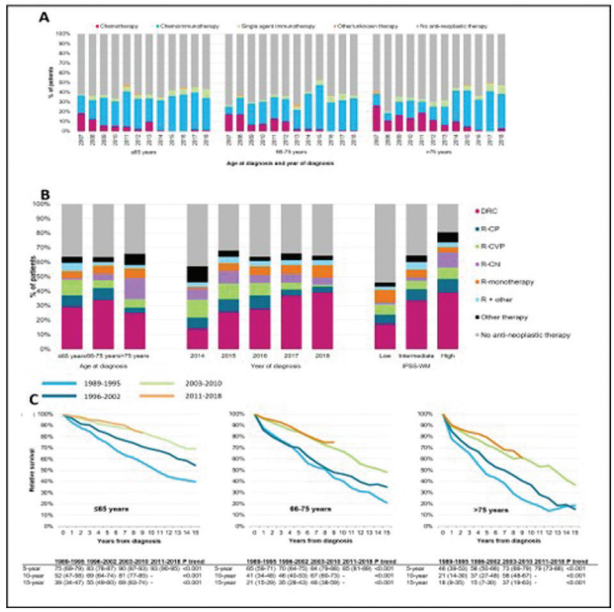
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Background: LPL/WM is a rare lymphoproliferative malignancy. Although therapeutic advances have been made in LPL/WM over the past decades, it is unclear how these advances have impacted the population-level survival of LPL/WM patients, especially among contemporary diagnosed patients. This inconclusiveness relates to the lack of population-based studies in LPL/WM.

Aims: This nationwide, population-based study aimed to assess trends in first-line therapy and relative survival (RS) among LPL/WM patients diagnosed in the Netherlands during a 30-year period.

Methods: All LPL/WM patients diagnosed between 1989-2018—with survival follow-up through 2020—were selected from the Netherlands Cancer Registry (NCR). Data on primary therapy—that is, no anti-neoplastic therapy (i.e. watch-and-wait) and anti-neoplastic therapy (e.g. chemotherapy)—were available in the NCR. Information on the use of rituximab was available for patients diagnosed as from 2007. Patients were categorized into four periods (1989-1995, 1996-2002, 2003-2010 and 2011-2018), and three age groups (<65 (*n*=383), 66-75 (*n*=384) and >75 years (*n*=386)). Data on the exact anti-neoplastic therapy, asymptomatic/symptomatic disease, and IPSS risk group were available for patients diagnosed as from 2014. The exact anti-neoplastic regimens were presented for patients with symptomatic disease, stratified by year of diagnosis, the three abovementioned age groups, and IPSS risk group (i.e. low, intermediate, and high). RS was calculated to estimate disease-specific survival.

Results: A total of 6,232 LPL/WM patients (median age 70 years; 61% males) were included in the study. Due to the broader application of an initial watch-and-wait approach, treatment with anti-neoplastic agents at diagnosis gradually decreased over time, irrespective of age. The proportion of patients receiving upfront anti-neoplastic therapy was 41%, 38%, and 40% across the three age groups during 2011-2018. Data from 2007 onwards showed that the use of chemotherapy alone decreased over time, following an increased application of chemoimmunotherapy (Figure 1A). Symptomatic disease was present in 60% of patients diagnosed during 2014-2018. Detailed data on primary therapy among 960 symptomatic patients revealed that DRC was the most frequently applied therapeutic regimen across all age groups, of which its use increased from 14% to 39% between 2014 and 2018. Consequently, the use of R-C(V)P decreased between 2014 and 2018. The use of anti-neoplastic therapy increased with advancing IPSS risk group (Figure 1B). Five-year RS increased significantly across all age groups between the first and last calendar period. Specifically, 5-year RS (95% confidence intervals) was 75% (69%>79%), 65% (59%>71%), and 46% (39%>53%) in 1989-1995 across the three age groups, compared with 93% (90%>95%), 85% (81%>89%) and 79% (73%>86%) in 2011-2018 (Figure 1C).The age-stratified multivariable analysis of RS demonstrated that RS between 2003-2010 and 2011-2018 did not improve further.



Summary/Conclusion: The use of chemotherapy alone in LPL/WM is almost entirely abandoned in contemporary clinical practice in the Netherlands. The impressive survival improvement over time may be accounted for by the increased use of rituximab-containing therapy since its introduction in early-mid 2000. The lack of survival improvement in the post-rituximab era warrant longer follow-up of our post-rituximab cohort to assess the effects of recently introduced novel agents, and should bolster forthcoming studies across various therapy lines to further improve survival in LPL/WM.

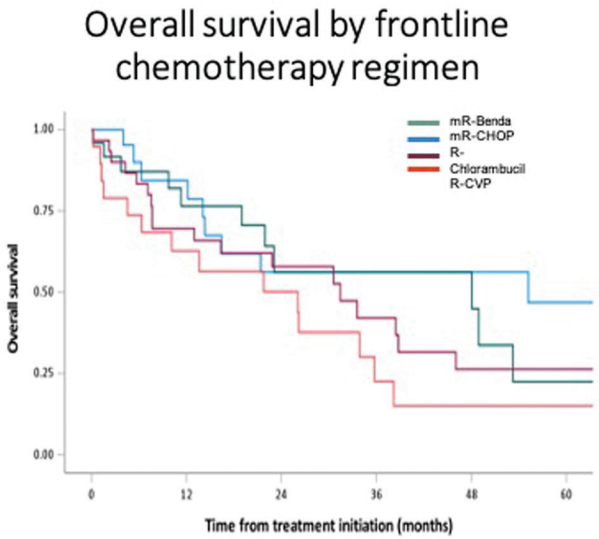
EP797 TREATMENT PATTERNS AND OUTCOMES OF ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA UNFIT FOR STANDARD IMMUNOCHEMOTHERAPY: A UK AND IRELAND ANALYSIS

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Background: Mantle Cell lymphoma (MCL) represents 3-10% of all non-Hodgkin B-cell lymphoma with a third of new diagnoses affecting patients (pts) aged >75 years. Although the treatment options for MCL have increased over the last years with the introduction of Bruton Kinase Inhibitors (BTKi), for older and unfit pts, treatment options are limited. Practice across the UK varies with regimens such as attenuated R-CHOP,

R-CVP, attenuated R-Bendamustine (R-B), R-Chlorambucil (R-CHL) used. Outcomes in this population are not fully characterised.
Aims: This study aims to identify treatment pattens and outcomes of the most commonly used attenuated and low intensity regimens used in pts with newly diagnosed MCL unfit for standard chemoimmunotherapy (i.e. full dose R-CHOP or R-B).
Methods: Data were retrospectively collected across 19 centres in the UK and Ireland between 1/1/2010 and 31/11/2020. All pts who were ineligible for standard regimens and had received at least 1 dose of an attenuated or low intensity regimen. Baseline characteristics, treatment characteristics and toxicity data were collected. Progression free survival (PFS) and overall survival (OS) were calculated using standard Kaplan-Meier analysis. Univariable and multivariable Cox regression analysis (MVA) was used to examine the associations between baseline factors, regimens, PFS and OS.
Results: 95 pts (attenuated RCHOP n=22, attenuated R-B n=24, R-CHL n=30, R-CVP, n=19) were analysed. Median age was 79 years (range:58-89) with baseline ECOG of 0, 1 and ≥2 for 22.1, 41.1% and 36.8% respectively. 50% were ≥80 years and median CIRS-G score was 6 (range:0-24). 93% had stage III-IV disease with 91% presenting with high MIPIb or MIPI score. 14.5% had blastoid morphology. Pts receiving R-CHL had higher age, with worse ECOG and along with those receiving R-CVP had greater CIRS-G than the other groups.
Overall response rate (ORR) for the whole cohort was 72% with a median duration of response (DoR) of 19.1 months (95% CI 12.9-25.4). Numerically higher ORR and DoR were observed in attenuated R-B and R-CHOP (83.3%, 33.8 months and 82%, 22 months). 60 pts progressed with 47 receiving further treatment including 36 receiving Ibrutinib.
Median PFS for all pts was 15 months (95% CI:8.7-21.2) and median OS was 31.4 months (95% CI:19.7-43.2). The median PFS and OS for attenuated R-CHOP pts was 16.7 months (95% CI 9.8-23.7) and 55.2 months (95% CI 1.9-108.4), attenuated R-B pts was 21.9 months (95% CI 0-46.3) and 48.1 months (95% CI 0-109.5), R-CVP pts was 7.4 months (95% CI 0.3-14.5) and 26.1 months (95% CI 2.7-49.4), and R-CHL pts was 12.0 months (95% CI 5.4-18.7) and 31.4 months (95% CI 17.9-45.0) respectively. By MVA, factors associated with an inferior PFS were bulk (>10cm) (HR:2.05, p=0.04) and blastoid morphology (HR:2.63, p=0.02). Higher treatment intensity (R-CHOP/R-B composite) provided a superior PFS compared with RCVP/R-CHL (MVA HR:0.48, p=0.01). Factors associated with inferior OS by MVA were age (HR:1.06), ECOG performance status (HR:2.50), blastoid morphology (HR:3.12) and POD24 status (HR:4.37).



Summary/Conclusion: Overall, PFS and OS following front-line dose attenuated immunochemotherapy is unsatisfactory. POD24 association with worse OS is now validated in elderly frail pts. Outcomes were generally poor, but attenuated R-CHOP or R-B may improve disease control compared to R-CVP or R-CHL. Clinical trials investigating novel agents such as BTK and BCL2 inhibitors in this specific clinical setting are warranted.

EP798 REAL-WORLD TREATMENT PATTERNS AND OUTCOMES OF 3455 PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA PATIENTS IN US ROUTINE CLINICAL PRACTICE

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Background: Mantle cell lymphoma (MCL) is a non-Hodgkin's lymphoma with heterogeneous biology and outcomes.
Aims: We characterized real-world (RW) treatment (tx) patterns and outcomes of patients (pts) with MCL to identify factors associated with outcomes in the US.
Methods: This retrospective study included adult pts with MCL diagnosed between January 2011 and November 2020 in the nationwide Flatiron Health EHR-derived deidentified database ("MCL-eligible"). Pt characteristics, tx patterns, RW time-to-next tx (rwTTNT, defined as start of first-line [1L] tx to subsequent tx or death), and RW overall survival (rwOS) were evaluated.
Results: 3455 pts were included, 85.3% from a community oncology setting. In 2946 (85.2%) pts with documented 1L MCL tx, median age was 69.5 years (range, 27.7-85.3); 9.5% had blastoid/pleomorphic MCL. 262 (39.6%) and 235 (35.6%) of 661 pts with available MCL international prognostic index had intermediate and high risk, respectively. 150/1253 pts (12.0%) with available Eastern Cooperative Oncology Group performance status (ECOG PS) had an ECOG PS ≥ 2. Chemoimmunotherapy was the most common 1L tx, including bendamustine plus rituximab (BR) in 1223 (41.5%), rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in 512 (17.4%), and cytarabine (ara-C)-containing tx in 414 (14.1%). 667 pts received R maintenance (MR). In 1036 pts < 65 years, 243 pts received 1L stem cell transplant (SCT), mainly autologous. In 1L-treated pts, with a median follow-up of survivors of 45.3 months (range, 0.03-117.2), median rwTTNT was 24 months; 36-month rwOS was 67%. The Table shows tx received and outcomes by age and SCT status. Multivariate analyses showed age ≥ 65 years, ECOG PS ≥ 2, lactate dehydrogenase/upper limit of normal ≥ 1, white blood cell count ≥ 10 × 10^9/L, bulky disease (≥ 5 cm), and blastoid/pleomorphic morphology were associated with shorter rwTTNT and rwOS; MR was independently associated with longer rwTTNT and rwOS. In pts < 65 years who were alive and did not initiate subsequent tx within 6 months of 1L tx ("SCT-eligible"), 36-month rwTTNT and rwOS were similar between pts treated with versus without SCT: 65% versus 59% and 86% versus 85%, respectively.

Table. Tx and outcomes in 1L MCL

	Age < 65 years at 1L tx (n = 1036)		Age ≥ 65 years at 1L tx (n = 1910)	
	No SCT (n = 793)	Received SCT (n = 243)	No SCT (n = 1835)	Received SCT (n = 75)
1L tx received, n (%)				
Ara-C-containing	189 (23.8)	130 (53.5)	67 (3.7)	28 (37.3)
BR	244 (30.8)	42 (17.3)	914 (49.8)	23 (30.7)
R-CHOP	172 (21.7)	48 (19.8)	273 (14.9)	19 (25.3)
Pt outcome, % (95% confidence interval)				
36-month rwTTNT	40 (36-44)	63 (57-71)	37 (35-40)	63 (51-77)
36-month rwOS	75 (72-79)	86 (81-91)	61 (58-63)	82 (72-94)

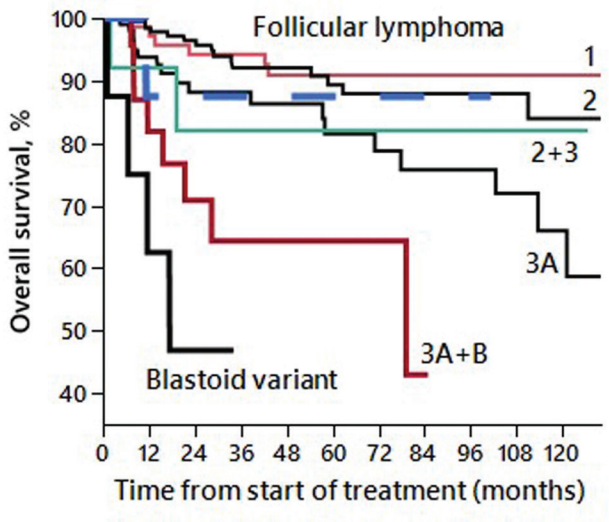
Summary/Conclusion: In this large RW cohort of primarily community-based US practices, median 1L rwTTNT for pts with MCL was ~ 2 years. BR was the most commonly used 1L tx. SCT was uncommon even in pts < 65 years, suggesting RW considerations may influence SCT eligibility and availability. Additionally, SCT was not clearly associated with rwOS. As with other reports, older age and high-risk disease features were predictive of worse outcome in RW, while MR appeared to be associated with better outcomes. Outcomes across the board appear worse than prospective trials, suggesting a need to focus on developing tx that can be delivered effectively in the community setting.

EP799 COMBINATION OF EZH2 GENE MUTATION AND BCL2 GENE REARRANGEMENT AS AN INDICATOR OF FAVORABLE PROGNOSIS OF FOLLICULAR LYMPHOMA

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Background: Follicular lymphoma (FL) is the second most common B-cell non-Hodgkin's lymphoma, accounting for 25% of all newly diagnosed lymphomas in Russia. The clinical course of the disease is variable and associated with tumor morphology: the prognosis for grade 1-2 and 3A is better than for grade 3B and for transformation into aggressive lymphomas (Fig. 1). The variability of the clinical course is also observed among indolent FL (grade 1-2 and 3A). The variability of the disease can be explained by the pathogenetic mechanisms ("linear" and divergent pathways) of the development of the tumor cell, which are confirmed by the detected genetic markers. *EZH2* is an early marker of FL and its changes confirm the «linear" pathway of tumor cell development. Today the pathogenetic aspects of FL are not fully understood and the data are contradictory.
Aims: To determine the mutational status of the *EZH2* gene in patients with indolent FL, to compare the results obtained with the immunomorphological and cytogenetic characteristics of the tumor; to determine predictive value.
Methods: A prospective comparative search study conducted from January, 2020 to December, 2020 at the National Research Center for Hematology (Moscow) included 64 patients (35 men and 29 women, with a median age of 53 years) with newly diagnosed FL. All 64 biopsies taken before therapy administration were investigated for the mutational status of *EZH2* gene exon 16 (Sanger sequencing) and for the rearrangement of the *BCL2* gene (karyotyping and FISH). All patients received anthracycline-containing regimens with rituximab (R-CHOP / R-EPOCH). Molecular, immunomorphological and cytogenetic data were compared blindly with the outcome of immunochemotherapy treatment.
Results: Mutations of *EZH2* gene *(mutEZH2) were* detected in 10/64 (16%) of cases. In the *mutEZH2* group of patients grade 1-2 of FL was diagnosed in 4/10 cases, and grade 3A - in 6 out of 10 cases. Rearrangement of the *BCL2* was found in 1-2 grade group in 3/4 cases, in 3A grade - in 3/6 cases. Adverse events (early relapse/progression/death from progression were determined in 4/10 (40%) patients and only in cases with *EZH2* mutations and without *BCL2* gene rearrangement. There were no deaths in cases with both *EZH2* mutations and *BCL2* gene rearrangement.
Wild type *EZH2* gene status *(wtEZH2)* was shown for 54/64 (84%) cases. In this group grade 1-2 FL was diagnosed in 26/54 (48%) cases, and grade 3A – in 28/54 (52%). *BCL2* gene rearrangement was detected in 19/22 (86%) grade 1-2 FL cases, and in 14/25 (56%) grade 3A cases. Adverse events in the group without *EZH2* mutations were found in 20/54(37%), and were twice as common in the absence of *BCL2* gene rearrangement (16% versus 82% in grade 1-2, and 36% versus 100% in grade 3A). Deaths from progression were observed in 12/54 (22%) patients.



Summary/Conclusion: *EZH2* gene mutations were detected in 16% of cases and were found equally in grade 1-2 and 3A groups of FL patients. FL cases with both *EZH2* mutations and *BCL2* rearrangement are characterized by a long persistently recurrent course. FL cases with wild type EZH2 gene and without *BCL2* gene rearrangement are associated with a high risk of transformation into DLBCL and high mortality.

EP800 LENALIDOMIDE PLUS RITUXIMAB IN PATIENTS WITH RITUXIMAB-RESISTANT INDOLENT B-CELL AND MANTLE CELL LYMPHOMAS: 10-YEAR FOLLOW-UP

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Background: Lenalidomide plus rituximab is now a standard-of-care option for indolent B-cell non-Hodgkin lymphomas (iNHL) and mantle cell lymphomas (MCL). We previously demonstrated the efficacy of combination lenalidomide and rituximab in patients (pts) with rituximab-refractory iNHL and MCL (Chong et al Clin Can Res 2015). We now report the longest experience to date with this regimen.
Aims: The aim of this retrospective review was to determine 5 and 10-yr outcomes for rituximab-resistant pts treated with lenalidomide and rituximab and to identify adverse events (AEs) leading to dose discontinuation.
Methods: We conducted an open-label phase II trial in pts with iNHL or MCL and rituximab resistance, defined as failure to respond to or progression of disease within 6 months of rituximab or a rituximab-containing regimen. Pts received lenalidomide 10 mg daily for 8 weeks, followed by 4 weekly doses of rituximab 375 mg/m^2 and continued lenalidomide maintenance until disease progression, toxicity or pt choice.
Results: 50 pts (30 FL, 14 MCL, 2 MZL, 4 SLL) were enrolled between 2008-2012. Median follow-up was 10.5 years (yr). Pts received a median of 3 prior therapies (range: 1–7). Progression free survival (PFS) for all pts at 5 and 10 yrs was 20.0% [95%CI 8-35] & 13% [95%CI 3-30%]; 5- and 10-yr response duration (RD) was 27% [95% CI 12-46] and 18% [95% CI 4-40], respectively; 5- and 10-yr overall survival (OS) was 58% [95%CI 43-70] and 45% [95%CI 30-58], respectively. 5-yr OS from the time pts were deemed rituximab-resistant was 64.0% and 10-yr OS 51.9%.
For pts with FL, 5- and 10-yr PFS were both 13%, and 5- and 10-yr OS were 60% and 40%. For MCL, 5- and 10-yr PFS were both 25% and 5- and 10-yr OS were 50% and 36%. At 10.5 yr follow-up, 4 pts (2 FL, 1 MCL, 1 MZL) remain in complete remission (CR), 3 of whom discontinued lenalidomide at 7.0-yr, 8.8-yr and 10.1-yr in CR. 1 pt with FL discontinued study in CR after 11.6-yr but continues on commercial lenalidomide at 5 mg daily.
The most common grade 1–2 AEs requiring dose reductions were neuropathy (n = 3) and diarrhea (n = 5), which all resolved with dose reduction. The most common grade 3–4 AEs requiring dose reductions were neutropenia (n = 6, 12%) and tumor flare (n = 3, 6%). Pts discontinued therapy due to toxicity at a median of 4.9 mo (range 0.3–25.7) from lenalidomide start due to grade 3–4 rash (n = 2), grade 2 abdominal pain (n = 1), and grade 3–4 thrombocytopenia (n = 2). Only 1 pt discontinued lenalidomide after >1 yr (25.7 mo); this was due to persistent diarrhea. The pt who developed grade 2 abdominal pain was retreated with lenalidomide without recurrence of pain and sustained a second CR for 5 yrs. 5 (10%) pts developed secondary cancers at a median of 15.5 mo (range: 0.8–50.5) from starting lenalidomide, including 2 hematological (acute myeloid leukemia, B-acute lymphoblastic leukemia) and 3 solid cancers (NSCLC, renal cell carcinoma, prostate cancer). Prior to enrollment, 4/5 of the pts with secondary cancers had received alkylating agents and 3/5 had received anthracyclines. Of all pts, 78% had previously received alkylating agents and 62% had received anthracyclines.

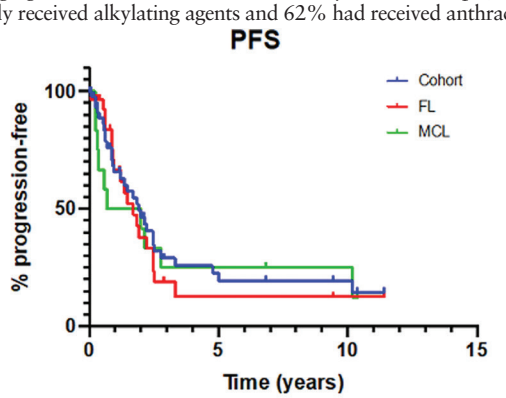


Figure 1:
Progression free survival (PFS) for the entire cohort and for patients with follicular (FL) and mantle cell (MCL) lymphoma.

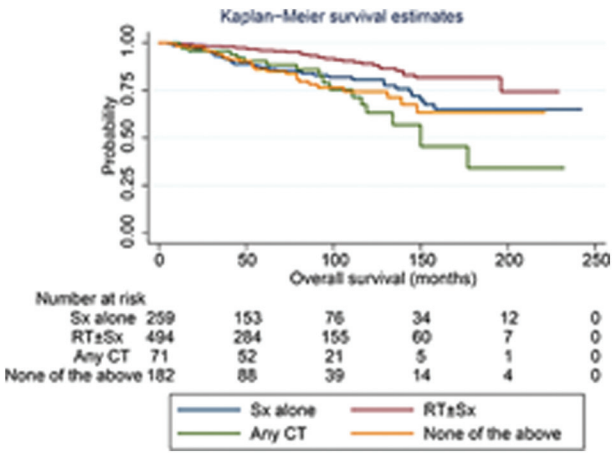
Summary/Conclusion: These data represent the longest reported outcomes for lenalidomide plus rituximab in iNHLs and MCL. We demonstrate durable responses and a manageable safety profile with rituximab plus low-dose lenalidomide.

EP801 EFFECTS OF CONVENTIONAL TREATMENTS ON EARLY-STAGE PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

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Background: Information on the outcomes and treatments of early-stage (I/II) primary cutaneous marginal zone lymphoma (PCMZL) is limited.
Aims: This study aims to identify the prognostic factors in early-stage PCMZL and compare long-term population-based survival outcomes of conventional approaches.
Methods: We extracted data on stage I/II PCMZL patients from the Surveillance Epidemiology and End Results (SEER) database and used the Kaplan-Meier plot, log-rank test, Cox regression, propensity score matching (PSM) analyses to explore the association of characteristics and therapeutic methods with survival.
Results: We identified 1,006 early-stage PCMZL cases between 1993 and 2016 in the SEER registry. Multivariate analysis indicated that age over 60 years at diagnosis, specific primary sites (i.e., face, scalp, neck, lower limb, and hip), diagnosis before 2005, and coexisting malignancy were unfavorable predictors for overall survival (OS), while radiotherapy (RT) with or without surgery (Sx) improved OS independently. Besides, we also noted that age over 60 years, diagnosis before 2005, and chemotherapy (CT) were adverse predictors for disease-specific survival (DSS). According to Cox regression and PSM analyses, RT improved the OS and DSS rates while CT reduced the OS and DSS rates. No data demonstrated a survival benefit with Sx in this study.



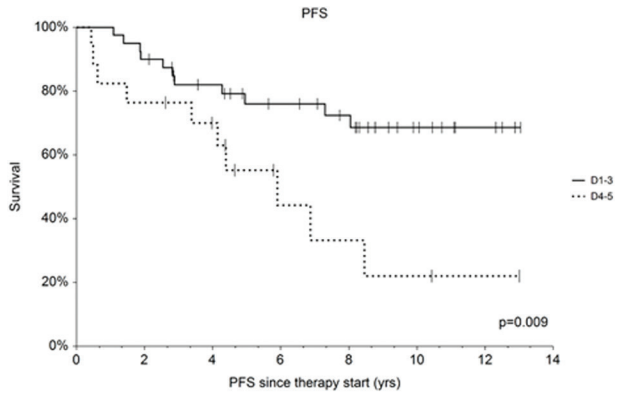
Summary/Conclusion: For early-stage PCMZL patients, RT can probably be an essential component for the initial therapy, and a combination with new treatment options, such as rituximab, could be considered in future studies. Sx has no survival benefit throughout this study but it is an available diagnostic workup. Systemic CT had inferior efficacy and is not recommended as an initial regimen for such an indolent tumor in an early stage.

EP802 EARLY INTERIM PET/CT PREDICTS THE OUTCOME IN HIGH-TUMOUR-BURDEN FOLLICULAR LYMPHOMA PATIENTS

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Background: High-tumour-burden follicular lymphoma (HTB-FL) is a highly heterogeneous disease. About one-fifth of patients experience poor response to frontline therapy or early relapse within 24 months of treatment (POD24). Identification of early progression of the disease is still an unmet prognostic need. Use of positron-emission tomography/computed tomography (PET/CT) in the interim setting remains controversial.
Aims: To assess the impact of early metabolic assessment on early disease outcome
Methods: We analysed 124 previously untreated grade I-IIIA HTB-FL patients undergoing PET/CT at diagnosis and after immunochemotherapy, with 57 of them having early interim PET/CT scans within 14-21 days after the 2nd chemotherapy cycle. Imaging studies were conducted using the Siemens Biograph 16 HI-REZ (2008-2015) and Siemens mCT 40 (2015-2017) systems with the same image acquisition protocols at the same centre. Both PET/CT scanners were accredited by EARL, a European Association of Nuclear Medicine research initiative. Images were read by two independent experts blinded for patient outcome.
Results: The cohort consisted of 35 females and 22 males with a median age of 56 years, with advanced (CS III/IV) disease in 96.5%. The FLIPI/PRIMA-PI percentages were as follows: low 12%/31%, intermediate 44%/43% and high 44%/26%. All but one of the patients were treated with a rituximab-anthracycline-containing regimen (1 R-bendamustine) and 34 received rituximab maintenance. Forty-six patients (81%) achieved CR, seven (12%) achieved PR and four (7%) had stable disease or progressed on therapy. After a median follow-up of 8.4 years, twenty (35%) relapsed and eight died. Eight of them (14%) progressed/relapsed within 24 months of therapy. Interim PET-2 was assessed as negative (Deauville 1-3) in 40 (70%) and positive (D4-5) in 17 (30%) patients. End-of-induction PET scans were obtained in all but two patients (1 PD on therapy, 1 refusal), with 47 (85%) negative (D1-3) and eight (15%) positive (D4-5) results. Five-year PFS reached 55.2% and 79.2% (p=0.009) and 5-y OS 88.2% and 94.9% (p=0.017) in the D4-5 and D1-3 groups, respectively. Positive and negative predictive values were 58.8%/72.5% for PFS events and 29.4%/92.5% for death. The risk of a POD24 was 24% and 10% in the D1-3 and D4-5 groups, respectively.



Summary/Conclusion: Early interim PET/CT negativity is associated with a high negative predictive value for progression or lymphoma-related death. The risk of developing a POD24 event is reduced by 58% in the negative (D1-3) group. Interim PET/CT might be useful in identifying HTB-FL individuals at risk for immunochemotherapy failure. Larger analyses are needed to establish the role of interim PET in decision-making.
Acknowledgement: supported by AZV NU21-03-00411 and IGA_LF_2021_001 grants.

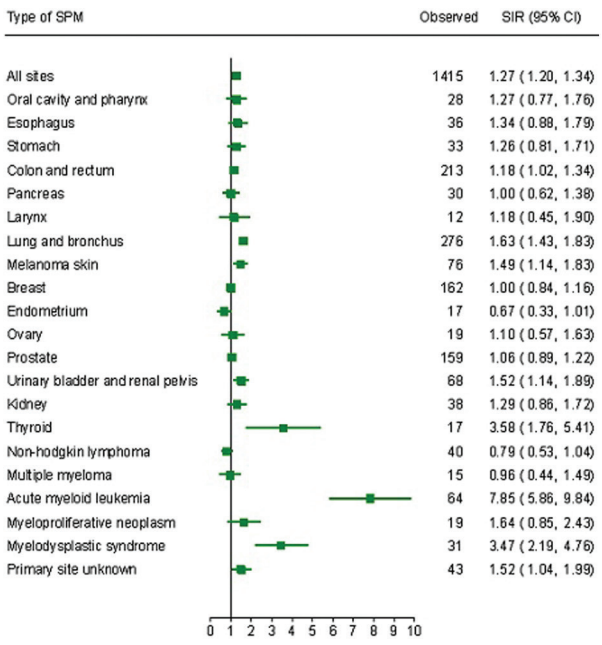
EP803 RISK OF SECOND PRIMARY MALIGNANCIES IN PATIENTS WITH FOLLICULAR LYMPHOMA: A POPULATION-BASED STUDY IN THE NETHERLANDS

M. Dinnessen [1,*], O. Visser [2], S. Tonino [3], E. Posthuma [4], N. Blijlevens [5], M. J. Kersten [3], P. Lugtenburg [6], A. Dinmohamed [1]

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Background: Some population-based studies demonstrate that the improved longevity of patients with follicular lymphoma (FL) is offset

by an increased risk of a variety of second primary malignancies (SPMs) compared to the general population. Awareness about the incidence of SPMs in patients with FL is important to mitigate potential sequelae of SPMs.
Aims: To complement and extend on the sparse literature on SPM development in FL, this nationwide population-based study aimed to assess the risk to develop SPMs in patients with FL in the Netherlands diagnosed during a 30-year period.
Methods: We selected all patients diagnosed with FL grades 1-3B between 1989-2018 from the Netherlands Cancer Registry (NCR) and followed these patients until SPM development, death, or end of follow-up (December 31, 2018), whichever occurred first. Standardized incidence ratios (SIRs) for all SPMs combined—except for basal and squamous cell carcinomas—and specific subtypes of SPMs were calculated by dividing the number of observed malignancies by the expected number of malignancies in an age, sex, and period matched population from the NCR. Synchronous malignancies diagnosed within six months from FL diagnosis (n=248; 1.8% of the total FL population) were excluded to minimize detection bias. We assigned 95% confidence intervals (CIs) for the SIRs by assuming a Poisson distribution for the number of observed SPMs.
Results: We included 13,656 FL patients (median age, 62 years, 49% females) in this study, of whom 1,415 patients (10%) developed at least one SPM after a median follow-up of 5.2 years from diagnosis (interquartile range (IQR), 2.0-10.2 years) at a median age of 69 years (IQR, 62-75 years). Of the 1,415 patients, 550 patients (38%), 432 patients (31%), and 432 patients (31%) were diagnosed with an SPM at 0.5-5, 5-10, and 10-30 years from diagnosis. The cumulative incidence of SPMs was 7.3% (95% CI, 6.8-7.8%) and 14.9% (95% CI, 14.1-15.8%) at 5 and 10 years, respectively.
The risk of developing an SPM for patients with FL was statistically significantly elevated compared to the general population with a SIR of 1.27 (95% CI, 1.20-1.34; Figure 1), irrespective of sex. The increased risk was more pronounced among patients 18-60 years at diagnosis (SIR, 1.52; 95% CI, 1.40-1.64) compared to patients >60 years at diagnosis (SIR, 1.10; 95% CI, 1.02-1.18), possibly due to a higher baseline risk among patients 18-60 years. The excess risk of SPMs diminished, albeit it did not disappear, among patients diagnosed in the post-rituximab era (>2002) compared to patients diagnosed in the pre-rituximab era (SIR, 1.15; 95% CI, 1.07-1.24 and SIR, 1.38; 95% CI, 1.28-1.49, respectively). A significantly greater risk was observed for acute myeloid leukemia (7.85), and myelodysplastic syndrome (3.47), and solid tumors of the following sites: thyroid (3.58), lung and bronchus (1.63), primary site unknown (1.52), urinary bladder and renal pelvis (1.52), melanoma of the skin (1.49), and colon and rectum (1.18; Figure 1).



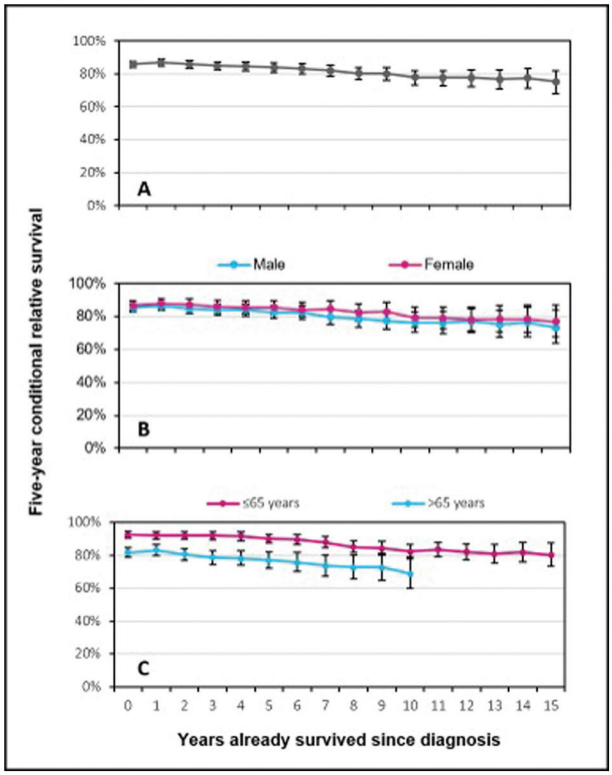
Summary/Conclusion: This nationwide, population-based study demonstrates that FL patients have a 1.27 times greater risk of SPMs than the general population that persists for patients diagnosed in the rituximab era. SPMs could reflect late sequelae of treatment or the effect of shared etiologic factors, environmental exposures, and host characteristics. Surveillance of SPMs among FL survivors can be considered in the survivorship care of these patients—particularly among patients aged 18-60 years at diagnosis—to prevent SPMs or reduce the impact of SPMs.

EP804 CONDITIONAL RELATIVE SURVIVAL IN LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRÖM'S MACROGLOBULINEMIA (LPL/WM): A POPULATION-BASED STUDY IN THE NETHERLANDS

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Background: Population-based studies in LPL/WM are limited. Nevertheless, these studies revealed that the introduction of rituximab improved the population-level survival of LPL/WM patients across all age groups. The improved survival necessitates measures that capture the prognosis for long-term LPL/WM survivors because survival estimates measured from diagnosis can be rather discouraging due to patients who die within the first years post-diagnosis. Conditional relative survival (CRS) is a concept that refers to the probability of survival—corrected for the life expectancy in the general population—after having survived from a specified time since diagnosis. Studies on CRS in LPL/WM lack to inform long-term LPL/WM survivors about their prognosis at a specified time since diagnosis.
Aims: This nationwide, population-based study examined up-to-date estimates of 5-year relative survival (RS) at diagnosis and for each year survived up to 15 years post-diagnosis among LPL/WM patients in the Netherlands.
Methods: All patients diagnosed with LPL/WM between 1989-2018—with follow-up for survival until December 31, 2019—were selected from the Netherlands Cancer Registry. RS was calculated to estimate disease-specific survival. RS is defined as the ratio of the observed to expected survival, of which the latter is matched to the patient by age, sex, and calendar year. We calculated 5-year RS at diagnosis and 5-year CRS for each additional year survived up to fifteen years after diagnosis, conditional on being alive at the beginning of that year. Up-to-date survival probabilities for patients diagnosed during 1989-2018 who were alive between the follow-up interval of 2008-2019, were generated using the hybrid approach. These survival probabilities can be interpreted as the predicted survival probabilities for patients diagnosed during 2008-2019. Survival statistics were computed for the overall cohort and according to sex and age at diagnosis (≤65 and >65). Survival differences between the point estimates were assessed by 95% CI overlap.
Results: A total of 6,234 LPL/WM patients (median age, 70 years; and 61% males) were diagnosed in the Netherlands during 1989-2018, of whom 4,296 (69%) were at risk under the hybrid approach. The overall 5-year RS measured from diagnosis was 86% (95% CI, 84%>88%) and gradually decreased with additional years survived to 75% (95% CI, 68%>82%) at 15 years post-diagnosis (Fig. A). This trend was emulated according to sex, with no sex differential in survival over time (Fig. B). However, there were significant differences in 5-year RS at diagnosis with increasing age, namely 93% (95% CI, 91%>95%), and 82% (95% CI, 79%>85%) across the age groups, respectively (Fig. C). Five-year CRS decreased with each additional year survived among patients aged ≤65 and >65 years at diagnosis. Consequently, the age-related survival gap persisted during the follow-up period.



Summary/Conclusion: This study highlights that contemporary diagnosed LPL/WM patients, as compared to the general population, continue to experience excess mortality regardless of having survived up to 15 years post-diagnosis. This gradual increase in excess mortality might result from the incurable nature of this disease characterized by multiple relapses throughout the disease course. CRS estimates offer LPL/WM patients information about their survival expectations with each year survived post-diagnosis and provides means to physicians to tailor surveillance and follow-up activities. Our study results touch upon the need for novel treatment strategies to reduce short- and long-term excess mortality in LPL/WM patients.

EP805 EFFICACY AND SAFETY OF ZANUBRUTINIB VERSUS RITUXIMAB-BASED CHEMOIMMUNOTHERAPY IN WALDENSTRÖM MACROGLOBULINEMIA: MATCHING-ADJUSTED INDIRECT COMPARISONS

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Background: There is a lack of randomized trials directly comparing zanubrutinib with chemoimmunotherapy in Waldenström Macroglobulinemia (WM).
Aims: This study aimed to indirectly compare zanubrutinib with bendamustine-rituximab (BR) and with dexamethasone-rituximab-cyclophosphamide (DRC) separately through matching-adjusted indirect comparisons (MAIC).
Methods: MAIC were conducted to re-weight the individual data of 102 WM patients (83 relapsed/refractory [R/R] and 19 treatment-naïve [TN]) treated with zanubrutinib in the ASPEN trial (NCT03053440) so that the weighted average baseline characteristics of patients treated with zanubrutinib matched those of 71 R/R patients treated with BR, and 72 TN patients treated with DRC separately. Matching variables for MAIC with BR included age, prior lines of therapy, IgM concentration, International Prognostic Scoring System for WM score, and extramedullary disease (EMD); and for MAIC with DRC included age, platelet count, hemoglobin concentration, and EMD. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) of comparators were digitized to re-create patient-level data. Comparisons of survival and adverse event incidence between treatments were conducted using Cox proportional hazards models and modified Poisson models.
Results: Compared to DRC, zanubrutinib was associated with significantly longer PFS (hazard ratio [HR]: 0.39 [95% confidence interval 0.18-0.82] and 0.35 [0.14-0.86] pre- and post-matching, respectively) and insignificantly longer OS (HR: 0.56 [0.20-1.53] and 0.47 [0.14-1.62] pre- and post-matching, respectively), and insignificantly higher incidences of neutropenia (risk ratio [RR]: 1.63 [0.71-3.77] and 1.47 [0.58-3.74] pre- and post-matching, respectively). Compared to BR, zanubrutinib was associated with significantly longer PFS (HR: 0.32 [0.15-0.69] and 0.37 [0.15-0.91] pre- and post-matching, respectively), significantly longer OS (HR: 0.31 [0.12, 0.80] and 0.29 [0.10-0.85] pre- and post-matching, respectively), significantly lower incidences of neutropenia (RR: 0.45 [0.26-0.78] and 0.50 [0.27-0.91] pre- and post-matching, respectively) and insignificantly lower incidences of pneumonia (RR: 0.18 [0.02-1.55] and 0.26 [0.03-2.28] pre- and post-matching, respectively).

		MAIC of zanubrutinib vs DRC		MAIC of zanubrutinib vs BR	
Outcomes	Zanubrutinib pre-matching (N=102)	Zanubrutinib post-matching DRC (N= 53)	DRC (N=72)	Zanubrutinib post-matching BR (N=50)	BR (N=71)
PFS, 12-month rate, %	94	92	85	94	79
PFS, 24-month rate, %	85	90	68	81	59
OS, 12-month rate, %	97	95	92	98	87
OS, 24-month rate, %	90	94	85	88	77
Anaemia, %	5.0	4.2	NR	3.6	NR
Hypertension, %	5.9	3.1	4.2	9.5	NR
Neutropenia, %	15.8	14.3	9.7	17.5	35.2
Pneumonia, %	1.0	0.6	NR	1.5	5.6
Thrombocytopenia, %	5.9	4.4	0.0	5.2	NR

NR, not reported

Summary/Conclusion: Zanubrutinib demonstrated longer PFS than DRC, longer PFS and OS than BR in WM, and lower incidence of neutropenia before and after matching adjustment based on patient characteristics.

EP806 P53 IMMUNOHISTOCHEMISTRY DETECTS NON-PATHOGENIC MUTATIONS IN MANTLE CELL LYMPHOMA NECESSITATING TP53 NGS FOR CLINICAL DECISION MAKING

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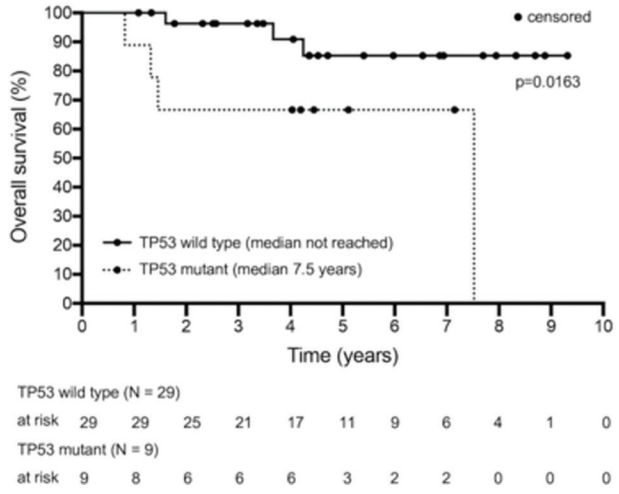
Background: Despite recent improvements in chemo-immunotherapy and novel therapies for mantle cell lymphoma (MCL), patients continue to experience heterogeneous clinical outcomes. Validated predictors of high-risk for adverse outcome include high-risk MCL International Prognostic Index (MIPI), Ki-67 ≥30% and blastic or pleomorphic histological variants. MCL harbouring pathogenic TP53 mutations treated on Nordic MCL2/MCL3 clinical trials have an inferior outcome, therefore detecting these mutations prior to treatment initiation may alter the treatment pathway utilising targeted therapy or a clinical trial. Missense TP53 mutations lead to accumulation of p53 within the cell, which is detectable by immunohistochemistry, whereas clinically relevant deletions or other TP53 mutations are only detected by Next Generation Sequencing (NGS).
Aims: We aimed to evaluate (1) the concordance of p53 immunohistochemistry and TP53 NGS in detecting high-risk missense TP53 mutations, (2) incidence of non-missense TP53 disruption in diagnostic specimens of MCL patients treated on the Nordic MCL2 protocol.
Methods: We identified patients treated between 2007-2019 on a modified Nordic MCL2 protocol (alternating Rituximab-CHOP/Rituximab-Cytarabine induction followed by BEAM-conditioned autologous stem cell transplantation). All patients undergoing HD-ASCT achieved VGPR/CR with induction therapy, as determined by Lugano criteria and were MRD negative. p53 expression by immunohistochemistry in diagnostic specimens was compared with NGS of TP53 and correlated

with clinical outcomes. Tumour sections with ≥30% of neoplastic cells staining positive for TP53 by IHC were defined as p53 positive as previously described. NGS called pathogenic TP53 mutations occurring at ≥5% VAF, with pathogenicity inferred from well-curated databases. All data is calculated from date of commencing Nordic protocol to date of censoring (death or end of study).

Results: 42 patients were treated with MCL2 between 2007-2019, of whom 38 had either DNA, tumour block or both available for TP53 mutation analysis. 34 (81%) patients were male and the median age was 59 years (range 37-67). 16 (41%) of patients had high-risk MIPI and 4 (9.5%) had non-classical MCL subtypes. Median overall survival (OS) was not reached and disease-free survival was 6.5 years. There was no transplant-related mortality. High-risk MIPI (p=0.078), Ki67≥30% (p=0.50), SOX11<10% (p=0.06) and non-classical MCL subtype (p=0.56) were not associated with inferior OS, likely due to the small cohort size.

Pathogenic TP53 mutations by NGS (6 cases) or p53 expression by IHC (4 cases) were detected in 9 patients (24%) and associated with inferior OS (p=0.0163) (Figure 1). Paired p53 IHC was unavailable for 5/6 TP53 mutated cases by NGS, however P53 was expressed in the remaining case. One of 4 P53 IHC positive cases lacked a corresponding NGS sample. Two P53 positive cases occurred in patients with NGS detectable mutations not classified as pathogenic: these patients remain in CR1 at 38 and 55 months from HD-ASCT respectively. There was 100% concordance between paired TP53 wild type cases and TP53 <30% by IHC (20 cases).

Figure 1. Overall survival



Summary/Conclusion: The presence of pathogenic TP53 was associated with adverse overall survival in this cohort. P53 IHC flagged two cases with TP53 mutations of uncertain significance by NGS. The implications of this finding must be explored in larger patient series, but suggest that IHC may not detect pathogenic TP53 mutations with sufficient accuracy to direct treatment pathways. All detected TP53 mutations were missense, reflecting the small study cohort.

EP807 OBINUTUZUMAB SHORT-DURATION INFUSION (SDI) IN PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA: RESULTS FROM THE END OF INDUCTION ANALYSIS OF THE PHASE IV GAZELLE STUDY

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Background: Obinutuzumab (G)-chemotherapy (chemo) has demonstrated improved progression-free survival compared with rituximab (R)-chemo in previously untreated advanced follicular lymphoma (FL). G is currently administered by intravenous infusion over ~3–4 hours. A shorter duration of infusion in Cycle (C) 2 and subsequent cycles, as is standard practice with R, could improve convenience for patients (pts) and efficiency for infusion facilities.

Aims: We report the primary analysis of the prospective, open-label, multicenter, single-arm, Phase IV, GAZELLE study (NCT03817853), which evaluated the safety of G administered as a 90-minute (min) SDI from C2 onwards in pts with FL.

Methods: Pts with previously untreated FL who met Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria received G (1000mg) intravenously on Day (D) 1, 8 and 15 of C1, and on D1 thereafter, plus chemo (bendamustine, CHOP or CVP) for 6–8 cycles. In C1, pts received G at the standard infusion rate. Pts without a Grade (Gr) ≥3 infusion-related reaction (IRR) in C1 were eligible to receive G as a 90-min SDI from C2. Pts with a Gr 3 IRR in C1 received the standard G infusion in C2, and were eligible for G SDI in subsequent cycles if no Gr ≥3 IRRs occurred. Pts with a second Gr 3/4 IRR discontinued G. At the end of induction (EOI), responding pts received maintenance G (1000mg) as SDI for 2 years or until disease progression (PD). The primary endpoint was incidence of Gr ≥3 IRRs during C2. IRRs were defined as any event occurring ≤24 hours from infusion judged to be related to treatment. Secondary endpoints included adverse events (AEs) and investigator-assessed overall response rate at EOI.

Results: As of December 3, 2020, 113 pts had received study treatment. Median age was 62.0 years, 50.4% were male, 61.9% had stage IV FL and 45.1% were classified as high-risk FLIPI. Of the 110 pts who were eligible for G SDI from C2, no pt experienced a Gr ≥3 IRR with SDI in C2 (**Table**). One pt experienced a Gr 3 IRR with SDI in C5, presenting hypertension. All other IRRs with SDI were Gr 1/2. No Gr 4/5 IRRs were reported. Other AEs were similar to those observed in previous studies. At the clinical cut-off date, 104 pts had a CT imaging-based response assessment at EOI and 9 pts had no response assessment; 76/113 (67.3%) pts had a complete response, 22 (19.5%) had a partial response, and six pts (5.8%) had PD.

Table. IRRs by cycle

	C1											
IRR, n (%)	C1 overall	D1	D2*	D8	D15	C2	C3	C4	C5	C6	C7	All cycles
All Gr	65/113 (57.5)	57/113 (50.4)	4/51 (7.8)	6/112 (5.4)	5/111 (4.5)	13/110 (11.8)	9/108 (8.3)	7/108 (6.5)	6/107 (5.6)	5/105 (4.8)	2/55 (3.6)	71/113 (62.8)
Gr ≥3	6/113 (5.3)	5/113 (4.4)	1/51 (2)	0	0	0	0	0	1/107 (0.9)	0	0	7/113 (6.2)

*timepoint applicable to pts treated with bendamustine

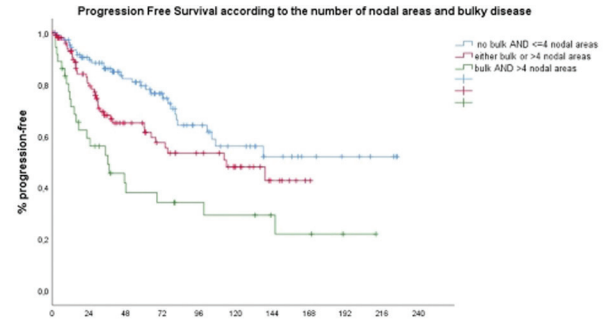
Summary/Conclusion: In GAZELLE, G SDI in C2 and beyond appeared to be safe. No Gr 3 IRRs were observed in C2 and only one Gr 3 IRR was reported in subsequent cycles. No new safety signals were reported and 67.3% of pts achieved a CR. These data suggest that the safety and efficacy profile of G SDI is comparable with the established profile of G in advanced FL.

EP808 EXAMINATION OF FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI) SCORE FOR FOLLICULAR LYMPHOMA PATIENTS IN THE RITUXIMAB ERA OUTSIDE CLINICAL TRIALS

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Background: FLIPI is the most frequently used prognostic tool even nowadays, although it was developed in the pre-Rituximab (R) era with overall survival (OS) as the endpoint. It has not been extensively studied, whether it can predict progression free survival (PFS) and if it still has a strong prognostic value for OS in R-treated patients, especially outside clinical trials.
Aims: To identify prognostic factors and examine the prognostic significance of FLIPI in a series of FL patients, treated in the R era outside clinical trials
Methods: 282 consecutive patients with FL diagnosed and treated between 2000 and 2020 from a single Unit were retrospectively studied. Several prognostic parameters were analyzed for OS, PFS and disease-specific survival (DSS).
Results: 112 patients (40%) were males with a median age of 56.7 years. 206 cases had histologic grade 1/2 (73%) and the remaining 76 (27%) grade 3A. The distribution of clinical stages was as follows: 71 (25%) stage 1, 35 (13%) stage 2, 42 (15%) stage 3, 132 (47%) stage 4; 12% had B symptoms, 21% elevated LDH, 25% bulky disease (>7cm), 7% had peripheral blood involvement and 41% had bone marrow involvement. 43% had >4 involved nodal areas. The most frequent treatment was R non-anthracycline chemotherapy, followed by RCHOP; 61% received maintenance after first line treatment. Median PFS was 114 months; 5- and 10-year PFS were 67.5% and 49%, respectively. For PFS, FLIPI score was not significant, whereas, bulky disease (p<0.0001) and number of nodal areas (p=0.018) were the only significant factors by univariate analysis; bulky disease remained significant by multivariate analysis (p<0.0001). A simple score based on nodal areas (0 points for ≤4 vs 1 point for >4) and bulky disease (0 points for no bulk vs 1 point for bulk) could stratify patients into three groups with a significantly different PFS (p<0.0001, figure). FLIPI score was prognostic for OS (p<0.0001) and DSS (P=0.004), but low- and intermediate risk groups had similar outcomes, especially for DSS. When low-and intermediate risk groups were grouped together (FLIPI 0-2) against high-risk (FLIPI 3-5), 5- and 10- year OS was 95% and 90.4% for FLIPI 0-2 vs 76% and 59% for FLIPI 3-5. 5- and 10- year DSS were both 96% for FLIPI 0-2 vs 90% and 76% for FLIPI 3-5. Considering the 5 parameters of FLIPI and bulky disease, by multivariate analysis, hemoglobin, age and bulky disease were the ones that were significant for OS, whereas, only bulky disease was significant for DSS.



	Group	Events/Cases	5-year PFS (%)	10-year PFS (%)
1 (0 points)	No bulk and ≤4 nodal areas	31/115	80	56
2 (1 point)	Either bulk or >4 nodal areas	39/106	65	48
3 (2 points)	Bulk and >4 nodal areas	23/36	38	29

Summary/Conclusion: In real world, outside clinical trials, with the observed improvement of survival of patients with FL in the R-era, FLIPI is still prognostic for OS, but may have limited predictive capacity for PFS. Bulky disease seems to be a potent marker for PFS, OS and DSS and should be further integrated and validated in easily applicable prognostic scores.

Infections in hematology (incl. supportive care/therapy)

EP809 IMMUNONOLOGICAL BIOMARKERS OF FATAL CORONAVIRUS DISEASE 2019 (COVID-19): A STUDY OF 513 PATIENTS INCLUDING HEMATOLOGICAL CASES

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Background: Knowledge on the immunopathobiology of COVID-19 is rapidly increasing but most studies analyzed relatively small series of patients and immune features predictive of fatal outcome are unavailable for routine stratification. Furthermore, an increased risk of death in patients with hematological cancer infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified, but it remains unknown if this is related to possible immunosuppression caused by cancer itself and cytotoxic treatment.
Aims: Characterize the immune response to SARS-CoV-2 in a large cohort of patients to identify high-risk immune biomarkers and evaluate the association between COVID-19 severity and immunosuppression in patients with hematological cancer.
Methods: Multidimensional flow cytometry was used to conduct holistic and unbiased analyses of 17 immune cell types on 780 peripheral blood samples obtained from 513 COVID-19 patients, 24 cases with non-SARS-CoV-2 infection and 36 age-matched healthy adults. 167 COVID-19 patients had 207 longitudinal samples collected over time. RNA sequencing on FACSorted cells and high-resolution flow cytometry were used to perform a deeper characterization of various myeloid and lymphoid subsets in 14 COVID-19 patients and 4 healthy adults.
Results: Immune profiles of COVID-19 patients were generally similar to those of age-matched patients with non-SARS-CoV-2 infection, but significantly different from those of age-matched healthy adults. When compared to the later, COVID-19 patients showed increased percentages of neutrophils, $CD4^{+}CD56^{+}$ T-cells, and plasmablasts, whereas levels of basophils, eosinophils, and non-classical monocytes, as well as double-negative, $CD8^{lo}CD56^{-}$, $CD8^{-/lo}CD56^{+}$ and $CD8^{hi}CD56^{-}$ T-cells, and B-cells were decreased. Both transcriptional and immunophenotypic data in myeloid and lymphoid subsets suggested an association between COVID-19 severity and neutrophil activation, as well as significantly reduced levels of specific adaptive immune cell types. Unsupervised clustering analysis of 513 patients revealed three immunotypes in response to SARS-CoV-2 infection. One of them, present in 14% of patients (n=74), was characterized by significantly lower percentages of all immune cell types except neutrophils and plasmablasts, and was significantly associated with more severe disease. Of note, 50% of COVID-19 patients with blood cancer displayed this immunotype. Accordingly, hematological patients showed a significantly higher frequency of admission into intensive care units (50% vs 5%, *P*<.001) and death (30% vs 4%, *P*<.001) than patients without tumor did. On multivariate analysis incorporating age and comorbidities, the frequency of B-cells and non-classical monocytes were independent prognostic factors for overall survival. Indeed, <1% B-cells in peripheral blood was most strongly associated with risk of death. Among patients with immune monitoring during follow-up, significant changes in the relative distribution of eight immune cell types, including basophils, $CD8^{lo}CD56^{-}$ T-cells, and B-cells, were observed from the first to last peripheral blood sample between patients who survived or died.

Summary/Conclusion: Our results accelerate our understanding of the immunopathobiology of COVID-19 and unveil an association between altered immune profiles in patients with hematological cancer and their poorer outcome. Reduced percentages of B-cells and non-classical monocytes are high-risk immune biomarkers that could be readily implemented in routine practice for risk-stratification of COVID-19.

EP810 PRESEPSIN AND RESPONSE TO ANTIBIOTIC THERAPY IN FEBRILE NEUTROPENIA OF ONCOHAEMATOLOGICAL PATIENTS

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Background: Febrile neutropenia (FN) is a potential life-threatening complication of the administration of chemotherapy in oncohematological patients. Only 20% of FN episodes have microbiologically-proven bacteremia. In most of cases, the therapeutic approach is based on the clinical picture and the laboratory evaluation of surrogate markers. More recently, soluble CD14 subtype, also known as presepsin (PS), has been proposed as a novel biomarker of microbial infection. Whether PS may have a role in predicting response to treatment is still unexplored.
Aims: We aimed to assess the kinetic of PS concentrations in a cohort of adult febrile neutropenia patients with haematological malignancies with particular interest to the time course in relation to the appropriateness of first-line empirical antimicrobial treatment.
Methods: From April 2018 to December 2019, consecutive patients admitted to our Unit for high dose chemotherapy alone or followed by autologous bone marrow stem cell transplantation were considered. Three categories were considered: *Sepsis*, *Bacteremia*, and *fever of unknown origin (FUO)*, As index tests, we considered PS, which was measured as follow: at patient admission; on the first day of chemotherapy (CT); at the onset of neutropenia (onset FN-); between 90 and 120 minutes from fever onset (onset FN+, before any broad-spectrum empirical antibiotic therapy); between 48 and 72 hours from the start of antibiotic therapy; between 24 and 48 hours from neutropenia resolution. Changes in presepsin concentration ([72 hours from empirical antibiotic - fever onset]/ fever onset) were categorised according to tertiles. The response to antibiotic therapy and the time to fever resolution according to tertiles of PS concentration were analysed considering in the model the factor tertile. The statistical significance was declared for p<0.05.
Results: 273 episodes (148 subjects, 80 males and 68 females) were eligible for this study. Reason for treatment was acute leukemia in 106 episodes, multiple myeloma in 68, lymphoma in 99. Autologous stem cell transplantation was performed in 68. In neutropenic patients with fever (FN+) or without fever (FN-), there was a statistically significant effect of the febrile status (p=0.0126), the time point considered (p<.0001) and their interaction (p=0.0006). At onset FN+ compared to FN- had higher levels (p<.0001, fold-change 1.82, 95% CI: 0.26 – 2.64; fig.1A). PS concentration was significantly higher in patients with documented bacterial infection (670 ng/L, [165–1267] ng/L than in those with negative cultures (358 ng/L, [105–1134] ng/L (p<0.0001, not shown). A statistically significant reduction was observed at 48-72 hours from antibiotic therapy (median 244 ng/L, range 89-721, p<0.0001; fig.1B). Patients with major reduction of presepsin concentrations from fever onset to antibiotic therapy, according to tertiles, tended to have received early appropriate antibiotic therapy (21/34, 61.7% in tertile 1, < -46%; 11/35, 31.4% in tertile 2, -45 to -17%; 5/35, 14.3% in tertile 3, -16% to +246%; p = 0.0009 for trend; fig.1C). Response to therapy probability was higher in tertiles 1 and 2 compared to tertile 3 ($OR_{1\ vs\ 3}$=3.5 and 95%CI: 1.0-12.4, p=0.0482; $OR_{2\ vs\ 3}$=9.7 95%CI: 2.2-42.5; fig.1D). A graded decrease in fever duration was observed across tertiles of changes for PS (trend *p*= 0.0004).

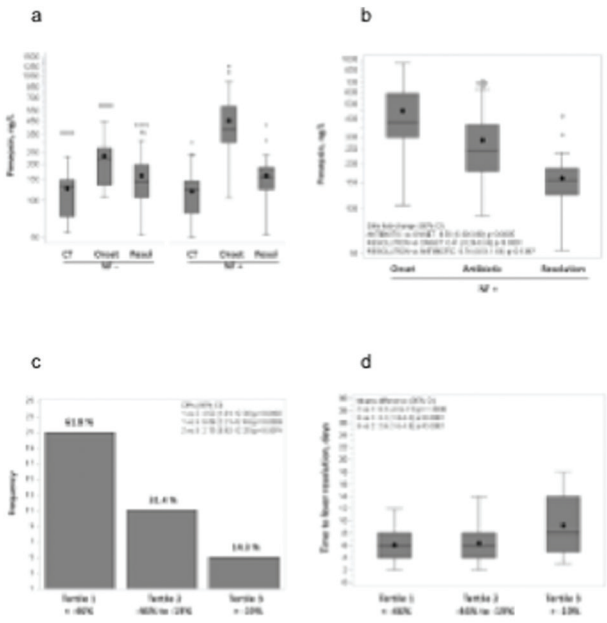


Figure 1

Summary/Conclusion: In conclusion, our study provides preliminary indications that PS has a role in monitoring appropriate antibiotic therapy in oncohematological patients with FN.

EP811 INCREASED USE OF ANTI-INFECTIVE AGENTS AFTER DIAGNOSIS OF MYELODYSPLASTIC SYNDROMES

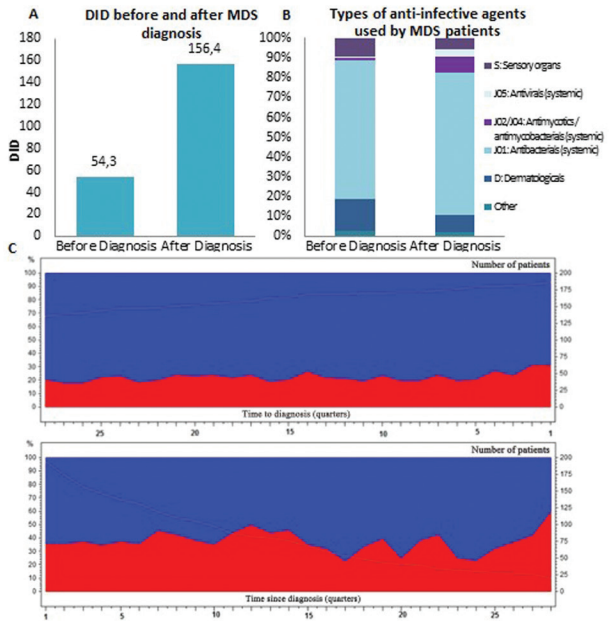
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Background: Infections in patients suffering from myelodysplastic syndromes (MDS) have a negative impact on quality of life, health care costs and are associated with mortality. Little is known about the burden of infections in MDS patients. Current estimates of infection rates are based on results from clinical trials or retrospective analyses that only reviewed hospital records. There are no population-based real-world studies that investigate the burden of infections by the use of anti-infective agents in MDS patients in first and second line care.
Aims: The primary objective of this study was to analyse the increase in susceptibility for infections in patients diagnosed with MDS. Therefore, the prescriptions of anti-infective agents in Dutch MDS patients, both before and after diagnosis of MDS, were collected. Dutch policies on prescribing anti-infective agents are strict and therefore are an accurate reflection of infection rates.
Methods: We performed an observational, population-based study using the HemoBase population registry, including all MDS patients diagnosed between 2005 and 2017 in Friesland, a Dutch province with circa 650.000 inhabitants (Rozema et al. (2021), accepted, Blood Advances). Informed consent was obtained. Community pharmacies provided information about the use of anti-infective agents from 10 years before MDS diagnosis to end of follow-up (Dec. 2020). These data were combined

with HemoBase registry data. Results were presented as prescriptions/year, treatment days/year or defined daily dose per 1000 patient days (DID). Descriptive analyses and Wilcoxon Signed Rank tests were performed using IBM SPSS version 24.

Results: A total of 292 MDS patients were identified, of whom in 201 patients (70%) information on prescribed anti-infective agents was obtained. The response rate was 91.4% for pharmacists and 56.5% for dispensing general practitioners. Patients received significantly more prescriptions/year after diagnosis (median 2.5; 95% CI: 2.1-3.0) than before diagnosis (median 0.8; 95% CI: 0.7-1.0; p<0.01). Likewise, the number of treatment days/year significantly increased (p<0.01) from a median of 7.7 (95% CI: 5.4-10.2) treatment days/year before diagnosis to 23.7 (95% CI: 16.8-31.0) after diagnosis. This corresponds to 54.3 DID (95% CI: 53.7-55.0) before diagnosis and 156.4 DID (95% CI: 154.6-158.2) after diagnosis (rate ratio: 2.9 (95% CI: 2.8-2.9); p<0.01, Fig. 1A). As shown in figure 1C, the prescriptions gradually increased over time. Patients with high-risk MDS did not seem to use more anti-infective agents than low-risk MDS patients (p=0.27). Before diagnosis, 26 patients (12.9%) were admitted to hospital due to an infection, compared to 78 patients (38.8%) after diagnosis; the rate ratio for an infection-related hospital admission was 3.0 (95% CI: 1.9-4.7). Patients mostly received antibacterial agents for systemic use (ATC group J01): 69.6% before diagnosis and 71.3% after diagnosis (Fig. 1B).



Summary/Conclusion: This study showed a significantly increased use of anti-infective agents in patients after diagnosis of MDS in both low-risk and high-risk MDS patients. After the diagnosis MDS, patients had a 3-fold higher risk for infections in an outpatient setting and a 3-fold higher chance for an infection-related hospital admission compared to before MDS diagnosis. To our knowledge, this is the first descriptive population-based study that provides an overall insight in prescribed anti-infective agents both in- and outside the clinical setting in a well-defined representative MDS patient cohort.

EP812 IMPACT OF THE CLINICAL MANAGEMENT OF HYPERTENSION, INFLAMMATION AND THROMBOSIS ON THE SURVIVAL OF HOSPITALIZED COVID-19 PATIENTS

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Background: The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) usually resolves with no further complications. However, in some patients, an unbalanced immune response and the occurrence of thrombotic events lead to severe clinical manifestations; with age, gender and comorbidities (namely, arterial hypertension [AHT] or diabetes) as acknowledged risk factors. The clinical management of these hospitalized patients is still a matter of debate, and the effectiveness of certain treatments (angiotensin-converting enzyme 2 inhibitors [ACE2-Is], angiotensin receptor blockers [ARBs], non-steroid anti-inflammatory drugs [NSAIDs], corticosteroids, and low molecular weight heparin [LMWH]) to handle said manifestations and comorbidities has been questioned.

Aims: In this study, we aim to assess the impact of the clinical management of arterial hypertension, inflammation and thrombosis on the survival of COVID-19 patients.

Methods: This observational retrospective study is composed of two Spanish cohorts, one from HM Hospitales and another from Hospital Universitario Central de Asturias, with 2035 and 72 laboratory-confirmed COVID-19 adult patients, respectively. The global analysis was performed in the HM cohort after stratification to study the impact of the different treatment arms, having as control group on each arm the respective untreated patients. The HUCA cohort was used as validation of the implementation of thromboprophylaxis in hospitalised patients. The primary end point was the time from hospital admission to discharge or death. Cox proportional-hazards regression, Kaplan-Meier survival curves and propensity score matching were employed, to further control for potential bias and the non-randomized treatment administration. Demographic variables (sex and age), comorbidities (diabetes and AHT), and treatment arms (when opportune) were included as co-variates. All analyses and figures were generated using R software (version 3.6.1).

Results: Cox regression identified age (older), sex (males) and AHT (but not diabetes) as risk variables in the HM cohort. Among the treatment arms of study, all treatment regimens, including LMWH alone or in combination with corticosteroids and anti-AHT drugs, conferred a significant advantage, as opposed to corticosteroids alone or in combination. Furthermore, the management of AHT with ACE2-Is or ARBs is not detrimental, as initially reported, and neither was the use of NSAIDs. On the contrary, our analysis shows that the use of corticosteroids, including dexamethasone, is not beneficial. Importantly, the therapeutic or prophylactic management of thrombosis in COVID-19 patients with LMWH, significantly improves the survival of hospitalized patients.

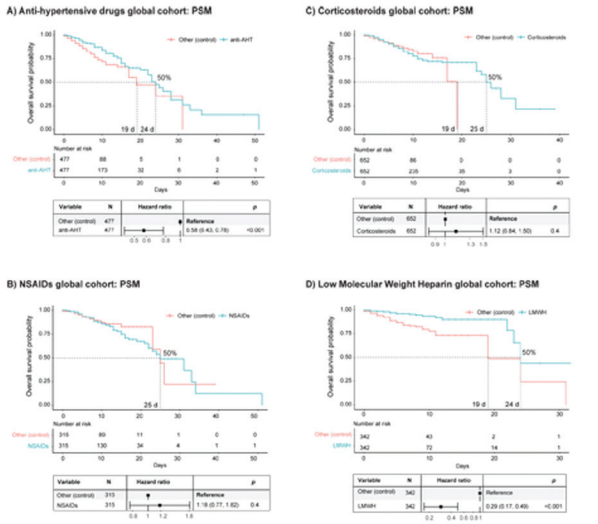


Figure 1. Impact of the different treatment arms on the survival of COVID-19 patients. Kaplan–Meier curves and forest plots obtained from Cox regression after propensity score matching (PSM) of COVID-19 patients treated or not with anti-AHT drugs (ACE2-Is and ARBs) **(A)**, NSAIDs **(B)**, corticosteroids **(C)** and LMWH **(D)**.

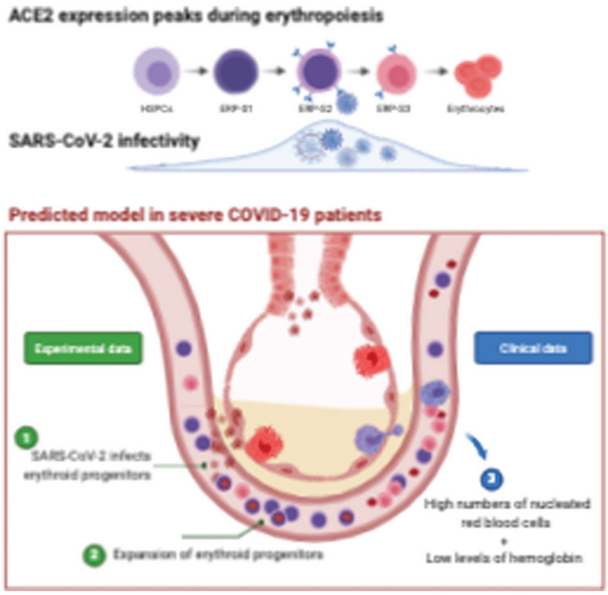
Summary/Conclusion: These results suggest cautiousness when administering corticosteroids for immunosuppression, and whether to limit said administration to the situations that require it (i.e., to facilitate pulmonary capacity as part of the general guidelines in patients with respiratory distress), but not as a protocolized guideline to treat hospitalized COVID-19 patients in general. In particular, dexamethasone may potentially be detrimental to patients in general wards (not critically ill and without respiratory distress). Additionally, they support the effectiveness of thrombosis prophylaxis with LMWH on COVID-19 patients as a first-line treatment, without the need to compromise the treatment of comorbidities.

EP813 HUMAN ERYTHROID PROGENITORS ARE DIRECTLY INFECTED BY SARS-COV-2: IMPLICATIONS FOR EMERGING ERYTHROPOIESIS IN SEVERE COVID19 PATIENTS

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Background: An aberrant increase of erythroid progenitors in circulation have been reported in severe COVID-19 cases and correlates with severity and mortality. The infectivity of SARS-CoV-2 in HSPCs and more particularly in erythroid progenitors have not been characterized. In this report, we have studied HSPCs and different erythroid progenitor populations to assess if they can be infected by SARS-CoV-2.
Aims: Demonstrate that SARS-CoV-2 can infect erythroid progenitors and disrupt erythropoiesis causing the aberrant increase of nucleated red blood cells observed in severe COVID-19 patients.
Methods: Clinical data: A sample of 30 patients who were being treated for COVID-19 on intensive care units at King's College Hospital; **RNAseq data import and analysis of ACE2 expression:** RNAseq dataset was downloaded from GSE118537; **Isolation of mononuclear cells from human cord blood, bone marrow and peripheral blood; Flow cytometry analysis and cell sorting; mRNA quantification by RT-qPCR; Immunostaining, confocal microscopy and immunofluorescence quantification of ACE2 and TMPRSS2; SARS-CoV-2 production and infection; Colony-forming Unit (CFU) assay**
Results: - Patients treated for severe COVID-19 show a rapid and profound decline in hemoglobin following admission. Interestingly, this is associated with the appearance of circulating nucleated red cells.
- Publicly available datasets indicate that ACE2 and TMPRSS2 expression is scarce among hematopoietic cell types, and absent on human HSPCs. Progenitors of the erythroid lineage appear to be the only cell types expressing both ACE2 and TMPRSS2 among the cells present in the bone marrow (The Human Cell Atlas Bone Marrow Single-Cell Interactive Web Portal). Intrigued by this observation, we used detailed datasets of in vitro human erythropoiesis and we found that ACE2 expression peaks during erythropoiesis. Erythroid progenitors of Stage 1 (ERP-S1) can be defined as CD34+CD117+CD71+CD235a-, ERP-S2 as CD34-CD117+CD71+CD235a- and ERP-S3 as CD34-CD117-CD71+CD235a+.
- ERP-S2 cells are highly susceptible to SARS-CoV-2 infection. Importantly, our results showed that SARS-CoV-2 can infect and amplify its genome in erythroid progenitors of Stage 2 and Stage 3 but is not able to bind and infect HSPCs from the bone marrow.
- We also infected the erythroid progenitors from peripheral blood at lower MOI and we obtained similar results. After being in the presence of SARS-CoV-2, erythroid progenitors produce more colonies. We detected the virus in the colonies from ERP-S2, indicating that SARS-CoV-2 remains in ERP-S2 after 14 days of the initial infection.
Summary/Conclusion: We document here that intensive care COVID19 patients suffer a profound decline in hemoglobin levels but show an increase of circulating nucleated red cells, suggesting that SARS-CoV-2 infection either directly or indirectly induces stress erythropoiesis. Early erythroid progenitors, defined as $CD34^{-}CD117^{+}CD71^{+}CD235a^{-}$, show the highest levels of ACE2 and constitute the primary target cell to be infected during erythropoiesis. SARS-CoV-2 causes the expansion of colony formation by erythroid progenitors and can be detected in these cells after two weeks of the initial infection. Our findings constitute the first report of SARS-CoV-2 infectivity in erythroid progenitor cells and can contribute to understanding both the clinical symptoms of severe COVID19 patients and how the virus can spread through the circulation to produce local inflammation in tissues, including the bone marrow.



EP814 HUMORAL IMMUNITY RESPONSES AFTER VACCINATION FOR HEPATITIS B VIRUS IN AUTOGRAFTED PATIENTS: A SINGLE CENTER EXPERIENCE

N. Al Musailem [1,*], A. Al Shami [1], A. Estanislao [1], J. Bacal [1], M. Al Enazi [2], N. Al Mulhem [3], A. Bahrani [3], R. Attas [3], H. Al Hashmi [1], P. Kaloyannidis [1]

[1]Adult Hematology & Stem Cell Transplantation Department, [2]Family Medicine Department, [3]Department of Pathology and Laboratory Medicine, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Background: Vaccination against hepatitis B virus (HBV) is highly recommended for hematopoietic stem cell transplantation (HSCT) recipients who have no protective antibody titers against the surface antigen (anti-HBs). The effectiveness of vaccination, reflecting the immune system functionality, represents a reliable marker for the qualitative immune reconstitution post HSCT. However, it is subjected to several factors (pre-immunization, HSCT type, conditioning regimen, graft source, etc.) thus complicating the drawing of secure conclusions as for the efficacy of vaccination programs post HSCT. With regard to autologous HSCT (AHSCT), the general aspect is that the immune system recovers soon after AHSCT therefore patients (pts) after a period of approximately 6 months post AHSCT are considered to be as immunocompetent as healthy individuals.
Aims: We evaluated the HBV vaccination responses in pts autografted for malignant diseases who had anti-Hbs titers <10 IU/ml both before AHSCT as well as the time of vaccination and were in remission and off chemotherapy post-transplant.
Methods: Twenty seven pts aged 51,6 (22-67) years (ys), autografted for lymphoma (n=19), multiple myeloma (n=9) and leukemia (n=1) were included in the study. The median CD34+ infused cells were $6{,}4\times10^{6}$/kg. The engraftment was successful and regarding the lymphocytes recovery, the median absolute count at +100 day was 1740 (450-4090)/mm^3. After a median of 4,3 (0,6–8,5) ys post AHSCT, the recombinant HBV vaccine Genevac-B® (Serum Institute of India Pvt. Ltd) was given monthly, in a 3 doses schedule (20 mg/injection). The median lymphocytes count during the vaccination period were 374/mm^3, 1643/mm^3, 628/mm^3, 844/mm^3, and 301/mm^3 for the B, CD3+, CD4+, CD8+ and NK cells respectively; all within normal ranges. We considered as effective response the presence of >10 IU/ml anti-HBs titers and the ultimate response rates of pts who successfully completed the 3 vaccine doses, were compared with an internal group of healthy individuals (control group) who were also vaccinated in our centre with the same product during the study period.
Results: After the 1st dose the response rate was 11% (3/27 pts), reaching to 81% (21/26 pts) after the 2nd and to 88% (23/26 pts) after the 3rd

dose. In univariate (student's T-test) and multivariate (logistic regression) analysis, no factor significantly affected the achievement of protective anti-HBV responses after vaccination completion, probably due to the size of our study group. The observed response rates after each dose were lower compared to the reported ones based on the reported product's efficacy profile (19%, 86% and 100% after the 1st, 2nd and 3rd dose respectively). In the direct comparative analysis with our control group, a strong trend for inferior responses was noticed for the autografted pts (88% vs 100%, p=0,07).
Summary/Conclusion: This study on a relatively homogenous group of pts is, to our knowledge, the only one that directly compares the HBV vaccine responses in autografted pts with healthy individuals who were vaccinated in the same area, similar period with the same product, thus providing an accurate comparative analysis. Although the intervention was offered late post AHSCT and pts had already adequate lymphocytes subpopulations counts at the time of vaccination, the response rates were lower compared to healthy individuals. Our results, in agreement with others, are indicative of a long lasting immune impairment post AHSCT highlighting the necessity of prolonged surveillance and intensified vaccination programs for autografted pts.

EP815 DETECTION OF SARS-COV-2 INFECTION PREVALENCE IN 474 HEMATOLOGIC PATIENTS UNDER THERAPY WITH A TRIPLE SCREENING PROCEDURE INCLUDING TRIAGE, MOLECULAR NASOPHARYNGEAL SWAB AND RAPID SEROLOGICAL TEST.

A. Candoni [1,*], G. Petruzzellis [2], S. Volpetti [1], G. Facchin [1], R. Stocchi [1], J. Olivieri [1], C. Marcon [1], A. Sperotto [1], V. Radici [1], R. Mullai [1], C. Comuzzi [1], F. Calabro' [1], R. Fanin [1]

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Background: There are still limited epidemiological data regarding the efficacy and performance of screening procedures to detect the prevalence of SARS-CoV-2 infection (including symptomatic cases and asymptomatic carriers) in hematologic outpatients undergoing active anticancer therapy.
Aims: The primary endpoint of the study was to estimate the effective prevalence of SARS-CoV-2 infection (including silent and symptomatic cases) in consecutive and unselected hematologic outpatients under anticancer therapy.
Methods: Between May 1, 2020, and June 15, 2020 (under first wave of SARS-CoV-2 pandemic), 474 consecutive hematologic patients (pt) undergoing anticancer therapy, were evaluated and tested for SARS-CoV-2 with a combined screening procedure, including triage, molecular nasopharyngeal swab (NPS) and rapid serological immunoassay (for anti- SARS-CoV-2 IgG/IgM). The most frequent neoplasms was: lymphoma in 198 case, multiple myeloma in 103 cases, acute leukemia in 83 cases.
Results: Overall, 1263 SARS-CoV-2 NPS (median/pt=3 NPS, range 1-9) and 474 serological tests (one for each pt), were performed. At triage questionnaire, a total of 60 (13%) pt self-reported symptoms potentially COVID-19 related. The presence of symptoms (mainly fever > 37°C) was more frequent in pt with acute leukemia (23%), myelodysplastic syndromes (50%) and lymphomas (14%). SARS-CoV-2 NPS was positive in 0% of cases, but in 8 pt (1.7%) the specific serological test was positive (4/8 IgM and IgG positive and 4/8 only IgM positive). The prevalence of SARS-CoV-2 infection, in this tested neoplastic population, was 1.7% and, of the 60 cases who declared symptoms potentially COVID-19-related (positive triage), only 1/60 (1,6%) was found to be SARS-CoV-2 positive.
Summary/Conclusion: 1) This is a large study detecting the prevalence of SARS-CoV-2 infection (including asymptomatic cases) in oncohematologic pt receiving active therapy, during the first epidemic peak and under the restrictive lockdown measures, in one of the active areas of the SARS-CoV-2 circulation. Our findings suggest that a questionnaire-based triage system, even if accurate and important, has a low predictive value for the identification of cancer patients with SARS-CoV-2 infection since a differential diagnosis between tumor related symptoms (such as fever, cough or dyspnea) and COVID-19 related symptoms is always very difficult.
2) Lacking specific recommendations for the detection of asymptomatic SARS-CoV-2 infection carriers, a combined diagnostic screening (including triage +NPS +serological test) could be useful in detecting the right prevalence of SARS-Cov-2 infection in neoplastic pt populations including silent infection cases. This prevalence data can obviously be variable according to the territorial context, to the entity of the restrictive measures adopted and to the epidemic curve. Nevertheless, its knowledge is important to balance risks/benefits of oncologic treatments and to avoid, if the prevalence is low, the reduction of dose intensity or a selection of less intensive, but also less effective, anticancer therapies.

EP816 COVID-19 INFECTION IN MULTIPLE MYELOMA PATIENTS – CZECH EXPERIENCE

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Background: COVID-19 disease caused by SARS-CoV-2 coronavirus has affected millions of people worldwide. The mortality of this infection varies with age and comorbidities up to more than 10% in very elderly population. The aim of our study was to determine the mortality rate and healthcare utilization among multiple myeloma patients and describe the potential risk factors for death.
Aims: The aim of our study was to determine the mortality rate and healthcare utilization among multiple myeloma patients and describe the potential risk factors for death.
Methods: We retrospectively analyzed entries in the Czech Registry of Monoclonal Gammopathies from patients who were infected with SARS-CoV-2 from March 2020 until January 2021. Demographic data, treatment patterns, comorbidities, symptoms of COVID-19, treatment modalities and healthcare utilization was compared in survivors and non-survivors.
Results: Overall, 158 patients with MM and COVID-19 with known outcome of the infection were identified. There were 72.8% (115/158) survivors and 27.2% (43/158) deceased patients. Both groups were balanced in gender, ECOG, M protein isotype, ISS stage and comorbidities. Non-survivors were significantly older (median 71.5 years vs 67.9 years, p=0.046). There were no differences between previous treatment lines in either group. Patients received median one prior line of therapy (range 0-6, p=0.994). 95% of patients were exposed to IMiDs (150/158), 89.9% to proteasome inhibitors (142/158) and 18.4% (29/158) to anti-CD38 antibody. Autologous stem cell transplantation was used in 36.7% (58/158) of patients. There were no differences in administered treatment in both groups. Inpatient treatment due to COVID-19 was required in 46.8% (74/158) of patients. Survivors hospitalization rate was 31.3% (36/115) and 88.4% (38/43) in non-survivors. In-hospital mortality was 51.4% (38/74). Non-survivors had more intensive care unit stays (4.3% vs 55.8%, p<0.0001) and needed more ventilation support (0.9 % vs 23.3%, p<0.0001). Mortality of patients who needed ICU was 82.8% (24/29 ICU stays) and 32.7% (16/49 ward stays) in patients who needed standard ward inpatient therapy. Mortality of patients needing artificial ventilation was 90.9% (1/11). Mortality of patients needing non-invasive ventilation or high flow nasal oxygen and 85.0% (17/20). Mortality of patients needing

low flow nasal oxygen was 50% (19/38). Table 1 shows results in detail.

Type of care	Survivors (n=115)	%	Non-survivors (n=43)	%	p value
Outpatient (N, %)	79	68.7	5	11.6	<0.0001
Hospitalized (N, %)	36	31.3	38	88.4	<0.0001
Standard ward (N, %)	33	28.7	16	37.2	0.4029
ICU (N, %)	5	4.3	24	55.8	< 0.0001
Length of stay (median, range)	11	(4-40)	10	(2-42)	0.4691
Oxygen support					
Without O2 (N, %)	85	73.9	5	11.6	< 0.0001
NIV / HFNO (N, %)	3	2.6	17	39.5	< 0.0001
ALV (N, %)	1	0.9	10	23.3	< 0.0001
Oxygen (low flow) (N, %)	19	16.5	19	44.2	0.0006
Symptoms of COVID-19					
Symptomatic (N, %)	76	66.1	39	90.7	0.0038
Fever (N, %)	49	42.6	29	67.4	0.0093
Cough (N, %)	38	33.0	26	60.5	0.0033
Dyspnea (N, %)	24	20.9	28	65.1	< 0.0001
Chills (N, %)	3	2.6	3	7.0	0.4174
Muscle pain (N, %)	11	9.6	2	4.7	0.4995
Headache (N, %)	13	11.3	3	7.0	0.6127
Sore throat (N, %)	1	0.9	0	0.0	0.6076
Loss of taste or smell (N, %)	12	10.4	1	2.3	0.1849
Treatment					
Convalescent plasma (N, %)	2	1.7	2	4.7	0.6397
Hydroxychloroquine (N, %)	0	0.0	1	2.3	0.6076
Remdesivir (N, %)	7	6.1	7	16.3	0.0907
Complications					
Bacterial superinfection (N, %)	11	9.6	15	34.9	0.0003
Relation to neutropenia (N, %)	0	0.0	3	7.0	0.0275
Thrombotic complications (N, %)	0	0.0	2	4.7	0.1265

ICU: intensive care unit, NIV: non-invasive ventilation, HFNO: high-flow nasal oxygen, ALV: artificial lung ventilation

Summary/Conclusion: The mortality of MM patients with COVID-19 was very high especially in patients in need of any type of ventilation support. Healthcare utilization was high with almost half of the infected myeloma patients needing inpatient treatment. No apparent risk factors in terms of disease status or previous treatment were identified.
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EP817 EPIDEMIOLOGY AND MORTALITY IN BACTERAEMIA IN ADULT PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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Background: Patients with hematological malignancies have higher risk of acquiring infectious complications and bacterial bloodstream infections.
Aims: The aim of the study evaluated epidemiology, outcome and risk factors of mortality in *bacteraemia in adult patients with hematologic malignancies*.
Methods: In this retrospective study, all adult patients with hematologic malignancies who developed documented bacteraemia between January 2010 and December 2019 were evaluated. Risk factors with a P-value less than 0.20 were initially included in the binary logistic regression model to determine the independent risk factors for mortality Bloodstream infection in adult hematologic malignancies. Then the model was reduced by means of manual backward elimination. P values of 0.05 or less were considered statistically significant.
Results: Two hundred and thirty one bacteraemia episodes were identified in 174 patients. Acute myeloid leukaemia (AML) was the most common and accounted for 57.1% followed by acute lymphocytic leukaemia (ALL) for 31.2%. The bacteraemia occurred in 140 patients (60.6%) with uncontrolled/relapse or refractory disease (89 (38.5%) of them during induction chemotherapy). Neutropenia was observed in 207 episodes (89.6%), during more than 10 days in 172 episodes (74.5%) and more than 80% have severe neutropenia. Gram-negative and Gram-positive bacteria accounted for 179 (77.5%) and 52 (22.5%) of bacteraemias pathogens, consequently. In blood cultures; Klebsiella pneumonia, Escherichia coli and Staphylococcus aureus were detected in 34.6%, 17.3% and 15.6% of the samples, respectively. Fifty-eight of the bacteraemias pathogens were multi-drug resistant bacteria (25.1%). Thirty-five (15.2%) of the cultured Gram-negative bacterias were extended spectrum beta-lactamase (ESBL). Carbapenemase positive culture was in 25 episodes (10.8%) in Gram-negative bacteria cultures. During 90 (39%) episodes of bacteraemias, patients had sepsis related organ failure or organ dysfunction. Forty-seven died related to a bacteraemias (K. pneumoniae bacteraemias had the highest case-mortality (25 cases)). The independent risk Factors influencing mortality were: MASCC<21 (P: 0.039) and qSOFA>2 (P: $<10^{-3}$).
Summary/Conclusion: Our study shows that Gram-negative bacteria are predominant for this population. In our population, MASCC<21 and qSOFA>2 increase the mortality rate.

EP818 COVID-19 INFECTION IN PATIENTS WITH HEMATOLOGICAL DISEASES IN BRAZIL: CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS

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Background: The COVID-19 pandemic had a high burden in Brazil. To date, data on mortality and prognostic factors of COVID-19 infection in Brazilian patients with hematological disorders are scarce.
Aims: To describe the characteristics and outcomes of patients with hematological disorders admitted to the hematological COVID care unit of a reference center in Brazil;to analyze the impact of prognostic factors on in-hospital mortality.
Methods: This prospective, single-center study,included 118 patients who have been admitted to the hematological COVID care unit of the Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo, Brazil, from March to September 2020.All patients had >18 years,an underlying hematological disease and a moderate or severe COVID-19 infection.For analyses, patients were grouped in:(1)benign or no oncological treatment(n=43),(2) intensive chemotherapy,including induction protocols for acute leukemia and stem cell transplantation conditioning(n=44) or(3) intermediate chemotherapy,including lymphoma regimens,myeloma triple treatment or continuous treatment(n=31).The primary outcome was in-hospital mortality;secondary outcome was overall survival after admission in the COVID-19 unit.Univariate analysis(UVA) used odds ratio(OR) for baseline characteristics and ROC curve analysis for laboratory tests collected at admission.Multivariate analyses(MVA) were adjusted by age and hematological disease status group.The median follow-up and survival time after COVID-19-unit admission were estimated by Kaplan-Meier method.All statistical tests were two-sided;p-values<0.05 were considered significant.
Results: Median age was 58(19-90) years and 55% of patients were male. Most patients(83%)had hematological malignancies,-mainly non-Hodgkin lymphoma(29%) and multiple myeloma(19%). The most frequent benign disease was sickle cell disease(5%).12 patients had undergone hematopoietic stem cell transplantation (HSCT),4 allogeneic and 8 autologous.70% had at least one comorbidity, mostly arterial hypertension and diabetes mellitus. Thromboembolic events occurred in 9%. Median hospital stay in the COVID-19 unit was 12(1-63) days;54% needed intensive care and 41% mechanical ventilation.In-hospital mortality rate was 41%[95%CI 32-50];most deaths occurred in patients with malignancies.Median follow-up was 73(95%CI 61-81) and 54(95%CI 39-66) days after admission and discharge from the COVID-19 unit, respectively.UVA showed a risk of death increased by 25% every 10 years old.The risk of in-hospital death was 3-fold and 5-fold higher in groups 2 and 3 compared with group 1.MVA showed higher risk of death in patients from group 2(OR=11.1,95% CI 2.9-54.8) or group 3(OR=9.7,95%CI 2.4-47.5]),who had lactate dehydrogenase(LDH)>440 U/L(OR=16.8,95%CI 4.9-71.8),C-reactive protein(CRP)>100 mg/L(OR=4.1,95%CI 1.4-13.6) or platelet count<150x10e9/L(OR=3.7,95%CI 1.3-11.7), regardless of age(OR=1.2,95%CI 1.0-1.5).79% of in-hospital deaths were from COVID-19; others were mainly due to hematological disease.The

overall median survival time after admission was 92 days(95% CI 34-NA) and the 75-day survival probability was 51%(95%CI 41-60).25% of patients had hospital readmission,mostly due to other infections.
Summary/Conclusion: In line with other reports,patients with hematological diseases are at higher risk of mortality from COVID-19 infection,particularly in low and middle income countries.In our cohort, prognostic factors were status of disease,platelets count,LDH and CRP. These findings might help risk stratification and prioritization of vaccines in this setting.

EP819 CLINICAL OUTCOMES OF COVID-19 IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES TREATED IN THE COMMUNITY SETTING IN CROATIA

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Background: The coronavirus infectious disease-19 (COVID-19) has caused a pandemic. Patients with hematological malignancies COVID-19 have worse clinical outcomes when compared to the general population; however, data regarding the outcomes of patients with hematological malignancies suffering from COVID-19 treated outside academic centers are scarce.
Aims: To analyze the clinical course of COVID-19 in patients with hematological malignancies treated in the community setting.
Methods: In this multicenter retrospective study patients suffering from hematological malignancies in whom COVID-19 was diagnosed from March 1, 2020, to February 16, 2021, were included from three community hospitals in Croatia (General Hospital "Dr. Josip Benčević", General Hospital Šibenik and General Hospital Zadar). These hospitals cover area of about 405 000 inhabitants that accounts 10% of total Croatian population.
Results: During the study period there were a total of 21 745 people diagnosed with COVID-19 in that area and 66 (0.3%) had malignant hematological disease; most of them were male (65.15%) with a median age of 70 years (20-92). The majority of the patients (56%) became infected with COVID-19 during the second wave (November and December 2020). Lymphoproliferative disorders were recorded in 41 (62%) patients and 25 (38%) had myeloproliferative disorders. Among lymphoproliferative disorders, 16 patients had chronic lymphocytic leukemia, 18 had non-Hodgkin's lymphomas and 7 multiple myeloma. In the myeloproliferative group, 14 patients had Ph-negative or Ph-positive chronic myeloproliferative neoplasms, 2 acute myeloid leukemia and 9 had myelodysplastic syndrome. The majority of patients with lymphoproliferative disorders were not in active treatment (54%) while 34% and 12% of patients acquired COVID-19 during the first- or later lines of treatment, respectively. A total of 45 (68%) patients needed hospitalization; the majority had lymphoproliferative disorders (64.4%). Among hospitalized patients, 42 (93.3%) patients had pneumonia and 38 (84.4%) needed oxygen therapy and 8 (17.7%) were treated in the intensive care unit (ICU). Four patients had thromboembolic complications and two had hemorrhages during hospitalization (a total of 13.3%). Out of 66 patients with COVID-19, 12 patients died (18.1%) and the total mortality rate of hospitalized patients was rather high (27%), with the majority of them suffering from lymphoproliferative disorders (75%).
Summary/Conclusion: The COVID-19 pandemic is strongly affecting patients with hematologic malignancies. These data gathered from a community setting demonstrated that patients with hematological malignancies suffering from COVID-19 have poor clinical outcomes with a high rate of pneumonia, frequent hospitalizations and a high mortality rate. More worrisome, patients with lymphoproliferative disorders were shown to have particularly poor outcomes; thus, future studies evaluating reasons for poor clinical outcomes in patients with COVID-19 and lymphoproliferative disorders are of utmost importance. Education, social distancing and development of new drugs against COVID-19 are important strategies to protect this highly vulnerable population.

EP820 INFECTION BY SARS-COV-2 IN HEMATOLOGIC PATIENTS: AN UNICENTRIC RETROSPECTIVE STUDY

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Background: The coronavirus disease 2019 (COVID-19) pandemic has imposed several constrains in the medical practice, especially in hematologic patients (pts) where a higher mortality rate is expected. In our center strict measures were implemented earlier, with the use of personal protective equipment, hand wash at all times, internal separated circuits, frequent prophylactic tests, teleconsultation and rapid isolation of positive cases. However, data is still limited and risk factors for increased susceptibility remain unclear.
Aims: Characterize our pts with COVID-19 regarding the type of hematologic disease, the respective treatment, infection severity and identification of any possible risk factors that may have impact in the outcome.
Methods: Pts with a positive quantitative RT-PCR from nasopharyngeal swab between 18/03/2020 and 02/02/2021 were identified. Epidemiologic, laboratory, and clinical characteristics were retrospectively collected. Chi-square and Mann-Whitney-U tests were performed to identify statistical differences between groups and logistic binary regression to assess predictive risk factors. Severity of illness was defined by level of care [ambulatory, general inpatient wards and intensive care unit (ICU)], need for respiratory support, incidence of thrombotic events, acute kidney injury and/or death. Active hematologic treatment was defined as therapy within 6 months of COVID-19 diagnosis.
Results: A total of 81 pts were identified, with a median age of 61 years (19-88), 52% were male, 63% had an ECOG PS 0 and 69% had at least one comorbidity (hypertension 36%, dyslipidemia 21%, cardiovascular disease 21%, diabetes mellitus 14% and pulmonary disease 11%). Regarding the hematologic disease, 83% had a neoplastic malignancy (non-Hodgkin lymphoma 30%, myeloproliferative neoplasms 16%, acute myeloid leukemia 11% and multiple myeloma 11%), 64% were in active treatment and 43% had active disease. Concerning the COVID-19 infection, 46% required hospital admission among which 65% needed respiratory support and 9% admitted to an ICU. Median overall survival (OS) was not reached (84% at 1 month) and the mortality rate was 17%, mainly in pts with active disease and neoplastic malignancy. Non-survival pts had a lower hemoglobin level (8,3g/dL vs 12g/dL; *p-value* 0,016), a higher CRP (218mg/L vs 22mg/L; *p-value* 0,041), acute renal failure (36% vs 6%; *p-value* 0,014), more need of respiratory support (71% vs 27%; *p-value* 0,004) and mechanical ventilation (21% vs 5%; *p-value* 0,022). There were no statistical differences regarding age, absolute lymphocyte count, platelet count and LDH. Regression analysis revealed hemoglobin level (*p-value* 0,026), CRP (*p-value* 0,05) and respiratory support (*p-value* 0,003) as predictive factors for death. In our pts there were no thrombotic events.
Summary/Conclusion: Nearly half of the pts were admitted to the hospital and discharged. In our analysis low hemoglobin level, high CRP and respiratory support were associated with poorer survival, however, given our small sample, these findings need to be confirmed. Contrary to most of the published results, the number of confirmed COVID-19 positive cases was surprisingly low, with only 81 cases in 11 months, with a mortality rate similar to the general population and lower than expected. We believe that implementing early and rigorous protective measures as well as create self-awareness may be the key to improve mortality rate in this highly susceptible population.

EP821 MEASUREMENT OF VARICELLA ZOSTER IGG ANTIBODY IN CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Children treated for acute lymphoblastic leukemia are at increased risk of severe infection with varicella zoster virus (VZV) that causes significant morbidity and mortality. Previous studies have reported the risk of disseminated infection in these patients, in the absence of prophylaxis to be approximately 50%. Hence the importance of identifying patients who have unprotective serum levels of Varicella antibodies as candidates for vaccine after completing their chemotherapy protocol.
Aims: Determine the level of varicella IgG antibody in children treated for acute lymphoblastic leukemia and assess the need for their vaccination after end of therapy.
Methods: A prospective study conducted on 2 groups, each consisting of 44 children treated for acute leukemia at the Pediatric Hematology and Oncology Unit of Alexandria University Children's Hospital. Children in group 1 were on maintenance chemotherapy and in remission ≥ 1 year, while group 2 have completed chemotherapy ≥ 6 months. The level of varicella IgG antibody was assessed by VZV IgG ELISA, it was considered positive (protective) above 0.77 u/ml.
Results: In group 1 (patients on maintenance chemotherapy) males were slightly more represented than females (61.4% vs 38.6%). The median age at the time of the study was 6 years. Most of the studied patients were B-ALL (86.4%) while only (13.6%) were T-ALL. Only 5 (11.4%) were varicella IgG positive, while the remaining 39 (88.6%) were negative with a median IgG titer of 0.07 u/ml. In group 2 (off-therapy patients), 56.8% of patients were males versus 43.2% females. The median age at the time of the study was 10 years, and the median duration since completion of chemotherapy was 24.5 months. Most of the studied patients were B-ALL (93.2%) while only 6.8% were T-ALL. Only 9 (20.5%) were Varicella IgG positive while the remaining 35 (79.5%) were negative with a median IgG titer of 0.12u/ml. In both groups, age of diagnosis, the gender, duration of chemotherapy, type of ALL, and intensity of the treatment protocol did not significantly affect the varicella antibody titer.
Summary/Conclusion: Varicella zoster vaccine should be given to all leukemic patients after completion of chemotherapy as the varicella IgG level was unprotective in the majority of children.

EP822 INVASIVE ASPERGILLOSIS IN HEMATOLOGICAL PATIENTS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN SINGLE-CENTER STUDY

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Background: Invasive aspergillosis (IA) is dominant among fungal disease after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The emergence of new immunosuppressive drugs, the expanding use of antifungal agents with activity against *Aspergillus spp*. on the one hand, and the improvement of treatment, prophylaxis and diagnostic methods on the other hand affect epidemiology and treatment efficacy of IA.
Aims: To estimate the epidemiology of IA in large cohort of allo-HSCT recipients during 1-year period after allo-HSCT in a retrospective single-center study.
Methods: We analyzed 556 patients underwent allo-HSCT from 2017 to 2019 years in CIC 725. Transplantation from related donor was performed in 109 (20%), from unrelated donor – 286 (50%), haploidentical donor – 161 (30%). The median age - 36 years (18-69), men – 48,7%. The median follow up time was 15,6 months. During the observation period, 40 patients with proven and probable IA were included into analysis. According to EORTC/MSG 2019 criteria 2 proven and 38 probable cases were diagnosed in adults with hematological malignances and non-malignant hematological diseases after allo-HSCT.
Results: Thirty-four (6%) patients had IA before HSCT and the only one patient had IA after allo-HSCT. Incidence of IA during 1-year period after allo-HSCT was 7,1% (40/556). IA more common diagnosed in patients with acute leukemia – 35% and lymphomas – 30%. Most of the patients at the moment of IA diagnosis received antifungal prophylaxis with fluconazole (65%) or posaconazole (17,5%). The main site of infection were lungs 95%, sinuses – 5%. The diagnosis of IA were proved by bronchoalveolar (BAL) or sinuses liquid culture in 32,5% cases, and the etiology were: *Aspergillus niger* – 6 (46%), *Aspergillus fumigatus* – 5 (38%), *Aspergillus spp*. – 2 (16%). The median day of IA onset was day +172 (35-315) after allo-HSCT. Factors significantly associated with higher incidence of IA were CMV-infection (p<0.0001) and acute graft versus host disease (p=0.0478), but not disease status, conditioning regimen, donor type or history of IA. Overall survival at 12 weeks for patients with IA was 85%.
Summary/Conclusion: Pre-existing IA had 6% of allo-HSCT recipients. Incidence of IA after allo-HSCT during 1-year period was 7,1% with the median day +172. The main site of infection were lungs, etiology – *Aspergillus niger*. Only CMV-infection and aGVHD were associated with higher risk of IA in post-transplant period. Overall survival at 12 weeks for patients with IA was 85%.

EP823 IMPACT OF ADEQUATE EMPIRICAL BROAD-SPECTRUM ANTIBIOTIC FOR BLOODSTREAM INFECTION IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

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Background: Patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) are exposed to a wide range of severe complications. Bloodstream infection (BSI) is an emergency that occurs frequently and is one of the main causes of morbidity and mortality in these patients. Hence, the importance of knowing the principal microorganisms responsible for this complication and therefore, prescribing the most adequate broad-spectrum empirical antibiotic.
Aims: Our main objective is to describe episodes of BSI between days 0 to 100 in patients undergoing allo-HSCT in our center. Our secondary objectives are to analyze the role of prophylactic antibiotic therapy, the impact of inappropriate empirical antibiotic therapy on patients outcome and overall survival (OS) in patients suffering early BSI.
Methods: A one center retrospective study, with data obtained from the electronic clinical history, of the BSI in allo-HSCT in our center from 2015 to 2020. Statistical analysis has been performed with IBM SPSS.19 using appropriate tests for each case.
Results: Over the selected period, 154 patients underwent allo-HCST (follow-up median of 329 days), whose main characteristics are summarized on Table 1.
63 episodes of BSI were microbiologically identified in 50 patients (32.5% incidence). 12 patients (7.7%) died as a direct consequence of BSI. Having received allo-HCST, BSI occurred on day 11 (median) and day 51.7 (mean average), range of minimum and maximum values 0-100.
100 patients (64.9%) received prophylactic antibiotics, mostly quinolones (57.1%). 7.8% received early treatment with carbapenems. We were unable to establish a significant relationship between the incidence of BSI in patients who received prophylaxis and those who did not, (chi-square, p=0.7) nor for overall survival rate (logrank, p=0.4).
Gram negative bacilli were the most common group (37 BSI, 58.7%), mainly E. Coli (24 BSI, 38%), with 6 BSI caused by non-fermenting GNB (4 Pseudomonas aer., 6.3%). There were 21 cases of BSI (33%) caused by Gram positives (11 Staphylococcus spp - 7 S. epidermidis and 1 S. aureus -, 7 E. faecium, 1 E. faecalis, and 2 Strept. mitis) and 5 by anaerobic microorganisms.
The majority of BSI (60%) were treated empirically during the first hour with empirical antibiotic monotherapy (carbapenem in 66% of the cases). The empiric antibiotics used for 12 of the episodes of BSI (19%) were inadequate according to the microorganism's resistance profile, and 5 of them died as a direct consequence of the BSI (overall crude mortality rate due to BSI 7%, mortality rate directly related to inadequate antibiotic 41.6%).

There were statistically significant differences in overall survival (OS) between patients who suffered BSI during the first 100 days post HSCT and those who did not (log-rank-p<0,001).

Table 1. Characteristics of patients (n=154) undergoing allogeneic HSCT	
Gender	
- Male	90 (58,4%)
- Female	64 (41,6%)
Age (median), years	50 (15-70)
Hematologic Disease	
- Acute leukemia	51 (33,1%)
- Lymphoma	55 (35,7%)
- Myelodysplastic/myeloproliferative syndrome	38 (24,7%)
- Bone marrow failure	6 (3,9%)
- Multiple myeloma	4 (2,6%)
HSCT Conditioning	
- Reduced intensity	69 (44,8%)
- Myeloablative	62 (40.3%)
- Non-myeloablative	23 (14,9%)
HLA Matching	
- HLA-identical	112 (72,7%)
- HLA-mismatch	30 (19,5%)
- HLA-haploidentical	12 (7,8%)
Source of Stem Cells	
- Peripheral blood	147 (95,5%)
- Bone marrow	6 (3,9%)
- Umbilical cord	1 (0,6%)
Acute graft versus host disease	110 (71,4%)

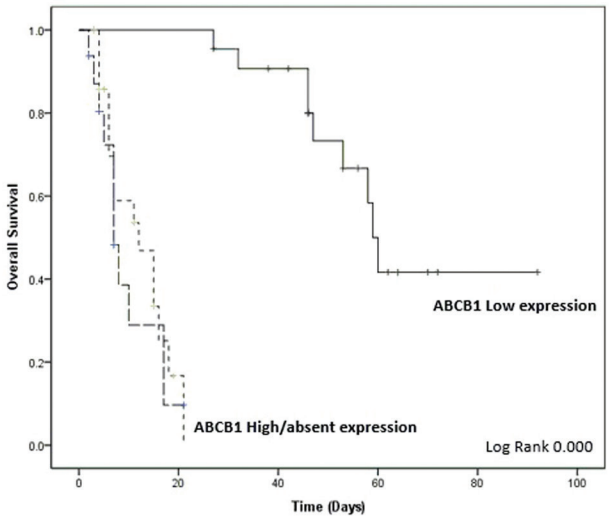
Summary/Conclusion: BSI after HSCT remains a clinical challenge. In our center, one-third of patients develop this complication. Gram negative bacilli are the main germs involved, especially E. coli.
It is absolutely essential to know our environment's epidemiology and the presence of multi-resistant germs, so as to fit empirical treatment to clinical practice. The use of an inappropriate antibiotic can result in a significant mortality increase.
From our experience, the use of prophylactic antibiotics is not indispensable to decrease the incidence of BSI.
We found significant differences in OS between patients who suffered BSI and those who did not. It is necessary to conduct multivariate studies in order to confirm this hypothesis.

EP824 IMPACT OF THE ABCB1 DRUG RESISTANCE GENE ON COMPLICATIONS ASSOCIATED WITH COVID-19

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Background: Overexpression of the ABCB1 gene has been associated with a poor prognosis in various hemato-oncological diseases due to resistance to different chemotherapy types. Usually, the gene expression is low, but drugs like steroids can stimulate it. The COVID-19 infection has affected much of the world, especially Latin America, where mortality is higher than expected, mostly due to hypertension, diabetes, and obesity. Since the beginning of the pandemic, different combinations (chloroquine, azithromycin, antivirals) have been used, some with a moderate benefit (Tocilizumab, convalescent plasma) but without establishing a group that could benefit. The ATP flow pump contributes to cell detoxification, including overdosing of drugs; some drugs are substrates of this pump and modify its operation
Aims: Describe the impact of ABCB1 drug resistance gene expression on mortality and ventilatory support in critically ill patients with COVID-19
Methods: Sixty-one patients (23 women and 38 men) were diagnosed with COVID-19 and included in the study. Mononuclear cells were isolated by Ficoll-Paque (GE Healthcare).RNA isolation was performed using Trizol ™ reagent (Invitrogen, Carlsbad, CA). The RNA obtained's concentration and purity was measured using Nanodrop ™ 2000 (Nanodrop Technologies, Wilmington, ME, USA). cDNA was synthesized from 1 µg of RNA using oligo (dT) and MML-V enzyme from Promega Biotech AB. The expression levels of the ABCB1 gene were determined by qPCR using the TaqMan ™ system (Hs01069047, Applied Biosystems, Inc. Foster City, CA, USA) and normalizing with the endogenous GUSB gene (Hs00939627) (Gene expression = 2 – ΔCT, where ΔCT = CT of the gene of interest - CT of the reference gene.) The expression levels were classified according to the known values in healthy donors.
Results: 61 patients diagnosed with COVID-19 with criteria for hospital care and supplemental oxygen. The majority were men (n = 36, 59%), obesity was the most frequent comorbidity (n = 28.45.9%), followed by diabetes (n = 22, 36.1%) and hypertension (n = 18, 29.5%). Treatment for COVID-19 included high-flow oxygen in combination with the best available therapy; 8.2% (n = 5) started with hydroxychloroquine, 44.3% (n = 27) were treated with metformin hydrochloride, 36.1% with azithromycin, 55.7% (n = 34) with atorvastatin and 95.2% (n = 58) with low molecular weight heparin. During the hospital period. 49.2% (n = 30) required ventilatory support. When analyzing the expression of ABCB1, 63.9% (n = 39) had a high or absent expression, 36.1% showed a low expression. Cases with high / absent expression showed a worse prognosis compared to low expression (Log Rank = 0.000). When comparing the different risk variables, the high / absent expression of ABCB1 was a significant risk factor for death (OR 3.08, [1.02-9.26], p = 0.045) and ventilatory support (OR 2.8, [0.98-8.5], p = 0.054). Other factors such as male gender (OR 2.54 [0.89-7.27], p = 0.081) and older age (OR 5.19, [1.48-18.2] p = 0.010) were associated with a poor prognosis. Diabetes had low impact (OR 1.11, [0.38-3.22], p=0838) on prognosis.



Overall survival according to the ABCB1 expression, low versus high/absent expression.

Summary/Conclusion: Similar to cancer treatment, the modification of the expression of the ABCB1 gene (high or absent) impacts the prognosis of patients with severe COVID-19 disease due to the overuse of drugs

EP825 A COMPARATIVE OUTCOME ANALYSIS OF COVID-19 VS INFLUENZA INFECTION IN PATIENTS WITH ACUTE LEUKEMIA

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Background: Patients with acute leukemia and concomitant SARS-CoV-2 infection suffer from a more severe course of their infection than patients without underlying disease including a higher admission rate to ICU and a higher death rate. Similar observations have been made for concomitant influenza infections.
Aims: The aim of this study is to compare the clinical courses of COVID-19 and seasonal influenza in patients with acute leukemia (AL). This could help to find evidence for certain therapy modifications in AL patients with COVID-19 based on long lasting experience in patients with AL and influenza.
Methods: This is a retrospective single center analysis including all patients with AL and concomitant influenza or SARS-CoV-2 infection who were treated in the department of oncology and hematology of

the University Medical Center Hamburg-Eppendorf, Germany, between February 2013 until now. Data of the clinical course were collected from the patient's electronic medical records. Statistical analysis was performed by using IBM SPSS Statistics, version 26.
Results: In the Influenza-group (n = 21), 71 % were male, the median age was 58 years (r: 20-81). 17 patients (81%) had acute myeloid leukemia (AML), four patients (19%) had acute lymphoblastic leukemia (ALL). 29% had newly diagnosed AL at influenza infection, 33% were in complete remission and 38% were under treatment due to refractory or relapsed disease. 95% were currently under chemotherapy treatment at diagnosis of influenza, 80% of them were treated with intensive chemotherapy. Median duration of aplasia was six days (r: 0-38), five patients had no aplasia during influenza infection. 18 patients were treated with Oseltamivir. 15 patients had an Influenza A with ten cases of H1N1, six patients had an Influenza B. The distribution in the COVID-19 group (n = 15) was similar: 73% were male, the median age was 59 years (r: 21-76). Nine patients (60%) had AML, six (40%) had ALL or acute lymphoblastic lymphoma. 27% had first diagnosis of AL, 27% were in complete remission, 46% had relapsed or refractory disease. All patients were under chemotherapy during SARS-CoV-2 positivity, 80% were treated with intensive chemotherapy protocols. Duration of aplasia during SARS-CoV-2 positivity was 0-36 days (median: 10 days), four patients had no aplasia. With 67% compared to 38% in the influenza group, we scored significantly more critical and severe courses in the COVID-19 group (p = 0.042, Mann Whitney U test) according to WHO-grading. We observed higher rates of pneumonia (93% vs. 67%) in COVID-19 patients with a rate of 40% of acute respiratory distress syndrome (ARDS) in the COVID-19 group compared to 19% of ARDS in the influenza-group. Rate of death due to COVID-19 after 90 days was 20% compared to influenza-associated deaths of 14%. Regardless of the type of infection (SARS-CoV-2 or influenza), we could show that a long aplasia duration is an adverse prognostic marker for 90-days mortality due to COVID-19 or influenza (p = 0.016, Mann Whitney U test).
Summary/Conclusion: Patients with acute leukemia and concomitant SARS-CoV-2 diagnosis present with more severe clinical courses than patients with concomitant influenza, even though the rates of ARDS and critical disease of patients with AL and influenza are high. Therapy regimes with expected long duration aplasia should be possibly avoided in both patient cohorts due to higher mortality in patients with late regeneration of the blood count.

EP826 RISK FACTORS AND OUTCOME OF SARS-COV-2 INFECTION IN HEMATOLOGIC PATIENTS – A SINGLE CENTER EXPERIENCE

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Background: Reports on outcomes of COVID-19 in hematologic patients vary.
Aims: To describe outcomes and risk factors of SARS-CoV2 infection in patients treated in a large university medical center.
Methods: We analyzed the outcomes of our patients diagnosed with COVID-19 between July 2020 and January 2021. The diagnosis was made by PCR from nasopharyngeal/oral swabs or bronchoalveolar lavage. Outcomes were classified as: recovered, persistently positive, died.
Results: We identified 116 patients. Median age was 59 years (range 20-92); 55% were male. 13% had no symptoms; 49% had mild disease with no need for oxygen therapy; 14% with moderately severe disease were treated with low flow oxygen therapy; 25% had severe COVID-19 with respiratory failure and/or septic shock. Except for seven palliative patients, severe cases were treated with noninvasive ventilation (3%), mechanical ventilation (13%) and ECMO (1%). 27% received no treatment for COVID-19; 38% were treated with antibiotics, corticosteroids and/or anticoagulant therapy; 34% received remdesivir, 6% in combination with convalescent plasma; 5% were treated with extracorporeal blood purification. 65 patients recovered (56%), 17 are still positive (15%) and 34 (29%) died.
All 4 untreated and 16 patients that were off treatment for more than 3 months recovered. The outcome of those on treatment is presented in Table 1. Allotransplanted patients had the worst outcome, 5 died, 3 are persistently positive and 1 recovered. Untransplanted patients with acute lymphoblastic and chronic myeloid leukemia fared best, 3 out of 3 in each group recovered. Treatment with anti-CD20 monoclonal antibodies (MoAbs) resulted in an increase in persistent positivity, frequently longer than 8 weeks. Of the 34 patients, 9 died, 12 have persistent infection and 13 recovered. There was no clear-cut correlation between outcome and other types of treatment within diagnostic groups.

TABLE 1 Outcome of patients on treatment

Diagnosis	No. of patients	Recovered	Persistently positive	Died
Allotransplanted	9	1	3	5
AML	11	6	1	4
ALL	3	3	0	0
MDS	5	3	0	2
CML	3	3	0	0
MPN JAK2+	3	1	0	2
Aggressive NHL	22	8	7	7
Indolent NHL	12	5	4	3
CLL	6	2	1	3
MM	20	10	2	8

Summary/Conclusion: COVID19 in hematologic patients, who are currently on treatment, follows a significantly worse course than in the general population or other cancer types. Allotransplanted patients have the highest mortality, while those treated with anti-CD20 MoAbs frequently have a persistent infection with dubious outcome.

EP827 ROLE OF ERYTHROPOIESIS STIMULATING AGENTS (ESAS) IN SUPPORTIVE CARE OF LOW-RISK MYELODYSPLASTIC SYNDROMES

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Background: Erythropoiesis stimulating agents (ESAs) are the frontline treatment in low-risk anemic MDS patients and an employment of this therapy in the earlier stage of the disease can delay the need for RBC transfusion, hypothetically by slowing the disease course. It's matter of debate whether the clinical response is a result of proliferation and maturation of the dysplastic clone or stimulation of residual normal erythropoiesis by ESAs.
Aims: Macrocytosis is one of the cytological hallmarks of dyserithropoiesis in MDS: an analysis of the erythropoietic response to ESAs therapy in a cohort of anemic non trasfusion-dependent MDS patients, enrolled in a retrospective register, RECAMDS, subgroup of Italian register, was performed.
Methods: 183 patients, treated with standard-dose ESAs, have been retrospectively analyzed. Data analysis was performed, according to IWG 2006 criteria, at the baseline, after 3 and 6 months of continuous treatment, with a subanalysis of the patients according to WHO and R-IPSS risk stratification. ESAs were started at mean Hb concentration of 9.31 g/dl, mean serum EPO concentration: 51 mU/L, after a mean time from diagnosis of 6 months (r.1-118).
Results: ORR was 83.6% (153/183), no difference among WHO and IPSS subgroups was found: 132/183 (72.1%) achieved response after 3 months of treatment, while other 21/183 (11.2%) after 6 months. 19 patients with stable disease (non-responders, according to IWG criteria), in which treatment was continued, achieved response after 9 months. In the macrocytic-responders group 83.2% exhibits again macrocytosis after 3 months, while 16.8% become normocytic. In the normocytic-responders group 89.8% exhibits again normocytosis, while 10.2% become macrocytic: in these patients, after 3 months, there was a contemporary worsening in neutropenia and thrombocytopenia, with transfusion-dependence, regarded as first signs of progression of disease. Non-responders were 30/183 (16.3%): in the macrocytic

non-responders group 89% exhibit again macrocytosis after 3 months, while 11% become normocytic; in the normocytic group 76% exhibits again macrocytosis, while 24% become normocytic.

MDS PATIENTS	183
M	89 (49%)
F	94 (51%)
ERYTHROPOIESIS	
BASELINE HB (mean, g/dL)	9.31 g/dL (r. 7.1-11.3)
BASELINE SERUM EPO (mean, mU/mL)	51 mU/mL (r.3-84)
OVERALL RESPONSE RATIO	
RESPONDERS	153/183 (83.6%)
RESPONDERS AT 3 MONTHS	132/183 (72.1%)
RESPONDERS AT 6 MONTHS	21/183 (11.4%)
RESPONDERS AT 9 MONTHS (NON RESPONDERS IN IWG 2006)	19/183 (10.3%)
NON RESPONDERS	30/183 (16.3%)

Summary/Conclusion: These preliminary data can suggest that, in the majority of MDS patients responsive to ESAs, the increase of Hb concentration occurs mainly stimulating erythroid production in MDS clones; in the minority of patients probably it happens recruiting residual polyclonal erythropoiesis. It is interesting to note that stimulating effects of ESAs last even when the expression of dysplasia progresses.

EP828 THE ASSESSMENT OF IMPACT OF COVID-19 IN PATIENTS WITH ACUTE LEUKEMIA

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Background: The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 and represented the pathogen agent that induced COVID-19. The onset and evolution of COVID -19 is severe when is associated with another comorbidities. Patients with acute leukemia present high risk for severe form of COVID-19
Aims: The main objective was to evaluate the particularities of COVID-19 in patients with acute leukemia.
Methods: Our study was prospective and included 49 patients with acute leukemia (27 male median age 64 and 22 female median age 54,5) who also were SARS CoV2 positive between April 2020- February 2021 admitted in Hematology and Intensive Care Unit Departments of Colentina Clinical Hospital Bucharest. The diagnosis was established using molecular test for SARS-Cov2
Results: In the group was included 32 patients diagnosed with acute myeloid leukemia (AML), 9 patients with acute lymphoid leukemia (ALL), 6 patients with acut promyelocytic leukemia and 2 patients with acute bifenotypic leukemia. Severe form of COVID-19 with ICU addmission was diagnosed in 16 patients (32,17%), almost all of them (15 patients) had unfavourable evolution compared with non-ICU patients group with only 1 deceased patient, p<0.0001. The recent chemotherapy followed by severe aplasia was the main negative factor that impacted patient evolution (rho=0.508, p=0.0002), 13 patients admitted in ICU Department and 12 patients in non-ICU. Severe pneumonia (more than 30% lung field) was diagnosed in 17 patients with recent chemotherapy and 4 untreated patients. The type of leukemia or refractory status have not any impact of patient evolution. Antiviral therapy – Remdesivir rapidly introduced in patient's therapy was followed by favourable evolution.
Summary/Conclusion: Patients with acute leukemia are negatively impacted by intensive chemotherapy during COVID-19 evolution. The key for good prognosis of these patients during COVID-19 are rapid diagnosis and antiviral therapy at the onset of the disease.

EP829 TREATMENT WITH REMDESIVIR, DEXAMETHASONE AND CONVALESCENT PLASMA TRANSFUSION IS SAFE AND BENEFICIAL IN HOSPITALIZED COVID-19 PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.

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Background: Adult patients (pts) with secondary immunodeficiency in the course of blood cancers are at risk of severe COVID-19 with an unprecedented 34% risk of death. So far, no standards have been established to manage pts with hematological malignancies (HM) infected with SARS-CoV-2. Rapid control of SARS-COV-2 infection and the prevention of its complicated course are essential for clinical management, especially in those pts who require urgent systemic anti-cancer therapy (SACT). The treatment with remdesivir, dexamethasone and convalescent plasma have been shown to be active in COVID-19 treatment.
Aims: Here we present our experience with the use of these agents in a difficult-to-treat population with various HM (in particular aggressive lymphomas, acute leukemias and progressive indolent lymphomas) whose SACT has been disrupted due to active SARS-CoV-2 infection.
Methods: The observational, single-centre study was conducted from 07 November 2020 to 26 February 2021. All pts were diagnosed with HM and active SARS-CoV-2 infection requiring hospitalization. The severity of COVID-19 was evaluated according to the World Health Organization (WHO) Clinical Progression Scale. The COVID-19 directed treatment included remdesivir (at the standard dose for 5 consecutive days), COVID-19 convalescent plasma transfusion and dexamethasone. All patients gave their written informed consent for the data collection, and ethical clearance was obtained from the Ethics Committee of the Institute of Hematology and Transfusion Medicine, Warsaw, Poland.
Results: At the time of analysis thirty-six pts were included. The median age at COVID-19 diagnosis was 58.5 years (23-86), with male predominance (21 men and 15 women). All pts were diagnosed with HM: 11 pts with acute myeloid leukemia (30.5%), 3 pts with acute lymphoblastic leukemia (8.3%), 6 pts with mantle cell lymphoma (16.7%), 5 pts with chronic lymphocytic leukemia (13.9%), 2 pts with chronic myeloid leukemia (5.5%) and 2 pts with myelodysplastic syndrome (5.5%). The COVID-19 was diagnosed before and during treatment for underlying HM in 5 and 30 pts, respectively. At the time of COVID-19 diagnosis, median WBC was 3.5 G/L (0.05-165), median ANC for myeloid and lymphoid disease were 0.19 G/L (0.0 – 6.3) and 2.3 G/L (0.7-27), respectively. The median serum concentration of hemoglobin and PLT count was 9.2 g/dL (5.4-14.3) and 91 (4-800), respectively. The maximum severity of COVID-19 according to the WHO score was as follows: 4, 5-6, ≥ 7 points in 36%, 42% and 22% of pts, respectively. All pts received remdesivir with dexamethasone. The convalescent plasma transfusion was applied to 21 pts (57%). There were no transfusion related adverse events. The median time of hospitalization was 19.5 days (4-59). In total, 8 pts (22%) died; 7 due to COVID-19 and 1 due to progressive HM. SACT was initiated in all COVID-19 survivors requiring treatment with the median time of 17 days (9-65).
Summary/Conclusion: Treatment with remdesivir, dexamethasone and COVID-19 convalescent plasma transfusion may improve outcomes of adult HM patients infected with SARS-CoV-2 and provide the benefit of early initiation of systemic anti-cancer therapy.

EP830 SLOW INFUSION OF ANTI-THYMOCYTE GLOBULIN SIGNIFICANTLY DECREASED THE INCIDENCE OF REACTIONS AND THE NEED FOR CRITICAL CARE SERVICES

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Background: Antithymocyte globulin (ATG) utilization in HSCT for prophylaxis of GvHD is increasing. ATG administration can be complicated by infusion reactions, sometimes severe leading to treatment interruption or discontinuation. At our center, two protocols have been used with different infusion times.
Aims: The aim from this analysis was twofold; to compare the incidence of reactions between the two infusion protocols and to identify factors associated with infusion reactions.
Methods: Following IRB approval, patients that underwent HSCT from 2011 to 2020 and received ATG were included. From 2011-2015, ATG was infused over 6 hours while from 2016-2020, ATG was infused over 24 hours split over 2 bags given at 12 hours each. All patients received pre-medications with acetaminophen 1000 mg, diphenhydramine 25 mg and hydrocortisone 50 mg with additional doses in case of reactions. All variables were retrospectively collected. Categorical and continuous variables were compared using chi-squared or Kruskal-Wallis, as appropriate. Logistic regression was used for multivariable analysis

incorporating variables with p values of ≤ 0.1 at the univariable stage as well as unbalanced factors between the groups. Specifically; age, gender, diagnosis, stem cell source, conditioning intensity and absolute lymphocyte count (ALC) prior to ATG.

Results: A. Baseline Characteristics: During the study period, a total of 74 patients received thymoglobulin ATG. The median age was 32 years (14-63) and 41 (55%) were males. Underlying diagnosis was malignant in 45 (61%) and non-malignant in the remaining 29 (39%). Myeloablative conditioning was used in 27 (36%) and 11 (15%) received TBI. Most donors (56, 76%) were matched related and 54 (73%) received peripheral blood stem cells (PBSC).

B. Stratification by Infusion Time: A total of 11 (15%) received ATG as short infusion while the remaining 63 (85%) received it via long infusion. The short infusion cohort was significantly younger with higher proportion of female patients (P = 0.041). PBSCs were used more commonly in the long infusion group (P = 0.035). NMA conditioning was significantly used more commonly in the short infusion cohort and accordingly, ALC at ATG infusion was significantly higher as well (P = 0.012 and 0.007, respectively). Other characteristics were similar between the two cohorts (Table 1).

C. Infusion Reactions: Patients receiving short infusion had a significantly higher number of any infusion reactions (P<0.0001) as well as moderate to severe reactions (P<0.0001). Activation of critical care response team (CCRT) and transfer to the intensive care unit (ICU) was significantly higher in the short infusion group (p<0.0001). Interruption or discontinuation of ATG infusion occurred significantly more frequently in the short infusion cohort (P = 0.0001 and < 0.0001, respectively). Time to neutrophil and platelet engraftment as well as incidence of cytomegalovirus reaction requiring pre-emptive therapy was similar in the two groups (Table 2). In multivariable analysis for infusion reactions, only ALC count was predictive with OR 5.9 (1.6-21.9; P = 0.0087) (Table 3).

Baseline characteristics stratified by ATG infusion time

Variable	Short Infusion (n = 11)	Long Infusion (n = 63)	P value
Age, median (range)	20 (14-53)	35 (14-63)	0.023
Female Gender, n (%)	8 (73)	25 (40)	0.041
Diagnosis, n (%)			0.075
Malignant Disease	4 (36)	41 (65)	
Non-Malignant disease	7 (64)	22 (35)	
ECOG, median (range)	1 (0-2)	0 (0-3)	0.39
Donor Type, n (%)			0.19
MRD	9 (82)	47 (75)	
MUD	1 (9)	10 (16)	
MMUD	1 (9)	0	
Haplo	0	3 (5)	
Auto	0	3 (5)	
Stem Cell Source, n (%)			0.035
PBSC	5 (45)	49 (78)	
BM	6 (55)	14 (22)	
Conditioning Intensity, n (%)			0.012
MAC	1 (9)	26 (41)	
RIC	1 (9)	15 (24)	
NMA	9 (82)	22 (35)	
TBI Used, n (%)	2 (18)	9 (14)	0.74
ALC, median (range)	0.9 (0.04-2.39)	0.17 (0-18.4)	0.007
ATG Dose, median (range)	5 (3-15)	5 (2.5-15)	0.21

Incidence of reactions stratified by ATG infusion time

Variable	Short Infusion (n = 11)	Long Infusion (n = 63)	P value
Any Reaction, n (%)	11 (100)	18 (29)	< 0.0001
Moderate-Severe Reaction, n (%)	6 (55)	1 (2)	< 0.0001
CCRT Activation, n (%)	5 (45)	1 (2)	< 0.0001
ICU Transfer, n (%)	3 (27)	0	< 0.0001
ATG Held, n (%)	7 (64)	8 (13)	0.0001
ATG Discontinued, n (%)	5 (45)	3 (5)	< 0.0001
Time to ANC Engraftment, median (range)	19 (12-26)	17 (8-26)	0.2
Time to Plt Engraftment, median (range)	15 (4-30)	14 (6-59)	0.66
CMV Reactivation Requiring Therapy, n (%)	4 (36)	28 (44)	0.61

Logistic regression univariable and multivariable analysis predicting infusion reactions

Characteristic	Univariable Analysis	Multivariable Analysis
Age > median	0.38 (0.15-1.01; 0.053)	0.4 (0.11-1.4; 0.16)
Female Gender	0.78 (0.3-2; 0.61)	1.4 (0.47-4.1; 0.54)
Malignancy Diagnosis	0.67 (0.26-1.76; 0.43)	3.3 (0.58-19; 0.17)
ECOG > 0	0.43 (0.16-1.14; 0.09)	0.4 (0.12-1.17; 0.09)
MAC vs. Other	0.68 (0.25-1.8; 0.44)	0.8 (0.18-3.1; 0.7)
TBI Used	1.35 (0.37-4.9; 0.64)	
PBSC vs BM	0.41 (0.14-1.16; 0.09)	0.8 (0.12-4.8; 0.78)
MRD vs. Other	1.14 (0.39-3.35; 0.8)	
ALC > median	4.3 (1.5-11.9; 0.0046)	**5.9 (1.6-21.9; 0.0087)**
Infusion > 2 days	1.35 (0.51-3.6; 0.55)	

Summary/Conclusion: Prolonging the ATG infusion time significantly decreased reactions leading to lower treatment interruption or discontinuation. Importantly, severe reactions or the need for critical care services was almost not seen in the long infusion group permitting smooth administration of the conditioning regimen. Reactions were also independently increased with higher ALC levels. These observations warrant further validation.

EP831 ANTIBIOTIC-RESISTANT GRAM-NEGATIVE BACTERIAL INFECTIONS IN PATIENTS WITH HEMATOLOGIC MALIGNANCY

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Background: Patients with hematologic malignancies are at high risk for infections caused by antibiotic resistant gram-negative bacteria.

Aims: This study aimed to evaluate the characteristics, antibiotic resistance patterns and prognosis of infections due to multidrug resistant (MDR) gram-negative bacteria in patients with hematologic malignancy.

Methods: Data were collected retrospectively and concerned all infections caused by MDR gram-negative in patients with hematologic malignancy from January 2010 and November 2019 in our department of hematology. Data analysis was initially performed using the univariate analysis (chi^2 and student test). Then, risk factors with a P<0.05 were included in the binary logistic regression model to determine the independent risk factors of mortality.

Results: In Total, 512 patients developed infections with 83 MDR gram-negative strains detected in 80 patients, most of them (68 patients) have an acute leukemia. The MDR gram-negative infection occurred in 58 patients with uncontrolled disease, and the majority of them occurred in the presence of severe neutropenia (62 episodes/74.7%). Bloodstream infection (BSI) (57episodes/68.7%) was the most common infection types. Klebsiella pneumonia was the most common Gram-negative isolates (44 episodes/53%). Complications occurred in 44 (53%) episodes. In 41 episodes, patients received an appropriate antibiotherapy. The isolated MDR gram-negative bacteria exhibited sensitivity to amikacin in 17%, imipenem in 32.5% (three isolates were resistant to colistin). Twenty-two patients died during gram-negative MDR infections. The independent risk factors influencing mortality was: qSOFA>=2. (p: 0.003) (table 1).

Summary/Conclusion: The burden of infections due to gram-negative MDR bacteria is considerably high in patients with hematologic malignancy, with Klebsiella pneumonia being the most predominant causative pathogen. Mortality in these immunocompromised patients remains high and more effort is needed to improve the prognosis of these individuals.

EP832 ARTERIAL AND VENOUS THROMBOTIC COMPLICATIONS IN HOSPITALIZED PATIENTS WITH COVID-19: EXPERIENCE FROM A MEXICO CITY HEALTH SYSTEM.

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Background: Patients with acute respiratory infection due to COVID 19 have an increased risk of thromboembolic disease. Coagulation activation, endothelial dysfunction, platelet activation and impaired fibrinolysis have all been proposed as directly involved in its pathogenesis. In Latin America, data regarding the incidence of acute thrombotic complications (venous and arterial) is scarce.

Aims: The aim of this analysis is to describe characteristics and outcomes of patients with confirmed COVID-19 infection with acute arterial and venous thrombotic events attended during a 10-month period, at a referral hospital in Mexico City.

Methods: We included consecutive critical and non-critical adult patients, hospitalized at Hospital Central Norte Pemex in Mexico City, between April 1, 2020 and January 31, 2021. All patients tested positive for SARS- CoV-2 using RT- PCR from nasopharyngeal and oropharyngeal swabs. Thrombotic events were diagnosed during clinical care. Thrombotic events included both venous (deep vein thrombosis [DVT]; pulmonary embolism [PE]) and arterial (myocardial infarction [MI], ischemic stroke, and other arterial thrombosis). All patients received thromboprophylaxis prior; and treatment (anticoagulation; platelet antiaggregation; a combination of both or other therapeutic interventions) at the time of diagnosis according to international and local recommendations.

Continuous variables (age, leucocyte count with differentials, hemoglobin, D-dimer, ferritin, LDH, etc.) are presented as mean ± standard deviation, (or median and range as appropriate) and were compared using the student-t or Mann-Whitney U test. All data were analyzed using SPSS

version 21 statistics software. A p value <0.05 was considered statistically significant.
Results: We analyzed 1379 hospitalized patients with confirmed COVID-19 infection. Twenty-five patients received a diagnosis of acute thrombotic events (1.81%): 13 cases (52%) of venous thrombosis (DVT: 1 case (4%); PE: 12 cases (48%)), and 12 cases (48%) of arterial thrombosis (acute Stroke: 6 cases (24%); MI/ACS: 5 cases (20%); and one case of Mesenteric thrombosis (4%)). Baseline characteristics are summarized in table 1. The mean age of all patients with thrombotic events was 62.96 14.4 years; and were predominantly male (64%).
Patients with venous thromboembolic events presented with higher D-dimer levels at the time of admission compared to those who had arterial thrombosis (mean 1965.38 vs 663.92, P= 0.014). We also observed a trend to higher hemoglobin levels at the time of diagnosis in patients with arterial events compared to cases of venous thromboembolism (mean 15.83 vs 14.01, P= 0.063). Comparison of patient's characteristics between venous and arterial thrombosis is found in table 2.
The overall mortality of the group with thrombotic events was 28%. The main cause for death was respiratory failure due to acute respiratory distress syndrome (5 patients, 71%).

Table 1. Baseline characteristics, by thrombosis site

	DVT	PE	Stroke	MI/ACS
Events; n (%)	1 (4)	12 (48)	6 (24)	5 (20)
Age (years)	27	61(51-82)	75 (60-82)	66 (50-72)
Leucocytes (x10^9/L)	11.3	10.8 (7.32-18.97)	6.37 (5-10.4)	11.7 (6.45-18.8)
Lymphocytes (x10^9/L)	2.73	1.31 (0.33-3.46)	0.76 (0.42-1.41)	1.8 (1.40-2.70)
Neutrophils (x10^9/L)	7.09	8.21 (5.08-13.86)	4.48 (3.48-8.31)	8.62 (4.55-13.4)
Monocyte (x10^9/L)	1.22	0.69(0.25-1.34)	0.44 (0.12-0.98)	0.78 (0.43-1.53)
Hemoglobin (g/dL)	17.4	13.65(9.9-18.2)	15.25 (12-17.2)	17.10 (14.10-20.30)
Platelets (x10^9/L)	266	243(112-303)	173.5 (11-324)	228 (25-272)
Viral load	7.06	1621(5-11503501)	188025 (12-1706674)	300 (6-11797)
D-dimer at time of admission (ng/ mL)	100	1480 (577- 4600)	470 (100-3110)	179 (100-1050)
D-dimer	100	3575 (825- 5000)	1559 (100- 5000)	1190 (178-4090)
LDH (UI/L)	432.3	430.5 (179-4182)	300.5 (0- 515)	453 (186-1764)
Ferritin (ng/ dL)	432	493.25(36-5177)	301 (122- 2266)	407 (105-1449)
SIC score	0	2 (1-3)	1 (0-4)	2 (1-2)
SOFA score	0	4 (0-4)	2 (0-6)	2 (1-5)
Days of hospitalization	1	8 (2-19)	13 (4-31)	17 (3-66)
Treatment	Rivaroxaban	Rivaroxaban (9/12) Enoxaparin (3/12)	Antiaggregant (6/6)	Antiaggregant + Enoxaparin (3/5) PTCA (1/5) Tenecteplase (3/5)
Deaths, n (%)	0 (0)	3 (25)	3 (50)	1 (20)

Table 2. Differences between venous and arterial thrombosis

Baseline characteristics	All patients	Venous thrombosis	Arterial thrombosis	P
Male sex, n (%)	16 (64%)	8 (61%)	8 (67%)	0.790
Age (years)	62.96 ± 14.4	58.69 ± 16.66	67.58 ± 10.22	0.125
Leucocytes (x10^9/L)	10.72 ± 4.76	11.01 ± 3.30	10.42 ± 6.11	0.765
Lymphocytes (x10^9/L)	1.41 ± 0.88	1.53 ± 0.95	1.27 ± 0.81	0.475
Monocyte (x10^9/L)	0.722 ± 0.36	0.79 ± 0.37	0.64 ± 0.36	0.330
Hemoglobin (g/dL)	14.88 ± 2.45	14.01 ± 2.48	15.83 ± 2.12	0.063
Platelets (x10^9/L)	213.62 ± 83.66	235.46 ± 56.13	189.96 ± 105.0133	0.180
Viral load	795978.48 ± 251488.9	1260541.45 ± 344691	2284959.2 ± 547299	0.388
D-dimer at time of admission (ng/ mL)	1424.72 ± 1363.3	1965.38 ± 1517.51	663.92 ± 762.86	0.014
Maximum D-dimer levels (ng/ mL)	2743.16 ± 1831.5	3238.08 ± 1686.62	2207.00 ± 1900.68	0.164
LDH (UI/L)	685.24 ± 912.7	873.39 ± 1187.89	460.58 ± 455.062	0.271
Ferritin (ng/dL)	959.90 ± 1194.8	979.84 ± 1377.05	938.29 ± 1022.25	0.933
SIC score	2 (0-4)	2 (0-3)	2 (0-4)	0.406
SOFA score	2 (0-6)	1 (0-4)	2 (0-6)	0.900

Summary/Conclusion: Our analysis shows a low venous thromboembolic rate compared with other groups, and similar to another series reported in our country. Interestingly, we observed a significant proportion of arterial thrombotic complications. However, this study has limitations. Venous thromboembolism may have been underdiagnosed because of limited imaging studies. Also, neurological or ischemic cardiac symptoms may have been underestimated in patients with severe COVID-19 infection. Changes in prophylactic anticoagulation strategies, as well as in clinical practice, could affect the incidence of thrombotic events.

EP833 ACUTE LEUKEMIA AND SARS-COV-2 INFECTION: SINGLE CENTRE EXPERIENCE

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Background: During the past one year different protocols addressing the treatment of acute leukemia (AL) during the coronavirus disease 2019 (COVID-19) outbreak have emerged. However, reliable data regarding this topic are still deficient, since only case series with heterogeneous patient population with different hematologic malignancies are available.
Aims: To determine clinical characteristics of COVID-19 and to assess risk factors for mortality in patients with AL.
Methods: This prospective study included 51 consecutive adult patients actively treated for AL, with verified SARS-CoV-2 infection treated at two Clinical Centres in Central Serbia. The study enrolled all symptomatic and asymptomatic patients regardless of severity of the infection. Baseline data including age, sex, body mass index, comorbidities, AL type, disease status (newly diagnosed, complete remission (CR), relapsed/refractory (RR)), treatment (intensive, low-intensity chemotherapy, supportive care), time since AL diagnosis, outcome, laboratory parameters at the onset of infection were collected. Moreover, dana regarding COVID-19 symptoms, disease severity, COVID-19-specific therapies and time to PCR negativity were collected. Methods of descriptive and analytical statistics were used.
Results: Most patients (80.4%) had acute myeloid leukemia (AML). At time of COVID-19 diagnosis 35.3% of patients were newly diagnosed with AL. Concurrent diagnosis of COVID-19 and AML was made in 5.89% patients, 23.5% were RR and 41.2% were in CR. Intensive chemotherapy was administered in 80.4% of our patients. At the time of COVID-19 diagnosis 29.4% patients had bone marrow aplasia. Intrahospital transmission was probable in 50.98% patients. Five patients who were initially asymptomatic andwith negative PCR test at the time of admission developed COVID19 symptoms within the first 48 hours. The most common symptoms of COVID-19 were fever (70.4%), fatigue (66.7%) and dyspnea (39.2%). Asymptomatic, mild to moderate, severe and critical COVID-19 was registered in 9.8%, 43.1%, 37.3% and 9.8% patients, respectively. Median time to PCR negativity was 18 days (range 10-50). Mortality for the entire cohort was 17/51 (29.4%). In all cases death was associated with COVID-19 pneumonia. Among COVID-19 symptoms dyspnea (OR 12.536 (95% CI: 3.106 – 50.597)), cephalgia (OR 5.36 (95% CI: 1.200 – 26.482) and fatigue (OR 5.921(95% CI: 1.168 – 30.019) were associated with higher mortality. Patients newly diagnosed with AL (OR 6.00 (95% CI 1.133 – 15.188) and patients with bone marrow aplasia (OR 4.148 (95% CI 1.133 – 15.188) had a significantly worse outcome in comparison with patients in CR. Additionally, pneumonia severity (OR 14.963 (95% CI 3.212 – 69.700) and need for oxygen therapy (OR 6.455 (95% CI 2.56 – 20.262) were associated with higher mortality risk. Among laboratory parameters lower platelet count (OR 0.985 (95% CI 0.973 – 0.996)), prolonged prothrombin time (OR 1.554 (95% CI 1.104 – 2.186)), higher ISTH DIC score (OR 2.122 (95% CI 1.258 – 3.576), C-reactive protein (OR 1.011 (95% CI 1.004 – 1018) and LDH (OR 1.001 (95% CI 1.000 – 1.003) were predictive for death.
Summary/Conclusion: Baring in mind high mortality rate, and rate of intrahospital transmission, rigorous isolation of AL patients, permanent symptoms monitoring and prompt testing should be prioritized. Careful risk-benefit assessment regarding the continuing of anticancer therapy is required in patients receiving palliative therapy and intensive induction therapy. Conversely, there is no reason to withhold therapy for the patients in CR.

EP834 THE PROFILE OF FEBRILE NEUTROPENIA IN HEMATOLOGY-ONCOLOGY UNIT; EXPERIENCE OF CHILDREN WELFARE TEACHING HOSPITAL, MEDICAL CITY

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Background: Infections in pediatric cancer patients are the major reasons for morbidity and mortality. In cases of malignant diseases, fever may herald an upcoming life-threatening situation. This study tried to unleash few mysterious interrogation points about the nature of febrile neutropenic episodes in children.
Aims: To assess the overall and attributable mortality from febrile neutropenia and to evaluate the susceptibility pattern to antimicrobials in febrile neutropenia.
Methods: A prospective non-interventional observational study. All consecutive pediatric inpatients affected by haematological diseases or solid

tumours who were admitted at the pediatric oncology unit in Children Welfare Teaching Hospital / Medical City, with fever and neutropenia (Absolute Neutrophile count (ANC) <500/cmm) or developed fever and neutropenia during hospitalization were enrolled into the study until hospital discharge or death, started from September 1st 2019 till February 29th 2020. The total number of patients admitted to the pediatric oncology unit was 207 patients, with a total of 350 neutropenic episodes.
Results: The majority of reported underlying diagnoses belong to hematological malignancies in 236 patients (67.4%). Acute lymphoblastic leukemia was reported to be the most frequent in 197 episodes (56.3%), followed by acute myeloid leukemia in 39 episodes (11.1%), then neuroblastoma (6.3%), and brain tumors (5.1%). Forty percent of patients recalled or had shown respiratory symptoms. Abdominal complaints were reported in 178 patients (50.9%). Bleeding was recorded in 79 patients (22.6%). Mucositis was noted in 187 patients (53.4%), grade II being the most frequently notified in 83 patients (44.4%). Performance score according to Eastern cooperative oncology group showed that the majority have a score of II (48.4%). At time of admission, the mean WBC count 3,100 /cmm, and the mean ANC was 140 with a range of (0 – 500). Blood was withdrawn for culture and sensitivity at time of admission; Sixty-one episodes showed positive bacterial growth (18.2%), while 274 showed no growth (81.8%). The growth showed gram-positive bacteria in two-third of episodes (65.6%), while gram-negative was shown in one-third (34.4%). The majority of patients (84.0%) belong to high-risk febrile neutropenia, while fifty-six patients (16.0%) were low-risk patients. Out of the group, 46.4% were labelled as fever without origin as the final diagnosis, while 34.0% with a presumptive 'clinical infection' diagnosis. Microbiological diagnoses were reported in 68 patients; 61 blood, 2 skin, 2 sputum, 2 urine, and 1 ear. Out of the group, 21 patients (6.0%) died as a complication of febrile neutropenia. The mean duration of fever before admission for the deceased group was 9.1 days which was significantly longer than the duration for the alive group (mean duration 3.0 days). There was a significant statistical correlation between the fate of the patients and the following parameters: type of malignancy, phase of disease, and treatment lines.
Summary/Conclusion: Conclusion: Acute lymphoblastic leukemia was the most frequently encountered underlying malignancy, acute myeloid leukemia was associated with the worst outcome. The result of blood cultures was comparable to worldwide results. Gram positive organisms were the most commonly identified growth. High-risk febrile neutropenia was the commonest reported type, low-risk being lowest because of possible treatment outside the hospital on oral-based antibiotics. Finally, infection related mortality was high.

EP835 AUDIT OF CHEMOTHERAPY DISRUPTION DUE TO COVID19 PANDEMIC:

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PERSPECTIVE FROM A UK DISTRICT GENERAL HOSPITAL
Background: Patients with cancer undergoing systemic chemotherapy have been postulated to be at increased risk of mortality from COVID-19. Given this proposed risk, NICE issued COVID-19 rapid guidelines for safe delivery of systemic chemotherapy in March 2020. Based on this guidance local and regional guidelines were established.
Aims: The primary objective of this audit was to assess the impact of COVID-19 on patients undergoing systemic chemotherapy and their outcomes at Queen's Hospital Burton.
Methods: 115 patients undergoing active chemotherapy were identified using local records of chemotherapy administration. Retrospective data collection and analysis of these patients was undertaken from March 2020 to December 2020.
Results: Patients with a diagnosis of Myeloma (36%) who had a stable disease (42%) had treatment either delayed or suspended during the first wave. Bisphosphonate treatment in 12 out of 14 patients was stopped who already completed the anti-myeloma treatment. Similarly for lymphoma patients, maintenance immunotherapy with Rituximab (6) and Obinutuzumab (3) were suspended or stopped in all cases. Other patients with aggressive Lymphomas, CML, High risk MDS/AML and those with advanced CLL either continued with their treatment or new therapy was started as clinically appropriate.
In total, 31 patients had chemotherapy delayed or stopped completely. Only 2 patients on maintenance Rituximab had disease progression. COVID-19 was detected in 9 patients and sadly 4 patients passed away with COVID-19 related complications. Among these were 2 patients on Ruxolitinib, one on VMP lite and 1 on Zometa without chemotherapy at the time. Following the first wave of COVID-19, of the 31 patients 29 were re-commenced on chemotherapy. No patients on high dose chemotherapy had an increase in morbidity and mortality.
Summary/Conclusion: The impact of COVID-19 and systemic anticancer therapies is poorly described and based on limited small cohort studies. A few of these studies concluded that cancer patients are not only at risk to contract the virus but also at risk of developing more severe complications as compared with the general population. The UK CORONAVIRUS CANCER MONITORING PROJECT (UKCCMP), serving as a public health surveillance registry, concluded that cytotoxic chemotherapy within 4 weeks before confirmed COVID-19 is not a significant contributor to more severe disease, or a predictor of death from COVID-19, compared with cancer patients who have not received chemotherapy in that period. Again, this analysis was based on small data sets. Our audit also confirms the findings of UKCCMP and shows no significant increased risk in mortality in patients both on active chemotherapy and where chemotherapy was temporarily stopped. The overall risks and benefits of continuing or holding chemotherapy need to be discussed in details with patients. Withholding anti-cancer therapies may well present a greater individual risk of morbidity and mortality than COVID-19. Further studies are required to assess the impact of COVID-19 on morbidity and mortality, to better inform these discussions.
Whilst these factors become clearer, additional measures within our practice have aimed to ensure safe patient care in this new environment. These included telephonic and video consultations, home delivery of oral chemotherapy and blood monitoring at local GP surgeries to avoid hospital exposures.

EP836 COMPLICATION, ASSOCIATED WITH CATHETERISATION OF CENTRAL VEIN IN HEMATOLOGY PATIENTS

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Background: The central vascular access needs to provide a large volume of infusion therapy, a parenteral feeding, transfusions of the blood components in hematology patients (HP). However, the procedure of central vein catheterization (CVC) may lead to risks of serious complications.
Aims: To find out the incidence of individual complications associated with CVC in HP.
Methods: We studied the complications associated with procedure of CVC in HP (n=2856) for the period of above 17 years (2003-2020 years). Most procedures were performed by subclavian access (into the v. subclavia dextra – in 2346 (82.1%) cases and into v. subclavia sinistra – 502 (17.6%)), only 8 cases (0.3%) into v. jugularis interna. After each CVC procedure was done X-ray control. There were performed bacteriological analyses and identification of microbial pathogen in cases if we suspected an infectious complication.
Results: There were observed range of complications associated with CVC. The more frequently were found hemorrhagic complications: 1) hematoma – in 117 cases (4.1%), 2) puncture of an artery – in 79 (2.8%), and one case catheterization of arteria subclavian, 3) bleeding from the catheter passage area – in 54 (1.9%), 4) delayed bleeding (after 3-4 hours or more) – in 24 cases (0.8%), and 5) clinically significant lymphorrhea – in 41 cases (1.4%). The thrombotic complications included thrombophlebitis, infiltrate with thrombosis of subclavian vein and they were counted 74 cases (2.6%). Most of thrombotic complications were associated with different bacterial pathogens. More rarely we documented complications as pain, numbness, paresthesia of the upper limb were observed in 45 patients (1.6%), as well as weakness, allergic Quincke's edema, fainting or collapse associated with anesthesia were observed in 34 ones (1.2%). Among the dangerous clinically significant complications that required additional measures were pneumothorax (n=3; 0.11%) and pneumothorax with hemoptysis (n=2; 0.07%). The complications associated with bloodstream infection in the form of bacteremia or fungeremia, which were observed by bacteriological culture, were detected in 71 (2.5%) patients. Positive bacterial

cultures from venous blood were detected in 89 cases, and 12 blood probes of them had mixed infection (2 and rarely 3 bacterial pathogens). Analysis of the different microorganisms indicated the prevalence of Gram-positive pathogens – 61.8% (n=55): the most part was Coagulase-negative Staphylococcus – 50.6% (n=45), S. aureus – 9.0% (n=8), Enterococcus spp. – 1.1% (n=1) and Micrococcus spp. – 1.1% (n=1). Gram-negative microorganisms were detected in 30.4% (n=27) of cases: Escherichia coli – 15.7% (n=14) patients, Enterobacter spp. – 9.0% (n=8), Acinetobacter spp. – 1.1% (n=1), Pseudomonas aeruginosa – 2.3% (n=2), Neisseria spp. – 2.3% (n=2). Causative agents of fungal infections were found for 7.8% of patients (n=7). They included fungi of the genus Candida – 6.7% (C. albicans – 5.6% (n=5), C. crusei – 1.1% (n=1)) and Rhodotorula spp. – 1.1% (n=1).

Summary/Conclusion: we found the most of CVC's complications were associated with hemorrhagic as hematoma (4.1%), its rate depended on thrombocytopenia, coagulation disorders and technic of procedure in HP. Blood stream infections associated with CVC were caused by gram-positive microbes in more cases (coagulase-negative Staphylococcus), little less by gram-negative (Escherichia coli).

EP837 HEMATOLOGIC CHARACTERISTICS AND C-REACTIVE PROTEIN OF PATIENTS WITH SARS-COV 2 ADMITTED TO A UNIVERSITY HOSPITAL IN BRAZIL.

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Background: COVID-19 is a new infectious disease. The risk of death depends on previous comorbidities, but prothrombin time and low platelets count are also related to death.

Aims: In this study, risk factors for death on hospital admission were evaluated.

Methods: We included patients admitted to the Emergency Department of University Hospital Clementino Fraga Filho (HUCFF), Federal University of Rio de Janeiro (UFRJ), Brazil, from March to May/2020 with laboratory-confirmed Covid-19 infection. A confirmed case was defined by a positive result on a reverse-transcriptase–polymerase-chain-reaction assay of a specimen collected on a nasopharyngeal swab secretion. Admission results were collected through retrospective review of medical records. Death was the primary outcome. Data were expressed as median (range), or n/N (%); P values were calculated by Mann-Whitney or Fisher's exact test, as appropriate. A two-sided α of less than 0.05 was considered statistically significant.

Results:

We analysed 116 patients. The median age was 61 years (range 22-94), and most were male (55%). Ninety-nine (85%) had one or more chronic underlying diseases, mostly hypertension (69%). Ninety-six (83%) patients had pulmonary CT scan compatible with viral pneumonia on admission, 87% necessitated supplementary oxygen therapy, 38% needed mechanical ventilation, of which 71% died. Thirty-one (27%) patients died. Non-survivors were older (66 X 59 years; p=0.077), had a higher proportion of cardiopathy (45% X 13%; p=0.001), renal failure (36% X 9%; p=0.002) and diabetes (52% x 31%; p=0.050), and on hospital arrival, higher neutrophils counts (6.9 x 103/mm3 X 5.4x103/mm3; p=0,037), higher neutrophils / lymphocytes ratio (7.4 X 5.1; p=0.012), higher CRP (174.4 X 102.7; p=0.004) and higher LDH (478 X 376; p=0.009). Level of hemoglobin, white blood cells, RDW, platelet count, PT and APTT were similar in survivors and non-survivors. Most patients (97%) received any low molecular weight heparin (LMWH). All patients who died received LMWH.

Summary/Conclusion: That patients admitted with COVID-19 with respiratory symptoms who needed mechanical ventilation had a high mortality rate (71%). On admission, cardiopathy, renal failure and CRP level were independently predictive of death. Basic coagulation profile and blood counts (CBC) on admission were similar between alive and dead cases. Almost universal use of low molecular weight heparin precluded any further discussion on this subject.

EP838 GROWTH OF ANTIBIOTIC RESISTANCE IN THE HEMATOLOGY DEPARTMENT OF CENTRAL KAZAKHSTAN DURING THE COVID-19 PANDEMIC

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Background:

Infectious complications remain as a serious problem for hematological hospitals. Despite the fact that COVID-19 is a viral infection, the pandemic could have affected the development of antibiotic resistance. In Kazakhstan, at the beginning of 2020, the fear of bacterial complications, the emergence of available information about the possibility of using antibiotics in the treatment of patients with COVID 19 led to an increase in the consumption of antibacterial drugs, primarily azithromycin, ceftriaxone. This could negatively affect the selection and development of antibiotic-resistant microorganisms in the departments where patients are especially exposed to infectious agents. There are no data on monitoring of the etiological structure of bacterial pathogens and the level of antibiotic resistance during a pandemic among patients of hematology departments in Kazakhstan.

Aims:

To analyze the etiological structure and assess the level of resistance to antimicrobial drugs before and during a pandemic COVID 19.

Methods:

A retrospective analysis of the etiological structure and sensitivity to antimicrobial drugs of pathogens isolated from 108 patients in the hematology department of Karaganda for the period before the pandemic (from January 2019 to March 20, 2020) and 181 patients after the introduction of a lockdown due to the COVID 19 pandemic (from March 20, 2020 to

Table 1. Laboratory findings of patients infected with Sars-Cov-2.

Lab on arrival	Total (N=116) median (range)	Alive (N=85)	Dead (N=31)	P value	Reference values
Hemoglobin (g/dL)	13.3 (2.6-14.4)	13.4 (2.6-14.4)	12.3 (8.2-16.5	0.210	13.5-18.0 g/dL
White blood cell count (X 103/mm3)	7.4 (2.4-26.7)	7.1 (2.4-26.7)	8.6 (3.9-20.5)	0.060	4.0-11.0 X 103/mm3
Neutrophil count (X 103/mm3)	5.8 (0.75-23.2)	5.4 (0.8-23.2)	6.9 (3.1-18.4)	**0.037**	2.5-6.4 X 103/mm3
Lymphocyte count (X 103/mm3)	1.0 (0.2-3.8)	1.0 (0.2-3.8)	0.9 (0.2-2.7)	0.069	1.5-3.9 X 103/mm3
Neutrophil/Lymphocyte ratio	5.6 (0.5-98.0)	5.1 (0.5-22.5)	7.4 (254-98)	**0.012**	-
Platelet count (X 103/mm3)	206.5 (59.0-619.0)	212.0 (59.0-550.0)	184.0 (75.0-619.0)	0.330	150.0-450.0 X 103/mm3
CRP mg/dL	114.5 (0.4-424.0)	102.7 (0.4-351.8)	174.4 (5.0-424.0)	**0.004**	0.-1.0
LDH	393 (139-1,494)	376 (139-1,494)	478 (228-1,047)	**0.009**	140-271 U/L
	n/N (%)				
CRP high (≥ 115 mg/dL	57/114 (50)	35/84 (42)	22/30 (73)	**0.005**	-
LDH high (≥400 U/L)	52/110 (47)	34/82 (42)	18/28 (64)	**0.049**	-

PT: prothrombin time; INR: international normalized ratio; APTT: activated prothrombin time; CRP: C-reactive protein; LDH: lactic dehydrogenase

02/01/2021). The study included positive bacteriological cultures from 9 biotopes (blood, urine, sputum, catheters etc.). The bacteriological study was carried out by standard bacteriological methods with identification by time-of-flight mass spectrometry (Microflex-LT, Biotyper System, Bruker Daltonics, Germany), the determination and interpretation of sensitivity to antimicrobial drugs was carried out in accordance with the recommendations of CLSI M100-24. Statistical processing of the data obtained was carried out on an online platform for the analysis and exchange of antibiotic resistance data (AMRcloud, version: Beta, 01/27/2021).
Results:
The results of the study showed that in the structure of microorganisms isolated from patients of the hematology department for the entire period of the study, gram-negative flora prevailed. Significant differences in the structure of bacteria before and during the pandemic period were noted: increased *Pseudomonas aeurogenosa* strains from 29.7% to 55.3% (p = 0.022) and drastically decreased in the growth of *Enterococcus faecalis*, from 40.5% to 10.6% (p = 0.001). The appearance of *P. aeurogenosa* strains carbapenemase producers up to 30.4% (p = 0.01) during a pandemic was noted. Despite the fact that the ratio of gram-negative and gram-positive flora did not statistically change, after the lockdown the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) increased from 11.8% to 35%.
Summary/Conclusion:
During the COVID 19 pandemic, in non-infection departments, like hematology, the frequency of MRSA excretion increased by 3 times and a third of *Pseudomonas aeurogenosa* strains were resistant to carbapenems. Stricter infection control is needed, as well as monitoring the growth of opportunistic flora, which is often resistant to antibiotics and thus aggravates the condition of patients in the hematological compartments.

Iron metabolism, deficiency and overload

EP839 ALK2 IS A POTENTIAL THERAPEUTIC TARGET IN ANEMIA RESULTING FROM CHRONIC INFLAMMATION

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Background: Hepcidin, a master iron regulator that helps to maintain appropriate iron levels in circulation, is elevated in many diseases of chronic inflammation. Hepcidin is expressed, in part, in response to signaling through activation of the TGF-□□type-1 receptor ALK2 and acts to reduce iron export through ferroportin. We have previously demonstrated the effect of inhibiting ALK2 via either a small-molecule or biologic in iron refractory iron deficiency anemia (IRIDA), a genetic form of anemia that results from high hepcidin, in preclinical studies. In IRIDA, KTI-2338, a selective small molecule ALK2 inhibitor, decreased hepcidin and increased serum iron levels in an *in vivo* mouse model. Hepcidin is also increased in response to elevated IL-6 in chronic inflammation, resulting in secondary anemia of inflammation (AI) in chronic inflammatory diseases such as chronic kidney disease (CKD). Herein, we assessed the therapeutic potential of inhibiting ALK2 signaling on anemia arising from chronic inflammation and determined the effect of modulating BMP signaling in anemia resulting from IL6 and high hepcidin.
Aims: To characterize development of AI in a mouse model of chronic kidney disease (CKD) and to test the efficacy of ALK2 inhibition to increase circulating iron in this model.
Methods: To assess the role of ALK2 signaling in AI, we evaluated an adenine-induced model of CKD. Briefly, to induce CKD, C57BL/6 mice were dosed daily via PO administration with 50 mg/kg of adenine or vehicle. After 6 weeks of adenine administration, anemia was confirmed in subset of mice. Concomitantly, the remainder of CKD mice began dosing with either vehicle or KTI-2338 5 mg/kg PO daily while continuing to receive daily adenine for 10 days. The study was terminated at 52 days and hematology, serum hepcidin, and serum iron levels were assessed.
Results: 6 weeks of adenine administration led to iron deficiency anemia (37.6% decrease in serum iron) and was associated with increased circulating IL6 (2.42-fold) and hepcidin (3.49-fold). After 10 days of therapy, the vehicle treated group remained anemic with reduced circulating iron, red blood cell (RBC) count, hemoglobin (HGB) and hematocrit (HCT) compared to the controls not receiving adenine. In contrast, mice that were administered KTI-2338 had an increase in serum iron (2.09-fold) and improvements in RBC count, HGB and HCT compared to the vehicle cohort. Reticulocyte HGB content, a measure of the incorporation of iron into hemoglobin, normalized to baseline levels with KTI-2338 therapy. Given that reticulocytes are immature RBCs, the effect on reticulocyte HGB content is potentially predictive that RBC and HGB levels would also continue to increase over a longer time course.
Summary/Conclusion: We have characterized an established mouse model of chronic inflammatory disease, CKD, as a well-defined model of anemia of inflammation. This preclinical model recapitulates the high IL6 and hepcidin and decreased serum iron that characterizes clinical AI. In this proof-of-concept study, inhibition of ALK2 improved hematological markers of anemia, serum hepcidin, and serum iron levels in a mouse model of anemia of inflammation (AI) resulting from chronic kidney disease characterized by elevated IL6. Inhibition of BMP6 signaling alone can override iron deficiency anemias driven by inflammatory signaling, potentially substantiating that inhibitors targeting ALK2 may provide a viable therapeutic intervention for AI.

EP840 ADMINISTRATION OF ALK2 NEUTRALIZING ANTIBODIES TO CYNOMOLGUS MONKEYS LED TO A SUSTAINED DECREASE IN HEPCIDIN, INCREASE IN CIRCULATING IRON AND INCREASE IN ERYTHROCYTE HEMOGLOBIN

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Background: Hepcidin is a key endocrine mediator of iron metabolism that regulates dietary iron uptake and iron levels in blood. Hepcidin is expressed in part in response to signaling through the ALK2 receptor, a type I TGF-β receptor activated by complexing with the ligand BMP6 and the co-receptor hemojuvelin. Hepcidin signals to peripheral tissues and binds to and activates the degradation of the iron exporter, ferroportin. Thus, when hepcidin is high, iron is sequestered within cells and functions to increase tissue iron levels and reduce serum iron availability. Elevated hepcidin is associated with states of iron deficiency anemia such as iron-refractory iron deficiency anemia (IRIDA) and anemia of inflammation. We have previously reported that inhibition of ALK2 with a novel specific monoclonal antibody (KTI-mAb2.0) can suppress hepcidin and increase serum iron in healthy mice and in mice with iron deficiency anemia. KTI-mAb2.0 and KTI-mAb2.1 are two fully human antibodies that have been observed to specifically bind to and neutralize ALK2.
Aims: To determine the pharmacokinetic and pharmacodynamic properties of KTI-mAb2.0 and KTI-mAb2.1 in cynomolgus monkeys, a preclinical model highly representative of human biology.
Methods: Ad libitum-fed, female cynomolgus monkeys ranging in age from 2-4 years old were randomly assigned to receive KTI-mAb2.0 or KTI-mAb2.1 administered as a single subcutaneous dose (3mg/kg). Serum was sampled intermittently over a 56-day period and assessed for drug exposure, hepcidin and iron content. At a subset of timepoints, blood was sampled and assessed for reticulocyte and red blood cell hemoglobin content (RET-Hgb and RBC-Hgb, respectively). Hematological data was combined across both therapeutic groups.
Results: KTI-mAb2.0 and KTI-mAb2.1 were rapidly absorbed and reached Cmax within 48 hr and had half-lives of 33.9 hr and 49.1 hr, respectively. Robust and profound effects on hepcidin and serum iron were observed with both antibodies. Within 6hr of administration, KTI-mAb2.0 or KTI-mAb2.1 reduced serum hepcidin by 55.6% and 50.3%, respectively. The peak effect was observed beginning after 48 hr with reductions of 77.2% in the KTI-mAb2.0 treated group, and 77.8% in the KTI-mAb2.1 group and continued through day 10 before returning to baseline by day 14. The reduction in hepcidin corresponded to increased circulating iron with maximal changes occurring within 24hr of antibody administration. A 63.3% and 54.2% increase in iron was achieved with KTI-mAb2.0 and KTI-mAb2.1, respectively. Similar to hepcidin, the response was sustained through 10 days, returning to baseline by day 14. RET-Hgb increased by 4.9% at 3 days post dose and remained elevated for 10 days. Increases in RBC-Hgb content were observed initially 35 days post dose and remained 4.2% higher at study termination at day 56.
Summary/Conclusion: Our data demonstrate that both KTI-mAb2.0 and KTI-mAb2.1 reduced serum hepcidin and increased circulating iron in non-human primates, a preclinical model highly representative of human biology. Furthermore, the mobilized iron resulted in increased RET-Hgb and RBC-Hgb. These results provide evidence that treatment with KTI-mAb2.0 and KTI-mAb2.1 may be a viable approach to treating anemias that arise from elevated hepcidin, such as IRIDA and anemia of inflammation.

EP841 DISC-B, A SELECTIVE MATRIPTASE-2 INHIBITOR, ELICITED ROBUST INCREASE IN HEPCIDIN-25 AND REDUCTION IN SERUM IRON IN CYNOMOLGUS MONKEYS

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Background: Hepcidin is known as the master regulator of systemic iron homeostasis with reduction in synthesis leading to the development of iron overload. Hepcidin gene expression is negatively modulated by matriptase-2 (MT-2), a liver-specific type II transmembrane serine protease. MT-2 cleaves hemojuvelin (HJV), leading to the extracellular release of soluble HJV (sHJV) fragments and suppression of hepcidin expression. Therefore, inhibition of MT-2 represents a potential therapeutic strategy for diseases caused by inappropriately low hepcidin leading to iron overload or where therapeutic iron restriction may be used to control excessive erythrocytosis. DISC-B is a potent (MT-2 Ki =15 nM) and selective small molecule MT-2 inhibitor.
Aims: 1. To examine the dose-dependency of acute treatment of DISC-B on the key PD markers (hepcidin-25, sHJV, serum iron) in cynomolgus monkeys.
2. To determine the time to maximum decrease in serum iron upon multiple dosing.
3. To evaluate the effect of chronic treatment on key hematologic parameters.
Methods: A cross-over study was conducted in male cynomolgus monkeys (2-4-year-old; N=6). Animals were administered a single subcutaneous (SC) dose of DISC-B at 5, 15, 50 mg/kg or vehicle control, followed by administration of DISC-B once a day for 7 consecutive days; the washout period in between treatments was 2 weeks. For the single-dose treatments, blood samples were collected 48-hr prior to treatment (baseline) and at various time points after dosing. For the multiple dose part of the study, blood samples were collected 48-hr prior to dosing (baseline) and at various time points after the 1st and the 7th dose. All blood samples were processed to serum and sHJV, hepcidin-25, serum iron and total iron binding capacity (TIBC) were quantified. In addition, for the multiple dose part of the study, reticulocyte hemoglobin was determined at baseline and on Day 7. TSAT was calculated as the ratio of serum iron/TIBC x 100.
Results: Treatment of DISC-B resulted in a dose-dependent increase in hepcidin-25 with a maximum of 5-fold. Maximum serum iron percent reduction from baseline was 10%, 25%, and 50% for 5, 15, and 50 mg/kg, respectively. The magnitude of hepcidin-25 modulation was similar at 15 and 50 mg/kg dose. However, the serum iron reduction was higher with the 50 mg/kg group and responses were more consistent across different animals. Therefore, we selected the 15 mg/kg dose group to determine if the effect on serum iron would increase with subsequent days of dosing. After 7 days of treatment with DISC-B at 15 mg/kg serum iron decreased from 25% on day 1 to 45% at day 7 (~2-fold). The hepcidin-25 increase over baseline was comparable on day 1 and day 7. Importantly, all animals showed a reduction in CHr with a mean reduction of 1.3 pg (± 0.6) on day 7 compared to their baseline levels, suggesting the induction of iron-restricted erythropoiesis.
Summary/Conclusion: DISC-B modulates serum hepcidin-25 levels and iron homeostasis in cynomolgus monkeys in a dose-dependent manner. The consistent increase in hepcidin-25 and the increasing reduction in serum iron after 7 doses of DISC-B suggest that prolonged inhibition of MT-2 can lead to sustained, therapeutically relevant reduction in serum iron. Our data demonstrate that MT-2 can be successfully inhibited by a selective small molecule to increase hepcidin and decrease serum iron.

EP842 ALK2 INHIBITION, A NOVEL THERAPEUTIC APPROACH TO IRON OVERLOAD.

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Background: Iron overload is a condition whereby excess iron is stored in peripheral tissues and can be caused by genetic mutations, or introduced via blood transfusions, hemolysis or diet. Excess deposition of iron in liver, heart and endocrine organs leads to toxicity and loss of function. Hepcidin, a key endocrine regulator of iron metabolism, mediates dietary iron uptake and iron levels in blood. Hepcidin circulates to tissues and binds to and activates the degradation of the iron exporter, ferroportin. Thus, when hepcidin is high, iron is sequestered within cells resulting in increased tissue iron levels and reduced serum iron availability. Likewise, when hepcidin expression is suppressed, ferroportin-mediated iron efflux results in the mobilization of iron out of tissues. Hepcidin is expressed, at least in part, in response to signaling through the ALK2 receptor, a type I TGF-β receptor, and inhibition of ALK2 results in reduced hepcidin expression and increased serum iron. We have shown in pre-clinical and clinical studies that ALK2 inhibition suppressed hepcidin expression. Indeed, we have previously reported in a Phase 1 clinical trial that inhibition of ALK2 with KER-047, a small molecule ALK2 kinase inhibitor, elicited rapid, robust and sustained dose-related increases in serum iron that were associated with decreases in hepcidin. The potential of ALK2 inhibition to aid export of iron from tissues may increase the available therapeutic modalities for the treatment of iron overload.
Aims: To test the efficacy of modulating ALK2 activity to regulate hepcidin and mobilize hepatic iron in an inducible model of iron overload.
Methods: To induce iron overload, CD1 mice were dosed QD via IP administration with 100mg/kg of iron dextran or vehicle. Post 20 days of iron loading, a subgroup of mice was used to confirm iron overload. The remaining iron loaded mice were dosed QD with either KTI-2338, a small molecule selective ALK2 kinase inhibitor (5 mg/kg) or vehicle. Iron dextran administration continued throughout. Mice were sacrificed 16hr post the 1st dose (16hr) and 12hr post the 3rd dose (63hr) of KTI-2338 and livers dissected and weighed. Non-heme tissue iron was extracted via acid hydrolysis and iron levels determined using the bathophenanthroline disulfonate method.
Results: Iron overload was confirmed in the mice dosed with iron dextran (ID-Veh) with a substantial 30-fold increase in hepatic iron compared to mice not receiving iron (Veh-Veh) (Veh-Veh: 648.4±36.01mg/g v ID-Veh: 19291±513.7mg/g, p<0.0001). No differences were observed in hepatic iron at 16hr post dose. By 63hr of KTI-2338 dosing, significant reductions in liver non-heme iron content was observed, resulting in a 62% decrease compared to vehicle treated mice (63hr ID-Veh: 25162±974.5mg/g v 63hr ID-2338: 9559±339.2mg/g, p<0.0001).
Summary/Conclusion: In this proof-of-concept study, ALK2 inhibition in a state of severe iron overload led to rapid and marked reductions in liver iron. In the clinic, chelation therapy is used to remove excess iron from circulation; however, due to the efficiency of iron cycling, this procedure can be ineffective or require a lengthy therapeutic regimen. We hypothesize that in conditions with iron overload, ALK2 inhibition may potentially be used to export excess iron from the liver, allowing for more effective chelation therapy. Future studies will assess the efficacy of KTI-2338 to reduce ectopic iron in sensitive tissues such as the heart and determine if this can be combined with chelation to rescue the pathologies of iron overload.

EP843 ANEMIA AND IRON METABOLISM IN PATIENTS WITH SARS-COV-2 INFECTION: THE ROLE OF INFLAMMATION AND HYPOXIA.

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Background: Coronavirus Disease (COVID-19) could be considered as a human model of marked inflammation combined with severe hypoxia. In this setting, both erythropoiesis and iron metabolism appear to be profoundly affected by inflammatory and hypoxic stimuli, which act in the opposite direction. In patients with SARS-CoV-2 infection, Hb levels tend to be relatively high even in the context of severe disease and marked inflammation. A better understanding of erythropoiesis and iron metabolism in COVID-19 could contribute to elucidate the relationship between hypoxia and inflammation on erythropoietic control.
Aims: To investigate the prevalence of anemia, the alterations of iron homeostasis,and the relationship between inflammation,hypoxia and erythropoiesis in a cohort of COVID-19 patients admitted both to medical wards and intensive care unit (ICU).
Methods: We retrospectively analyzed data of 303 patients with COVID-19 (178 subjects admitted to medical wards and 125 subjects admitted to the ICU). Biochemical parameters were collected on admission (T0), after 7 days of hospitalization (T1) and at discharge/death (T2).
Results: The median age of the patients was 62 years (53-71) and 72% were males. ICU patients had lower mean Hb levels compared to non-ICU patients (11.3±1.8 vs 12.8±1.8 g/dL at T0, 10.2±1.6 vs 12.2±1.9 g/

dL at T1, 10±1.4 vs 12±1.7 g/dL at T2; p<0.001). Mean Hb concentration did not fall under 12 g/dl in the non-ICU group and under 10 g/dl in the ICU group during hospitalization. Hb decreased by approximately 1 g/dl in both cohorts during the first 7 days of hospitalization, then remained stable until discharge. ICU patients also showed increased inflammatory markers and ferritin levels (1401 vs 839 mcg/l at T0, p<0.001; 913 vs 832 mcg/L at T1, p ns; 764 vs 651 mcg/L at T2, p ns). There were no significant differences in other iron parameters between groups. Hypoxia was a prominent feature of ICU patients (P/F ratio 91 vs 224, p<0.001).
Patients who were anemic on admission maintained relatively constant Hb concentrations from T0 to T2 (10.8 g/dL at T0, 10.2 g/dL at T1 and 10.4 g/dL at T2), thus remaining in a range of mild to moderate anemia. Conversely, the non-anemic group displayed a greater reduction of Hb levels (13.7 g/dl at T0, 12.7 g/dl at T1, 12 g/dl at T2). Anemic subjects were more hypoxic than non-anemic patients (P/F 151 vs 292 at T0, p<0.001) and showed significantly higher levels of CRP (10.8 vs 6.6 mg/dL), IL-6 (60.3 vs 47.7 ng/L) and leukocyte count (7290 vs 6130 x109/L). Ferritin was higher in anemic patients at T0 and T1 (1220 vs 926 mcg/L and 852 vs 896 mcg/L, p ns), decreasing more at T2 (655 vs 763 mcg/L, p ns).
Median hepcidin levels, which were available for a limited subset of non-ICU patients, were elevated during the whole period: 233 ng/mL at T0, 95 ng/mL at T1 and 60 ng/mL at T2.
Summary/Conclusion: In patients with SARS-CoV-2 infection, two main factors influence erythropoiesis and iron homeostasis: systemic inflammation and profound hypoxia. Markedly high ferritin and hepcidin levels reflect a strong inflammatory response. However, COVID-19 patients tend to have disproportionately high Hb levels in the contest of the inflammatory milieu. The absolute reduction in Hb levels is more prominent in patients who displayed normal Hb on admission. Conversely, anemic and profoundly hypoxic subjects show constant mean Hb levels over time. Thus, we can hypothesize that the erythropoietic drive provided by hypoxia could counterbalance the effect of inflammation on hepcidin regulation, preventing Hb levels from falling dramatically during hospitalization.

EP844 ERYTHROFERRONE, THE MEDIATOR BETWEEN ERYTHROPOISESIS, HEPCIDIN AND IRON METABOLISM, DURING ALLOGENIEC HEMATOPOIETIC STEM CELLS TRANSPLANT.

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Background: Hematopoietic cell transplantation (HCT) is associated with important changes in erythropoiesis and alterations of iron metabolism. Production of hepcidin, the regulator of iron metabolism, is increased in iron overload or inflammation and decreased with iron deficiency or activated erythropoiesis. Erythroferrone (ERFE) has been recently identified as the erythroid regulator of hepcidin.
Aims: We investigated erythropoiesis and iron metabolism after before and up to 180 days after allogeneic HCT in 70 patients randomized between erythropoietin (EPO) treatment or no EPO. We investigated serially serum levels of CRP (marker of inflammation); soluble transferrin receptor (sTfR, quantitative measure of erythropoietic activity); serum iron and transferrin saturation (Tsat; iron availability for erythropoiesis) and ferritin (iron stores); hepcidin (regulator of iron metabolism); and ERFE (erythroid regulator of hepcidin). We also sought to identify biological and clinical factors associated with serum hepcidin and ERFE levels.
Methods: Serum hepcidin was measured by a liquid chromatography/tandem mass spectrometry method and serum erythroferrone by a specific ELISA kit (Intrinsic Lifesciences, The Bio Iron Company, USA), while the other parameters were measured by routine methods. A generalized linear mixed model (GLMM) was used to compare their evolution with respect to time and treatment arm. Univariate and multivariate linear regression models were used to identify biological and clinical factors (age, sex, diagnosis, disease risk index, HCT-CI, conditioning, donor type, graft type, ABO, red blood cell and platelet transfusions, CMV status, Graft-versus-Host Disease, infections and EPO treatment) associated with hepcidin and serum ERFE levels at different times after transplantation.
Results: Serum ERFE correlated overall with sTfR (p<0.0001), reticulocytes (p<0.0001) and inversely with hepcidin (p=0.0095). Serum ERFE paralleled sTfR levels, with a drop during conditioning followed by recovery during engraftment. Inversely, hepcidin peaked during conditioning and decreased during engraftment (Figure 1). ERFE and hepcidin levels were not significantly different between the control and EPO arms. Multivariate analyses showed that during conditioning and engraftment and at day 100 (R^2=0.17 to 0.61, p<0.001), the major determinant of ERFE was erythropoietic activity (sTfR or reticulocytes or serum Epo). Pretransplant hepcidin was associated (R^2=0.52, p<0.0001) with previous RBC transfusions (p=0.02) and serum ferritin (p=0.001). In the course of transplantation (day 0 to day 180), the major determinants of hepcidin levels (R^2 0.35 to 0.60, p<0.0001) were iron status (ferritin at all time points (all p<0.0001) and Tsat at day 56 (p=0.0003)) and erythropoietic activity (sTfR or reticulocytes or ERFE (p ranging from 0.05 to 0.0001)), while inflammation and clinical parameters had no detectable influence. Indeed, hepcidin levels remained significantly higher in patients with high compared to low pretransplant ferritin (p<0.0001).

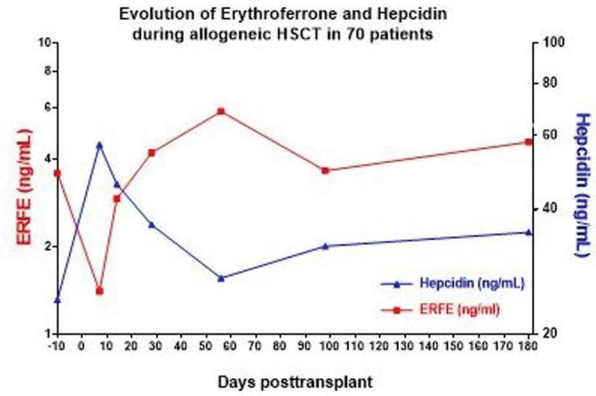


Figure 1

Summary/Conclusion: The evolution of ERFE, hepcidin and other parameters of iron status and erythropoietic activity after allogeneic HCT with or without EPO therapy confirms the strong impact of ERFE on hepcidin production and supports the erythropoietic origin of ERFE.

EP845 EFFICACY OF IRON SUPPLEMENTS GIVEN ON ALTERNATE DAYS VERSUS CONSECUTIVE DAYS IN THE TREATMENT OF IRON DEFICIENCY ANEMIA IN WOMEN OF REPRODUCTIVE AGE: NON-INFERIORITY, RANDOMIZED CONTROLLED TRIAL

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Background: The consecutive-day split dosing of iron supplements is the most common treatment of iron deficiency anemia (IDA) in clinical practice. Although recent ferrokinetic studies in iron-deficient young women demonstrated greater iron absorption with alternate-day single dosing compared to conventional twice-daily split dosing, there have been no studies evaluating long-term efficacy between these two schemes in treatment of IDA in reproductive-aged women.
Aims: This open-label, non-inferiority, randomized controlled trial (TCTR20200614001) primarily aims to evaluate efficacy and safety between alternate-day single dosing of iron supplements versus consecutive-day split dosing in reproductive-aged women with IDA.
Methods: Women aged 18-50 years were eligible for enrollment. IDA was defined by serum ferritin levels (sF) <30 µg/L. Patients randomized in alternate-day dosing were given single doses of ferrous sulfate 400 mg on alternate days, while patients in consecutive-day dosing were given ferrous sulfate 200 mg twice daily. The primary outcome was the proportion of patients with ≥ 2 g/dL hemoglobin (Hb) increase at day 30 (D30) post-treatment. The secondary outcomes were the proportion of patients with ≥ 1 g Hb increase at D30; Hb and sF at D30 and D90; and incidence of adverse events.
Results: Of 37 in preliminary analysis, 19 and 18 were randomized to alternate-day dosing and consecutive-day dosing, respectively. There were no statistical differences in pretreatment Hb (8.15 vs. 8.67 g/dL, *P*

= 0.288) and sF (5.42 vs. 7.29 µg/L, *P* = 0.175) between alternate-day dosing and consecutive-day dosing, respectively. At D30, the proportions of patients with ≥ 2 g/dL Hb increase were 63.2% vs 61.1% (absolute difference 2.1%; 95% confidence interval [95%CI] -28.7% to 3.3%, *P* = 0.14 for non-inferiority), while the proportions of patients with ≥ 1 g/dL Hb increase were 100% vs 83.3% (absolute difference 16.7%; 95%CI -0.16% to 38.6%, *P* = 0.002, for non-inferiority) in alternate-day dosing and consecutive-day dosing, respectively. There were no statistical differences in Hb (D30; 10.35 vs. 11.12 g/dL, *P* = 0.135, and D90; 12.02 vs. 12.32 g/dL, *P* = 0.603) and sF (D30; 39.36 vs. 47.33 µg/L, *P* = 0.349, and D90; 38.53 vs. 48.70 µg/L, *P* = 0.349) between alternate-day dosing and consecutive-day dosing at D30 and D90 post-treatment, respectively. Gastrointestinal disturbances were reported of 26.3% in alternate-day dosing vs. of 31.3% in consecutive-day dosing, *P* = 0.748)

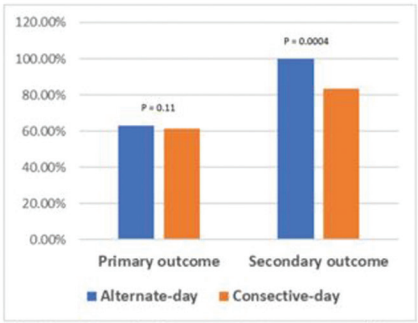


Figure: Proportions of patients with ≥ 2 g/dL Hb increase at day 30 post-treatment (primary outcome) and with ≥ 1 g/dL Hb increase at day 30 post-treatment (secondary outcome); p-value for non-inferiority of relative risk

Summary/Conclusion: Alternate-day single dosing of iron supplements may be an alternative treatment for IDA, especially in patients who do not require a rapid correction of anemia. This trial is actively enrolling.

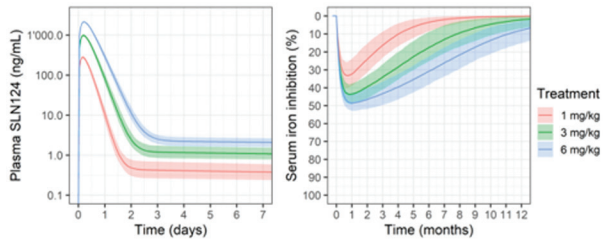
EP846 NON-CLINICAL SAFETY OF SLN124, A GALNAC CONJUGATED 19-MER DOUBLE-STRANDED SIRNA TARGETING TMPRSS6 FACILITATING EVALUATION IN CLINICAL STUDIES

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Background: Hepcidin, the central regulator of systemic iron homeostasis, is synthesized predominantly in hepatocytes, and dysregulation of its production leads to a variety of life-limiting iron disorders. SLN124 is a liver-targeted N-Acetylgalactosamine (GalNAc)-conjugated siRNA which works by increasing hepcidin by silencing its repressor TMPRSS6. SLN124 is pharmacologically active in the mouse & cynomolgus monkey.
Aims: The primary objective was to evaluate the non-clinical safety and PK/PD of SLN124 in relevant toxicology species (mouse & cynomolgus monkey) to enable evaluation of SLN124 in the clinic.
Methods: In vitro serum stability (mouse, monkey & human) and metabolism (human S9 fraction/lysosomes and plasma) was evaluated. Potential genotoxicity was determined in in vitro micronucleus and mammalian cell gene mutation assays. Cytokine release was evaluated in vitro in whole blood assays (human & monkey) and in vivo (mouse & monkey). Potential immunogenicity was assessed in vivo in rabbits using LPH-conjugated SLN124. Biodistribution was considered in the mouse, following subcutaneous dosing at 10 mg/kg over 21 days. In vivo, SLN124 was evaluated in mouse & monkey repeat dose studies, the longest duration study was 13-weeks in both species, with a 12-week recovery period. Mice & monkeys were dosed subcutaneously at 0, 10, 30 & 83 mg/kg Q2Wx6 with weekly dosing for the last 2 doses. Population PK/PD modelling & simulation of the mouse and cynomolgus monkey SLN124 PK/PD was used to estimate an appropriate clinical starting dose and dose range.
Results: SLN124 is stable in serum, plasma and human S9 fraction/lysosomes. SLN124 was neither clastogenic nor mutagenic in the completed in vitro genotoxicity studies. No cytokine release was noted in the human whole blood assay or in vivo in the mouse & monkey. As rabbit immunisation did not result in any antibody generation, SLN124 does not pose an immunogenicity risk. SLN124 showed a typical GalNAc siRNA distribution pattern, with significant levels in the mouse liver and kidney only (peak levels noted after 6 hrs, with 25% remaining in the liver after 7 days with 6% by day 21). In the 13-week repeat dose studies, SLN124 was clinically well tolerated in the mouse & monkey, with expected non-adverse changes in the liver (reversible hepatocyte degeneration/regeneration in the mouse & basophilic granules in Kupffer cells in the monkey), kidney (reversible minor increased kidney weight and renal tubular basophilia/vacuolation in the mouse) and lymph nodes (vacuolated macrophages in the monkey). The NOAEL was ≥83 mg/kg for both the mouse & monkey (highest dose tested). Population PK/PD modelling of the observed SLN124 exposure in plasma & serum iron levels in the mouse and/or monkey was used to predict human exposure and serum iron inhibition in the clinic. At 1 mg/kg (~30 fold below the human equivalent dose of the monkey NOAEL), the model predicts a maximum 34% reduction in serum iron levels (Figure 1).

Figure 1 - Predicted SLN124 plasma concentrations and serum iron inhibition of median (line), 5th and 95th percentile (area) of 500 simulated typical 70 kg human individuals using the standard error of the parameter estimates for uncertainty after single subcutaneous SLN124 doses 1, 3, 6 mg/kg



Summary/Conclusion: The non-clinical safety profile of SLN124 is consistent with the known GalNAc siRNA safety profile and supportive of clinical entry, with PK/PD modelling supporting 1 mg/kg as an appropriate safe starting dose. Two clinical studies are underway: NCT04559971 in healthy volunteers and NCT04718844 in non-transfusion dependent b-thalassaemia and VL and LR-MDS patients.

EP847 PRE-TRANSPLANT HYPERFERRITINEMIA CANNOT PREDICT TRANSPLANT OUTCOMES IN HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANT FOR SEVERE APLASTIC ANEMIA

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Background: Many patients with hematologic diseases are heavily transfused and have elevated levels of serum ferritin. Pre-transplant Hyperferritinemia has proved its association with adverse outcomes in hematopoietic stem cell transplant (HSCT) for various diseases, but data on haploidentical HSCT (haplo-HSCT) and severe aplastic anemia (SAA) is absent.
Aims: To determine the impact of hyperferritinemia on outcomes in haplo-HSCT for SAA patients.
Methods: We retrospectively analyzed outcomes of 250 SAA patients who received haplo-HSCT between 2010 and 2018, stratified by pre-transplant status of hyperferritinemia.
Results: The cumulative incidences of neutrophil engraftment at 28 days (95.16 ± 0.25% vs 90.63 ± 0.69%, p = 0.950) and platelet engraftment at 100 days (88.17 ± 0.45% vs 89.06 ± 0.47%, p = 0.105) in the two groups were similar. Hyperferritinemia independently increased the risk of grade II-IV acute graft versus host disease (aGvHD) (HR = 2.065, 95% CI 1.139-3.741, p = 0.017), while it had no impact on grade III-IV aGvHD and chronic GvHD. The risk of transplant-related mortality (TRM) at 100 days (6.45 ± 1.80% versus 9.38 ± 3.64%, p=0.413) and 1 year post-transplant (11.44 ± 2.35 % versus 10.96 ± 3.91%, p = 0.973) were not increased in patients with hyperferritinemia. The 3-year overall survival (85.23 ± 2.81% versus 89.04 ±3.91%, p = 0.648) and failure-free survival (83.32% ± 2.91% versus 82.75 ± 4.73%, p = 0.725) were also comparable between patients with and without hyperferritinemia.
Summary/Conclusion: Pre-transplant hyperferritinemia cannot predict transplant outcomes in haplo-HSCT for SAA, and transplant should not be postponed due to high levels of SF in SAA patients. The results should be confirmed in further studies.

EP848 CHANGES IN ERYTHROPOIESIS IN MALARIA-INDUCED ANEMIA

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Background: Severe malarial anemia (SMA) is a disease developed in the course of *Plasmodium* infection, which is often associated with increased rates of malaria-related morbidity and mortality. Despite high levels of erythropoietin (EPO), the occurrence of ineffective erythropoiesis is one of the main features of SMA. To gain new insights into the pathogenesis of malaria infection, changes in erythropoiesis associated with single or multiple infections with *Plasmodium chabaudi chabaudi* were investigated as well as the contribution of the immune system to the development of SMA.
Aims: Previous studies demonstrated that during anemia, proinflammatory cytokines suppress erythropoiesis by promoting iron sequestration through the hepatic hepcidin production. We confirmed that a similar response is presented in our SMA model by analyzing immune activation and the expression of iron metabolism associated genes. These data also showed that iron sensors expression levels, such as transferrin receptor 2 (*Tfr2*) and the hemochromatosis gene (*HFE*), are strictly associated with the disease severity. The extent of an immune response activation upon the exposure to this parasitic infection was also linked to the degree of induced SMA, with T cells playing a major role.
Methods: Flow cytometry analyses were used to show the bone marrow and spleen response during the infection.
Results: The results obtained demonstrated that malaria infection significantly alters the erythropoietic process through the dynamic interaction between inflammation and iron metabolism.
In order to regulate the erythropoietic response in malaria, the spleen increases erythrocyte production and compensate the loss of an appropriate bone marrow erythropoiesis during the infection. This directly correlates with parasite load.
Summary/Conclusion: In conclusion, malaria infection significantly alters the erythropoietic process through the dynamic interaction between inflammation and iron metabolism.

EP849 RELATIONSHIP OF PRE-TRANSPLANT IRON STATUS TO OUTCOMES POST KIDNEY TRANSPLANTATION: A RETROSPECTIVE COHORT

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Background: One of the most important aspects in the care of CKD patients is addressing anemia. Treatment includes iron replacement and blood transfusion which can lead to hemosiderosis. Abnormal iron balance, whether iron deficiency or iron overload is associated with increased mortality in CKD patients. Prospective cohorts showed increased mortality in kidney transplant patients with high post-transplant ferritin levels however no literature regarding the relationship of pre-transplant ferritin status has been published yet.
Aims: To determine the relationship of pre-transplant ferritin and transferrin saturation levels to outcomes post-transplant including overall survival, graft survival and renal function and incidence of hospitalizations.
Methods: The study design is a retrospective cohort. The subjects were 124 post-transplant patients divided into two groups (high ferritin vs. normal ferritin). Demographic data such as age, gender, transferrin saturation, etiology of CKD, duration and mode of renal replacement therapy, type of graft donor and history of blood transfusions were recorded. The outcomes investigated were: (1) Creatinine clearance at one- and three-years post-transplant (2) number of hospitalizations, (3) biopsy-proven graft rejection, (4) need for dialysis and (5) all-cause mortality. The statistical analyses used were univariate and bivariate analyses (chi-square) and multivariate analysis using multiple logistic regression (factor analysis and MANOVA).
Results: Demographic and clinical background for both arms were not significantly different (p >0.05). Patients with high ferritin were more likely to also have high transferrin saturation. (p 0.003). There was significant association between ferritin status pre-transplant and number of hospitalizations post-transplant (p 0.003) which can represent higher morbidity in this subset. No significant difference in terms of one- and three-year renal function, incidence of biopsy-proven graft rejection, need for dialysis post-transplantation or all-cause mortality was elicited between the two groups.

Table 2 Bivariate analysis of different outcomes post kidney transplantation in relation to ferritin levels pre-transplantation

			Normal Ferritin Group	High Ferritin Group	P value
1.	Kidney Function at Year 1	eGFR >60	37	51	0.220
		eGFR <60	15	17	
		Mean eGFR	75.12 (SD 23.6)	77.54 (SD 22.8)	
2.	Kidney Function at Year 3	eGFR >60	43	51	0.134
		eGFR <60	9	17	
		Mean eGFR	72.65 (SD 24.1)	76.98 (SD 23.7)	
3.	Number of hospitalizations		1.29	2.35	**0.003**
4.	Biopsy proven rejection		4	2	0.279
5.	Need for dialysis post-transplant		0	1	0.581
6.	All-cause mortality		1	5	0.198

Summary/Conclusion: There is a strong association between pre-transplant hyperferritinemia and number of hospitalizations after renal transplantations, and therefore a good predictor of morbidity especially infection-related complications.There is no difference in mortality and graft function between renal transplant patients with high and normal pre-transplant ferritin levels. Pre-transplant ferritin and transferrin saturation levels in this group may not be a good predictor for mortality.

EP850 TMPRSS6 POLYMORPHISMS AND A RISK OF IRON DEFICIENCY ANEMIA IN SCHOOL-AGED CHILDREN

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Background: In Thailand, the prevalence of iron deficiency anemia (IDA) in children is around 10-16%. Common etiologies of IDA include inadequate iron intake and chronic blood loss. Other than those, mutations in *TMPRSS6* gene have been reported. The *TMPRSS6* gene regulates hepcidin expression by encoding Matriptase-2, an enzyme which cleaves a cofactor promoting hepcidin transcription. With mutations to such gene, the patient has an elevated hepcidin level despite the iron deficiency status and is described as having iron refractory IDA (IRIDA). Several studies show that the *TMPRSS6* gene polymorphisms, for example rs855791 (p.V736A) and rs2235324 (p.K253E), associate with lower iron status. Whether these single nucleotide polymorphisms are associated with an increased risk of developing IDA in our population especially in children is an enticing question.
Aims:
1. To identify the prevalence of *TMPRSS6* gene polymorphism (p.V736A) in the study population
2. To identify the association between the *TMPRSS6* polymorphism (p.V736A) and the risk of iron deficiency anemia in Thai children

Methods: A total of 415 students aged between 9-15 years, from 3 schools were all included in this study. Their blood was taken for complete blood count, iron study and hepcidin assay. Directed by the results, they were then classified into normal, iron depletion (ID) and IDA groups, according to World Health Organization's definition. For DNA study, the DNA containing the p.V736A (c.T2321C) polymorphism was amplified by polymerase chain reaction (PCR) and identified by restriction fragment length polymorphism (RFLP) in all participants. Chi-square test was used to determine the difference in iron status with respect to genotypes (TT, CT and TT). Logistic regression analysis was used to determine its association with serum iron, ferritin and hepcidin levels.
Results: The T allele frequency in this population was 0.6. The percentage of TT genotype was highest in IDA group (48%) compared to ID (36.6%) and normal group (31.9%) although there were no significant differences, *p*-value= 0.226. The TT genotype had significantly lower serum iron when compared to the CT genotype (serum iron mean difference -7.9 [SE 3.2] mmol/L, *p*-value = 0.043 whereas it was not significant when compared to the CC genotype (mean difference -7.4 [SE 4.8] mmol/L, *p*-value = 0.354). There were also no significant differences of hepcidin and ferritin levels among genotypes.
Summary/Conclusion: The TT polymorphism of c.T2321C is common among Thai children with IDA and associates with a lower level of serum iron when compared to the other genotypes. Other polymorphisms of the *TMPRSS6* gene will be further studied to determine additional effects of combined polymorphisms to the iron status.

Lymphoma Biology & Translational Research

EP851 DISSECTION OF MANTLE CELL LYMPHOMA BONE MARROW B LYMPHOCYTES ON THE SINGLE-CELL LEVEL WITH FOCUS ON CLINICAL MARKERS AND SOXC FAMILY MEMBERS

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Background: Mantle cell lymphoma (MCL) is an often rapidly progressing accumulation of lymphocytes with generalized lymphadenopathy, and common involvement of peripheral blood and bone marrow (BM). Translocation t(11;14), leading to overexpression of cyclin D1 (CCND1), is one of the primary events in MCL development.
Aims: Here, we investigate the transcriptome of MCL cells from eight BM samples to provide insight into the complex and diverse molecular architecture of MCL at the single-cell expression level.
Methods: Transcriptome analysis was performed on viable $CD19^+$ cells sorted from diagnostic cryopreserved BM cells of eight MCL patients. All patients had nodal and BM involvement, were positive for CCND1 and SOX11 and displayed an otherwise heterogeneous clinical presentation. A concentration of 1400 cells/µl were used for single-cell mRNA sequencing (ScRNA-seq) using the 10x Chromium System and Illumina NovaSeq 6000. Data analysis was performed with Cell Ranger (10x Genomics) and R (Seurat 3.2).
Results: ScRNA-seq revealed transcriptional inter-tumor heterogeneity across the MCL patients. Expression analysis identified distinct subsets of non-malignant pre-pro B/pro-B cells with similar expression profiles across patients. MCL cells showed enrichment of genes involved in key pathways associated with B cell malignancies, such as PI3K/AKT/mTOR and NFκB.
Generally, the cell populations were transcriptionally defined as $CD20^+CD45^+CD5^{low/-}CD19^{low/-}CD23^{low/-}CD27^{low/-}$. While the light chain restriction was in overall concordant with the clinical laboratory analyses, we found a median of 9.5% (0.1–24.4%) of the light chain expressing cells that were both κ and λ positive. Also, on the single-cell transcription level, we demonstrated that CD23 was present in a subset of the $SOX11^+$ MCL cells (1.45–9.29%), supporting previous findings that some MCLs are CD23+, although this marker is frequently used to differentiate chronic lymphocytic leukemia from MCL. While 85% of all $SOX11^+$ cells were positive for IgM (35–98%) and 17% for IgD (1–43%), all patients had SOX11+ cells expressing IgA (2–47%) and IgG (1–15%), and patient 1–6 had a small $CD27^+SOX11^+$ fraction, suggesting that some of the MCL cells may be antigen-experienced although expected to originate from naïve B cells. While all patients displayed SOX11 and CCND1 expression in concordance to the clinical laboratory results, only 35% of the total single-cell cohort were marked SOX11+, and of the SOX11 positive cells 70.6% (44.59–81.47%) co-expressed CCND1 at a detectable level. Additionally, 4.49% of all cells expressed SOX4, a marker of more immature B cells, and 3.07% of these cells were $SOX11^+$. Not surprisingly, the expression levels of the classical MCL markers such as e.g. SOX11, CCND1, CD5, CD19 and CD20 were highly correlated ($p=0.02$, $\rho=0.99$), even though CD19 and to a larger degree CD5 were only detectable in a subset of cells.
We found that a blastoid MCL case (patient 1) was marked by a subset of cells expressing both SOX11 and SOX4 together with a presentation of protocadherin FAT1, which was exclusively expressed in this patient (20% of SOX11+ cells). FAT1 is a specific marker in acute lymphoblastic leukemia, and SOX4 plays a central role in survival of malignant lymphoblasts, thus these markers, posed for further investigation, may help establish differentiation state and possibly prognosis.
Summary/Conclusion: Our study demonstrates inter-tumor heterogeneity of MCL, characterizes MCL-specific expression profiles and provides insight into clinical markers at the single-cell transcription level.

EP852 WHOLE-GENOME CRISPR LIBRARY SCREENS IDENTIFY CD48 AS AN ESSENTIAL MOLECULE IN ADULT T-CELL LEUKEMIA/LYMPHOMA FOR DEFINING SUSCEPTIBILITY TO NATURAL KILLER CELL-MEDIATED CYTOTOXICITY

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Background: Adult T-cell lymphoma/leukemia (ATLL) is a mature T-cell neoplasm and its prognosis is poor. Human T-cell leukemia virus type 1 (HTLV-1) is the causative retrovirus of ATL and it infects infants' CD4 positive T cell through breast feeding. A fraction of the HTLV-1 infected individuals develops ATLL after more than 50 years. During the long latency period genetic alterations and aberrant gene expression accumulate extensively in ATLL cells. In particular, ATLL has high frequency of somatic mutations, genomic losses and epigenetic silencing in human leukocyte antigen (HLA)-A, HLA-B and β2 microglobulin, highlighting immune escape from T-cells as a hallmark of ATLL. In theory this "missing self" increases susceptibility to natural killer (NK) cell-mediated killing but it remains unknown how ATLL cells evade NK cell-mediated immunosurveillance. In fact, activation of NK cells is controlled by signal integration from multiple stimulatory and inhibitory receptors on their cell surface so that functional elucidation for the key mechanism by which ATLL cells evade NK-mediated immune surveillance remains challenging.
Aims: The aim of this study was to identify ATLL cell-intrinsic molecules which play essential roles for immune evasion from NK cell-mediated cytotoxicity against ATLL.
Methods: Two Cas9-expressing ATLL cell lines were lentivirally transduced with the human clustered regularly interspaced short palindromic repeat (CRISPR) Brunello pooled library (Addgene #73178) of 76,441 single-guide RNAs targeting 19,114 protein-coding genes, selected by puromycin, cultivated for 2 weeks enough to have genes fully inactivated by sgRNAs. The cells were co-cultured with human YT1 NK cells at 1:2 of effector:target ratio for 24-48 hours. Mogamulizumab, anti-human CCR4 monoclonal antibody, was added to the effector/target cell mixture, which enabled us to evaluate the responsible genes for both direct NK cytotoxicity and mogamulizumab-mediated antibody dependent cellular cytotoxicity (ADCC). Resistance genes were those for which the corresponding sgRNAs were enriched in the screening cell pool relative to the cell pool without screening. MAGeCK algorithm was used to rank target genes enriched in the screening.
Results: Twenty genes were overlapped between top-ranked 500 genes in two ATLL cell lines. As a proof of concept, CCR4 was identified as the best overlapped gene, confirming the reliability of our screening. One of the other overlapped genes was CD48, which is a signaling lymphocyte activation molecule (SLAM) family cell surface receptor and is an activating NK cell receptor by ligating 2B4 receptor on NK cells. Through further analysis, the ability of CD48 knockout ATLL cells for evading NK cell-mediated direct cytotoxicity was confirmed by using not only a NK cell line but also human primary NK cells with reduced interferon gamma induction and degranulation. Notably, we found that primary ATLL cells reduced their CD48 mRNA expression along with aggressiveness of clinical subtypes.
Summary/Conclusion: Our findings indicated that CD48 is an essential molecule in ATLL for defining susceptibility to NK cell-mediated cytotoxicity. Thus this study improved our current understanding of the mechanisms for immune evasion in ATLL and provides a rationale for evaluation of CD48 as a biomarker for NK cell-based immunotherapies in the future.

EP853 COMPREHENSIVE CHARACTERIZATION OF THE MUTATIONAL LANDSCAPE IN EPSTEIN-BARR VIRUS-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA BY WHOLE-GENOME AND TARGETED AMPLICON-BASED SEQUENCING

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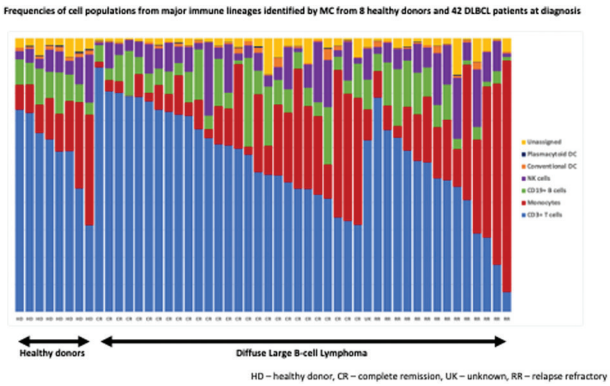
Background: The current World Health Organization (WHO) classification outlines the Epstein–Barr virus (EBV)-associated diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) as a distinct entity while its comprehensive genomic characterization remains fragmentary.
Aims: The substantial aim of the present study was to compile an extensive genomic landscape of EBV+ DLBCL (NOS).
Methods: In the current study, the genomic landscape of 47 cases of this rare entity has been characterized by whole-genome sequencing (WGS), targeted amplicon sequencing (tNGS) and fluorescence *in-situ* hybridization (FISH).
Results: Genomic data from WGS detected an accumulation of mutations with impact on WNT signalling (*FRAT1*, *SFRP5*), the nuclear factor κB (NFκB) pathway (*CSNK2A2*, *CARD10*), IL-6/JAK/STAT (*SOCS1/3*, *STAT3*) and alterations affecting immunological response like interferon-related signalling. Moreover, upon WGS-analysis there were several structural aberrations including 6q-deletions in 5/8 cases which underwent subsequent validation by FISH (14/32 cases). Present data reveal a distinctive genomic profile from EBV-negative DLBCL. Frequent typical DLBCL mutations could be identified in *ARID1A* (45%), *KMT2A/D* (32/30%), *ANKRD11* (32%), *NOTCH2* (32%) as well as EBV+ DLBCL (NOS) exclusive mutations in *CCR6* (15%), *DAPK1* (15%), *TNFRSF21* (13%), *CCR7* (11%) and *YY1* (6%).
Summary/Conclusion: We delineate the mutational landscape of EBV+ DLBCL (NOS) and comprehensively explore its pathobiological origin detecting several exclusive oncogenic drivers distinctive from other aggressive B-cell lymphoma subtypes. Moreover, we find deletions on chromosome 6 to be a highly recurrent cytogenetic feature of this rare entity. Current genomic findings contribute to the particular specification of the molecular taxonomy for aggressive B-cell lymphomas harbouring the potential to guide future treatment strategies.

EP854 DISEASE AND OUTCOME ASSOCIATED IMMUNE SIGNATURES AT DIAGNOSIS IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: Treatment failure after RCHOP is associated with poor outcome in DLBCL. Peripheral blood (PB) absolute monocyte (AMC) and lymphocyte (ALC) counts at diagnosis can predict outcome, but the mechanism is unknown.
Aims: To characterise and functionally define the PB immune compartment in DLBCL.
Methods: Full blood counts (FBC) from 116 healthy donors and 146 previously untreated DLBCL patients were assessed. Twenty cytokines were measured in duplicate in serum from healthy donors (HD, n=11) and DLBCL patients at diagnosis (n=64) using the mesoscale discovery electrochemiluminescence platform. Peripheral blood mononuclear cells (PBMCs) from HD (n=8) and DLBCL patients (n=42) were analysed by mass cytometry (MC) to phenotype immune cell populations in depth. An intracellular cytokine staining MC protocol was applied to a subset of these PBMC samples for functional assessment. A standard HD control sample was acquired with each MC batch. Normalised data were analysed using the OMIQ platform.
Results: The median AMC was higher and ALC lower in DLBCL ($p<0.0001$). The AMC / ALC prognostic score defined 3 groups with distinct outcome in DLBCL ($p<0.0001$). Eight of 20 cytokines analysed were elevated in DLBCL, with 5 of these cytokines (CCL3, TNF, IL1RA, IL6 and IL10, $p<0.05$) significantly higher at diagnosis in patients who subsequently had relapse/refractory disease post RCHOP (R/R) compared to those with maintained complete remission (CR). Cytokine levels were independent of cell of origin (COO) except for IL1RA which was elevated in non-GCB.
Gated immune populations identified by MC were assessed for significant differential abundance with edgeR (FDR<0.05). Intermediate and non-classical monocytes were higher in DLBCL, whereas CD4 effector memory (EM1) and CD8 central memory (CM) were higher in HD. Within DLBCL samples, non-classical monocytes and CD8 effector memory (EM3) were more abundant in patients with subsequent R/R disease. FlowSOM clustering followed by edgeR analysis revealed 3 monocyte clusters at diagnosis associated with disease relapse. The most differentiating cluster consisted of classical monocytes with a suppressor phenotype ($CD14^{hi}$, $HLA\text{-}DR^{lo}$) and expression of CD163 and CD184. The most differentiating T cell cluster associated with subsequent relapse had a CD8 EM3 phenotype. These findings were independent of COO.
Functional analysis revealed constitutive over production of CCL3 and IL6 in DLBCL, predominantly by CD14+ monocytes ($p=0.0025$). Stimulation with LPS demonstrated blunted cytokine production responses in DLBCL, most pronounced in cases that relapsed. Stimulation with PMA/inomycin demonstrated no evidence of PB T cell exhaustion, with hypersensitivity of TNF and IL2 production in DLBCL, predominantly by CD4 T cells. Activated granzyme B / perforin positive NK cells were increased in DLBCL.



Summary/Conclusion: We find distinct immune cell and cytokine signatures associated with DLBCL and with outcome following RCHOP. Specifically, we identify cytokine overproduction in DLBCL, the main PB source being CD14+ monocytes, suggesting a non-cell autonomous role for PB cytokine production in DLBCL. We identify immune populations by manual gating and FlowSOM clustering with differential abundance in DLBCL and in those cases that subsequently relapsed, reflecting immune dysfunction associated with disease and outcome. Our data provide an explanation for the prognostic nature of the AMC /ALC, support the challenge to identify biomarkers and provide insight into steps that may be required to overcome the immune defects in RCHOP refractory DLBCL.

EP855 ROLE OF PROTEIN KINASES CK1 ALPHA AND CK2 IN CHRONIC ACTIVE BCR-DEPENDENT SIGNALING NETWORK IN MANTLE CELL LYMPHOMA: EFFECTS ON BTK-DIRECTED THERAPY.

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Background: Mantle cell Lymphoma (MCL) is a B cell tumor, characterized by frequent relapses. Chronic activation of multiple signaling pathways, including BTK, PI3K/AKT and NF-κB are of pathogenic importance in MCL. New drugs targeting the B Cell Receptor (BCR) dependent signaling pathways, such as ibrutinib, acalabrutinib, zanubrutinb and other BTK inhibitors, have been proved therapeutically efficient in MCL, but the disease remains uncurable. To this regard, there is an urgent need to discover novel druggable targets. We and others

demonstrated that two Ser-Thr kinases, namely protein kinases CK1α and CK2, are essential kinases for the survival of multiple myeloma (MM) cell, acute myeloid leukemias, lymphomas and other hematological malignancies, regulating pivotal survival signaling events. We therefore sought to investigate a potential role of these kinases in MCL downstream the BCR signalling

Aims: In the present study we analyzed the role of CK1α and CK2, in the regulation of chronic active, BCR dependent signaling pathways in MCL, such as NF-κB, BTK and AKT, and the potential of their inhibition in association with the BTK inhibitor ibrutinib, to effectively reduce MCL cell growth and clonal expansion.

Methods: CK1α and CK2 expression and BCR signaling components were analyzed in MCL cells from patients, MCL cell lines and controls by western blot (WB). CK1α or CK2 silencing was obtained through the generation of anti-CK1α or anti CK2 shRNA IPTG-inducible MCL cell clones. CK1 or CK2 chemical inhibition was obtained with D4476 (CK1i) or CX-4945 (CK2i). Cell survival/apoptosis and proliferation were investigated with an array of standard techniques and the therapeutic interaction between drugs was analyzed through the Chou-Thalalay combination index method. CK2 knock down *in vivo* was obtained in xenograft NOD SCID mouse models.

Results: CK1α and CK2 are overexpressed in MCL cells compared to healthy B lymphocytes. CK1 or CK2 chemical inhibition with D4476 or CX-4945 respectively, caused, a reduction in the activating phosphorylation of S536 p65/RelA and S473 AKT, important signaling events downstream the BCR. CK1α or CK2 were shown to sustain MCL cell growth and proliferation, since their chemical inhibition or gene silencing caused MCL cell apoptosis and cell cycle arrest. We discover a novel, unanticipated potential role of these two kinases in regulating BTK function, since their chemical inhibition or silencing with RNAi, caused a reduction in the activating phosphorylation of BTK on Y223. We confirmed these results also in an *in vivo* xenograft mouse model of CK2 knockdown. As a result, a striking cytotoxic effect on MCL cells was obtained through the combination of CK1α or CK2 inactivation with ibrutinib, as demonstrated by increased apoptotic Annexin V positive cells, PARP cleavage, reduction in pro-survival protein expression such as Mcl1 and pro-caspase 3. CK1i or CK2i acted synergically with ibrutinib, since the calculated combination index between the drugs (according to the Chou-Talalay methods) resulted less than 1,

Summary/Conclusion: Our findings suggest that CK1α and CK2 are fundamental kinases for MCL growth, regulating chronic active BCR-linked survival signaling cascades. Our data also indicate that these kinases could antagonize ibrutinib -induced apoptosis. Therefore, CK1α and CK2 could be rational therapeutic targets for the treatment of MCL, particularly those aggressive, ibrutinib-resistant forms.

EP856 HIGH RISK AGGRESSIVE B-CELL LYMPHOMA ON THE LIQUID BIOPSY

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Background: Inadequate molecular recognition of high-risk diffuse large B-cell lymphoma (DLBCL) hampers the discovery of novel treatments for the patients with poor outcome. Clinical significance and prognostic impact of circulating tumor DNA (ctDNA) warrants establishment in prospectively collected samples from homogeneous patient populations.

Aims: We aimed to delineate molecular determinants of outcome within the ctDNA of the patients with aggressive B-cell lymphoma.

Methods: We applied whole-genome and targeted duplex DNA sequencing to serially sampled plasma cell-free DNA of 101 patients less than 65 years with high-risk (aaIPI 2-3 and/or site-specific risk factors for central nervous system (CNS) progression) aggressive B-cell lymphoma. The patients were treated in a Nordic Lymphoma Group phase II trial with dose-dense immunochemotherapy and early CNS prophylaxis (Leppä et al., Blood Advances 4(9):1906-1915, 2020).

Results: We found that the patients with high pretreatment ctDNA burden (log hGE/ml) were at high risk of relapse and early death from lymphoma. In contrast, non-lymphoma related treatment failures were mainly seen in the patients with low to moderate ctDNA levels. High ctDNA burden overcame the conventional measures of high tumor burden and other high-risk features including double-hit lymphomas, revealing that additional clinically meaningful heterogeneity exists within the established clinical and biological risk factors.

Treatment refractoriness exhibited diverging ctDNA kinetics during therapy, whereas late molecular responses, and end-of-treatment negativity for minimal residual disease characterized cured patients. As a proof-of-concept, we show that advanced ctDNA tools based on hypermutation patterns and fragmentome disparities can complement prediction of progression at the end of therapy, and provide tools to clinical challenges, including false residual PET positivity.

Lastly, we analyzed the potential of non-invasive ctDNA interrogation for somatic drivers, hypermutation signatures and variant haplotypes to offer novel translational information for diagnostics and understanding of treatment-refractoriness in patients with aggressive B-cell lymphoma. Genomic dissection of pretreatment ctDNA revealed a strong association between *TP53*-loss and high ctDNA burden – a duo that in the context of high-risk biology rendered lymphomas refractory to frontline treatment. In contrast, subclonal *MYC* lesions that were not detectable at diagnosis were positively selected at late relapses following complete responses to the initial therapy. We further identified that the limitations of tissue biopsies can culminate in diagnosis-changing discoveries in plasma ctDNA, including progression-driving transformation to high-grade B-cell lymphoma.

Summary/Conclusion: Our integrative approach with prospectively collected serial plasma samples reveals that quantitative, mutational and fragmentome features of ctDNA can be utilized as novel diagnostic and prognostic tools in aggressive B-cell lymphomas.

EP857 DDX3X LOSS IS ASSOCIATED WITH AGGRESSIVE PHENOTYPES IN NON-HODGKIN'S LYMPHOMAS

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Background: Non-Hodgkin's lymphoma (NHL) is a diverse group of haematolymphoid malignancies, encompassing the more common diffuse large B-cell lymphoma (DLBCL) to the rarer T-cell lymphomas such as cutaneous T-cell lymphoma (CTCL). Several groups have performed comprehensive genomic analysis of various subtypes of NHL including DLBCL using whole exome sequencing (WES) and identified frequent occurrence of mutation in the *DEAD box helicase 3, X-linked* (*DDX3X*) gene. DDX3X is an RNA helicase and, depending on tumour type, plays a tumour suppressive or oncogenic role in cancer. However, its role in NHL remains unclear.

Aims: - To examine the mutational status of DDX3X in NHLs.
- To determine the molecular effects of DDX3X loss in cells derived from NHLs.

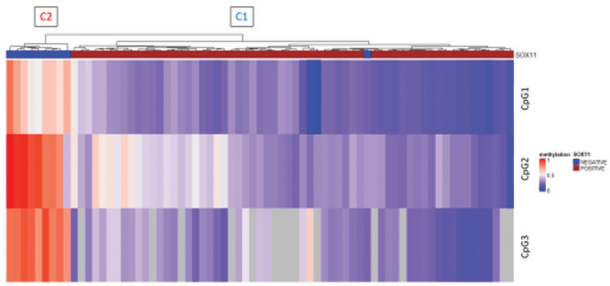
- To define functional involvements of DDX3X in NHLs.
Methods: We performed exome sequencing to identify genomic aberrations in *DDX3X* gene in DLBCL patients. Next, we generated CRISPR variants/ shRNA knockdown models of NHL cells line to mimic DDX3X mutation/loss. We determined the molecular effects of DDX3X loss by performing RNAseq analysis and immunoblot assay. We performed MTS and Annexin V/PI-based cell viability assays, BrdU proliferation assay, impedance-based metastasis assay and checkerboard assay to understand the functional involvement of DDX3X loss in NHLs.
Results: Targeted sequencing of *DDX3X* hotspots on exons 8-15 in a cohort of 158 unselected DLBCL subjects showed *DDX3X* mutations in 5 cases; whereas whole exome sequencing identified *DDX3X* mutations in 4 out of 9 patients with relapsed/refractory DLBCL treated with R-CHOP (rituximab + cyclophosphamide/ doxorubicin/vincristine/ prednisone). DLBCL patients (n=223) with *DDX3X* mutations had worse 5-year overall survival (22%) compared to patients with wild-type *DDX3X* (72%, p=0.021). Using NHL cell lines, we showed that the expression of mutant DDX3X-R475C or DDX3X knockdown caused significant up-regulation of cyclin-D1 and increased phosphorylation of oncogenic STAT3, Akt and p42/44. We demonstrated that DDX3X loss enhances proliferation and metastasis in DDX3X R475C-mutant/depleted NHL cells. DDX3X loss increased resistance to doxorubicin and histone deacetylase targeting drugs in DLBCL and CTCL cells, respectively. Importantly, B- and T-cell lineage DDX3X-depleted cells remained sensitive to STAT3 inhibition.
Summary/Conclusion: In conclusion, our data suggest that loss-of-function mutations in *DDX3X* are important molecular determinants of disease aggressiveness and treatment response in NHL. These data will help improve risk stratification of NHL may identify new therapeutic options for a subgroup of patients with poor prognosis.

EP858 A SIMPLE EPIGENETIC SIGNATURE DEFINES TWO BIOLOGIC GROUPS OF MANTLE CELL LYMPHOMA

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Background: Mantle cell lymphoma (MCL) is a mature B cell lymphoma with a generally poor prognosis. However, in the past decade a subset of MCL with more indolent clinical course and predominant leukemic disease, termed leukemic non-nodal MCL (nnMCL), has been identified. It is important to confidently diagnose the two MCL subtypes in order to tailor treatment decisions based on their remarkably different clinical course. Current strategies in the differential diagnosis between nnMCL and conventional MCL (cMCL) include SOX11 expression and a gene expression signature (L-MCL16, Clot G et al., *Blood* 2018), but both methods present limitations which pose difficulties in clinical practice (e.g. low or partial expression of SOX11, L-MCL16 designed for peripheral blood samples). The epigenetic characterization of MCL (Queirós AC et al., *Cancer Cell* 2016 and Nadeu F et al., *Blood* 2020) identified two disease subtypes (C1 and C2), which mostly represent cMCL and nnMCL respectively. Furthermore, a *SOX11* distal enhancer region was discovered, which is *de novo* demethylated in SOX11 positive MCL.
Aims: Our study aims to translate the epigenetic subtypes of MCL into a simple assay, which can be easily implemented in clinical practice and universally applied to all types of clinical samples. Secondly, we aim to analyze the impact of the epigenetic disease subtype on clinical outcome in an extended series of cases. Lastly, we aim to characterize the DNA methylation profile of regulatory regions of *SOX11* to better understand the relationship between its expression and the C1 and C2 MCL subtypes.
Methods: We identified a 3 CpG signature (Duran-Ferrer M et al., *Nature Cancer* 2020) that accurately subclassifies MCL into C1 and C2 MCL. To overcome limitations of previous methodologies, we designed pyrosequencing assays that can be applied to any type of clinical sample, including frozen and formalin-fixed paraffin-embedded (FFPE) tissues, as well as peripheral blood samples. Extracted DNA was bisulfite converted, amplified by PCR and pyrosequenced for quantitative methylation analysis. Benchmarking experiments for validation of the assays were performed assessing technical reproducibility and methylation level comparison between different source of samples from the same patient (frozen, FFPE, peripheral blood).
Results: Benchmarking experiments show an excellent technical reproducibility and high correlation between different sample types of the same patient. The exploratory study shows a clear separation in two groups, which correspond to C1 and C2 MCL (Figure). C1 MCL show SOX11 positivity by immunohistochemistry, except for one single cases of pleomorphic MCL. All SOX11 expressing MCL show a consistent demethylation in the *SOX11* distal enhancer and promoter region, whereas a majority of SOX11 negative cases have high methylation levels in one of the regulatory regions, indicating that the DNA methylation status of *SOX11* regulatory regions might represent a *bona fide* surrogate of its expression status.



Summary/Conclusion: Our study highlights the stability and applicability of a methylation signature to classify MCL subtypes. Analysis of the methylation signature in an extended series of cases is currently ongoing and will allow us to determine the prognostic significance of the epigenetic subtype of MCL. This epigenetic signature applicable to any type of clinical samples may represent a novel and accurate tool for the differential diagnosis of cMCL and nnMCL in clinical routine.

EP859 EZH2 INHIBITOR TAZEMETOSTAT DEMONSTRATES ACTIVITY IN PRECLINICAL MODELS OF BRUTON'S TYROSINE KINASE INHIBITOR-RESISTANT MANTLE CELL LYMPHOMA

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Background: Tazemetostat (EZM6438) is a potent, orally bioavailable small molecule inhibitor of EZH2, the enzymatic subunit of the polycomb repressive complex 2, which has been approved for treatment of epithelioid sarcoma and relapsed/refractory follicular lymphoma. EZH2 has been shown to play a key role in B-cell maturation and multiple B-cell malignancies are dependent on EZH2 for survival. Mantle cell lymphoma (MCL) is a rare subtype of mature B cell non-Hodgkin lymphoma characterized by the t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1, which plays a significant role in tumor cell proliferation via cell cycle dysregulation, chromosomal instability and epigenetic regulation. This disease most often presents at an advanced stage and while most of the patients respond to frontline therapy (including Bruton's Tyrosine Kinase (BTK) inhibitors) they eventually relapse. The rate of intrinsic and acquired resistance results in a high unmet medical need.
Aims: Investigate if tazemetostat, as monotherapy or in combination with standard of care (SOCs) or emerging therapies, could offer therapeutic benefit to the BTK inhibitor-resistant MCL population.
Methods: *In vitro* 14-day proliferation assays assessed the activity of tazemetostat in MCL cell lines. *In vitro* proliferation assays in a panel of MCL cell lines evaluated the combinatorial potential of tazemetostat and SOCs or emerging therapies by pre-treating cells with tazemetostat for 7 days followed by co-treatment for 7 days with tazemetostat and combination partners. *In vitro* 10-day assays evaluated the *ex vivo* effect of tazemetostat on tumor B-cell proliferation from MCL patient samples. MCL cell line murine xenograft study assessed tumor growth delay in response to treatment with tazemetostat, BTK inhibitor zanubrutinib and their combination. ELISA assessed the intratumoral levels of H3K27me3.

Results: We demonstrated that tazemetostat synergized with zanubrutinib and resensitized a subset of cell lines that were intrinsically resistant to BTK inhibitors. *In vivo* studies in the MCL MINO cell line-derived murine xenograft model confirmed these findings, showing a significant tumor growth delay in response to combination treatment of tazemetostat and zanubrutinib compared to the single agent treatments with concomitant decrease in intratumoral levels of H3K27me3. To understand if tazemetostat could offer therapeutic benefit in the BTK inhibitor-acquired resistant MCL population, we generated *in vitro* MCL models of acquired resistance to the BTK inhibitors ibrutinib and zanubrutinib. These cell lines retained the *in vitro* sensitivity to tazemetostat observed in the parental cell line, suggesting tazemetostat as a potential therapeutic option in the setting of acquired resistance to BTK inhibitor. In addition, synergy was observed in *in vitro* combination studies with tazemetostat and lenalidomide, glucocorticoid receptor agonists and venetoclax in these cell line models. Lastly, we showed that tazemetostat induced anti-proliferative effects in samples derived from MCL patients that were relapsed or refractory to one or more current standard of care agents, including the BTK inhibitor ibrutinib. Subsequent studies aim to identify the mechanisms of growth inhibition driven by tazemetostat in MCL models, sensitive and resistant to BTK inhibitors.
Summary/Conclusion: Our data suggest that tazemetostat treatment (alone or in combination with a BTK inhibitor, SOCs or emerging therapies) could be a therapeutic option in the treatment of the MCL patient population that is relapsed/refractory to BTK inhibitor therapy.

EP860 NEXT GENERATION SEQUENCING PROVIDES NOVEL MOLECULAR MARKERS FOR MINIMAL RESIDUAL DISEASE MONITORING IN FOLLICULAR LYMPHOMA: BIOLOGICAL RESULTS FROM FONDAZIONE ITALIANA LINFOMI (FIL) FOLL12 TRIAL

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Background: Despite immunochemotherapy provides durable responses in follicular lymphoma (FL) patients, the majority of them eventually relapse. Minimal residual disease (MRD) analysis, based on the detection of Bcl-2/IGH rearrangement by highly sensitive polymerase-chain reaction (PCR), is a standardized approach, able to early identify patients at risk of disease recurrence. Nevertheless, this tool has some limitations, including a 40% failure of marker identification. Next-generation sequencing (NGS) is going to overcome these issues, possibly increasing the number of patients eligible for MRD.
Aims: To screen by NGS a cohort of 120 FL who failed Bcl-2/IGH marker identification by standardized EuroMRD PCR, enrolled in the FIL "FOLL12" prospective clinical trial (EudraCT: 2012-003170-60), in order to identify new markers for MRD tracking during the follow-up (FU). First results of marker identification are here described, while complete MRD results will be presented elsewhere.
Methods: Advanced FL received upfront R-CHOP or BR, followed by a combined PET/MRD response-based post-induction therapy vs conventional maintenance with rituximab. Bone marrow (BM) samples were centralized at the Italian Network laboratories for MRD analysis. Baseline molecular evaluation was available for 615/628 cases who achieved PET negativity at end of induction. 270 of them (44%) lacked a conventional Bcl-2/IGH marker. Therefore, 163 (60%) were selected for BM lymphoma infiltration (median 25%, 1-90%), of whom 120 (74%) had available samples for analysis. Baseline gDNA was screened by IGH-NGS using EuroClonality-NGS framework region 1 (FR1) primers; IGH clonotypes identification was done by ARReST/Interrogate. In parallel, targeted locus amplification (TLA) on the IGH enhancer was used to identify novel Bcl-2/IGH rearrangements in a preliminary cohort of 15 patients. Finally, to test the reliability of newly identified markers, we generated patient-specific primers and carried out MRD analysis by ASO qPCR following EuroMRD guidelines in three cases.
Results: 111/120 (93%) sequenced samples passed the quality control (>10000 raw reads). A clonotype (>5% of IGH-VDJ annotated reads) was identified in 56% (63/111): 61 monoclonal and 2 biclonal, 54 productive and 9 unproductive IGH rearrangements (Figure 1). Moreover, in 8/15 (53%) patients screened by TLA a novel Bcl-2/IGH rearrangement was found; interestingly, TLA was able to identify a marker in 2 out of 5 cases failed by IGH-NGS. Finally, the reliability of these markers for MRD detection was preliminary assessed in three patients by ASO qPCR (targeting one Bcl2/IGH and two IGH rearrangements). The assays reached high level of sensitivity (from 1E-04 to 5E-05) and MRD kinetics in FU well described patients' outcome.

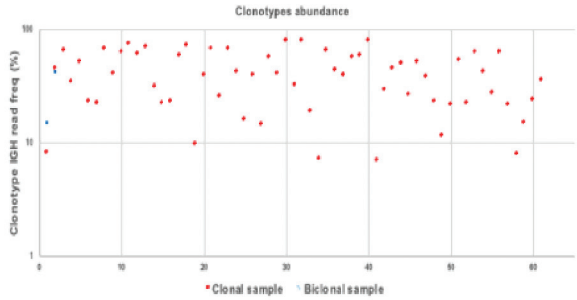


Figure 1.
Clonotypes identification in baseline BM of "no marker" patients by EuroClonality IGH-based NGS approach.

Summary/Conclusion: Preliminary data on wide NGS-based marker screening in FL patients lacking a conventional MRD marker in a clinical trial suggested that: 1) EuroClonality-NGS IGH approach was able to provide a new marker in more than half of the patients with BM infiltration; 2) TLA approach showed similar success rates in a small patients group (further experiments are ongoing); 3) the two techniques are not alternative and should rather be considered as complementary; 4) the new markers allowed to perform a "proof of concept" MRD monitoring by ASO qPCR, according to the strict EuroMRD rules. These data are highly promising to provide a MRD marker in the majority of FL patients: next steps of the present project will evaluate MRD by NGS in FU samples and assess its clinical impact.

EP861 PRMT5 INHIBITION RESTARTS A PRO-APOPTOTIC PROGRAM AND CREATES VULNERABILITY TO COMBINATION TREATMENT WITH BCL-2 INHIBITOR VENETOCLAX IN MANTLE CELL LYMPHOMA

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Background: Mantle cell lymphoma (MCL) is an incurable B cell malignancy comprising 3-6% of non-Hodgkin lymphomas diagnosed annually. MCL is associated with a poor prognosis due to emergence of resistance to immuno-chemotherapy and targeted agents. Due to the late median age of diagnosis, aggressive chemotherapy and stem cell transplantation are often not realistic options. The average overall survival of patients with MCL is 4-6 years and for the majority of patients who

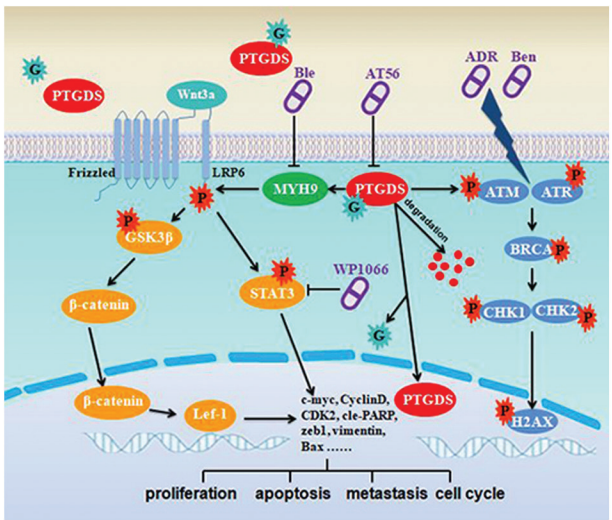
progress on targeted agents like ibrutinib, survival remains at a dismal 3-8 months. There is a major unmet need to identify new therapeutic approaches that are well tolerated by elderly patients to improve treatment outcomes and quality of life.
Our group has identified the type II protein arginine methyltransferase enzyme, PRMT5, to be dysregulated in MCL and to promote growth and survival by supporting cell cycle progression, survival, and drug resistance. While we have demonstrated that novel SAM-competitive PRMT5 inhibitors provide potent anti-tumor activity in aggressive preclinical models, we have seen resistance and relapse.
With PRMT5i we have seen a decrease in AKT activity which in turn releases FOXO1 from a phosphorylated, inactive form. Performing ChIP seq on FOXO1 resulted in over 800 target genes likely to be regulated by this transcription factor. Among these genes, pro-apoptotic BCL2 family proteins were seen as a potential indicators of a change of pro-apoptotic threshold with PRMT5i. This prompted us to pursue co-inhibition of PRMT5 and BCL as a synergistic treatment in MCL.
Aims: To validate PRMT5 and BCL2 inhibition as a synergistic combination strategy in in vitro and in vivo models of MCL.
To confirm the role of FOXO1 and the BCL2 family proteins in any seen synergy.
Methods: Nine MCL cell lines were treated with PRMT5 inhibitor PRT382, at their IC50 at day nine and collected on day six. Immunoblots and rtPCR were used to look at changes in protein and transcript levels. Cells were treated alone and in combination with venetoclax. Synergy was calculated with an MTS read out on day nine and analyzed with Combenefit. shRNA clones were generated with a lentiviral transfection and viability was measured with annexin V/PI flow cytometry. Two murine paitient derived xenograft models, PDX.AA.MCL and PDX.IR.96069 were engrafted via tail vein in NSG mice. Disease burden was monitored weekly via flow cytometry.
Results: Eight of the nine MCL reached an IC50 of <1uM after nine days of PRT382 treatment. Collected samples showed an upregulation of BAX, BAK1, BBC3, and BMF in at least one cell line on a transcript and protein level. BAX was found to be the most ubiquitously upregulated. While only four cell lines were found to be sensitive to venetoclax treatment, seven showed synergy when treated with both drugs. Cell death was confirmed to be intrinsic and synergy was found to be dependent on BAX expression. Combination treatment with well-tolerated doses of PRT382 and venetoclax in the MCL *in vivo* models showed synergistic anti-tumor activity without evidence of toxicity. Both PDX models showed an extension of life with combination treatment (P<0.001) and delayed disease progression (P<0.05).
Summary/Conclusion: This preclinical data provides mechanistic rationale while demonstrating therapeutic synergy and lack of toxicity in this preclinical study and justifies further consideration of this combination strategy targeting PRMT5 and BCL2 in MCL in the clinical setting.

EP862 TARGETING GLYCOPROTEIN PTGDS INHIBITS THE PROGRESSION OF DIFFUSE LARGE B-CELL LYMPHOMA THROUGH MYH9-WNT-B-CATENIN/STAT3 AXIS

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Background: Glycoprotein prostaglandin D2 Synthase (PTGDS) is a member of lipocalin superfamily and plays a dual role in catalyzing the conversion of PGH2 to PGD2 and transporting lipophilic substances. AT56 is a selective inhibitor of PTGDS. PTGDS has been involved in several cellular processes including cancer, yet its role in carcinogenesis is contradictory.
Aims: Herein, we aim to investigate the functional significance of PTGDS in DLBCL and propose a novel therapeutic strategy for DLBCL.
Methods: Peripheral blood mononuclear cells were obtained from healthy volunteers. Lymph node biopsies from 53 DLBCL patients and 28 reactive hyperplasia cases were collected with informed consents. $CD19^+$ B cells were purified by $CD19^+$ magnetic microbeads. Expression level of PTGDS was detected by western blotting and ELISA. Lentivirus vectors were transfected to stably knockdown or overexpress PTGDS. CoIP and mass spectrometry were performed to investigate molecular mechanism. Point mutations were created to verify glycosylation sites. BALB/c nude mice were subcutaneously injected with DLBCL cells and mice were imaged using *In-Vivo* small animal imaging system. $p < 0.05$ was considered statistically significant.
Results: Upregulation of PTGDS mRNA in DLBCL was identified based on Oncomine database. The expression level of PTGDS protein was high in DLBCL tissues and serum, which was associated with poor prognosis. High expression of PTGDS protein was also confirmed in DLBCL cells. PTGDS overexpression and rhPTGDS were found to promote cell proliferation. PTGDS knockdown significantly restrained cell proliferation, promoted cell cycle arrest and cell apoptosis. AT56 suppressed cell proliferation, induced G0/G1 phase arrest and increased cell apoptosis in a dose- and time-dependent manner. AT56 also enhanced sensitivity to Bendamustine and Adriamycin. Besides, *in vivo* studies indicated PTGDS knockdown and AT56 exerted anti-tumor effect in DLBCL.
CoIP and mass spectrometry indicated PTGDS interacted with oncogenic factor, MYH9. PTGDS inhibition reduced expression of MYH9 and inhibited activation of Wnt-β-catenin/STAT3 pathway. Moreover, Wnt3a rescued the inhibitory effect of AT56 on malignant behaviors, including cell proliferation, cell cycle arrest and cell apoptosis. Besides, the role of AT56 on Wnt pathway could be reversed by Wnt3a. The proliferation inhibition and apoptosis induction caused by AT56 were enhanced by WP1066 while WP1066 reversed proliferation promotion caused by PTGDS overexpression. The enhanced proliferation by PTGDS overexpression was restored by Blebbistatin and it restored the activation of Wnt-β-catenin/STAT3 pathway caused by PTGDS overexpression.
We confirmed the N-glycoprotein of PTGDS protein in Asn 51 and Asn78 via point mutation and the abnormal glycosylation resulted in nuclear translocation, prolonged half time and enhanced oncogenic role.



Summary/Conclusion: Our investigations identified for the first time the oncogenic role of PTGDS in DLBCL tumorigenesis. Expression of PTGDS was upregulated and associated with prognosis of DLBCL patients. Besides, *in vitro* and *in vivo* studies indicated that PTGDS knockdown and AT56 treatment exerted anti-tumor effect through regulating through MYH9-Wnt-β-catenin/STAT3 axis. This study suggests that PTGDS could be a potential molecular target for DLBCL treatment and highlights the potential role of AT56 as a novel therapeutic strategy for DLBCL.

EP863 A CIRCULAR RNA EXPRESSION SIGNATURE PREDICTS DISMAL OUTCOME IN MANTLE CELL LYMPHOMA: A STUDY OF YOUNGER PATIENTS FROM THE NORDIC MCL2 AND MCL3 CLINICAL TRIALS

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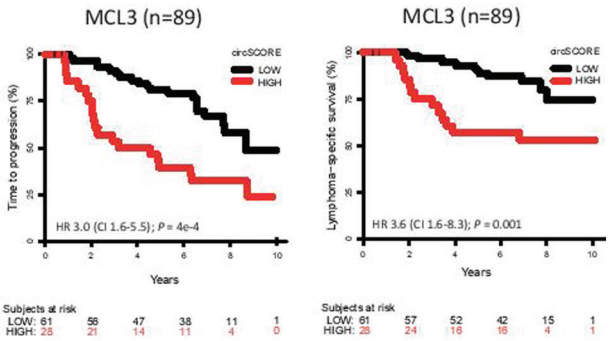
Background: The outcome for patients with Mantle Cell Lymphoma (MCL) has markedly improved after introduction of cytarabine-containing chemoimmunotherapy followed by autologous stem cell transplant (ASCT). Despite the improved survival, a continuous relapse pattern, even beyond ten years, is observed and consequently a strong need for prognostic biomarkers to support clinical decision making, persists.

Circular RNAs (circRNAs) are endogenous non-coding RNA molecules with tissue and disease specific expression patterns, that serve gene-regulatory functions in cells, and might be implicated in carcinogenesis. Because circRNAs are highly stable with much longer half-lives than mRNAs they are promising for use as biomarkers in cancer. We have previously shown that circRNAs can be accurately quantified in samples from patients with B cell malignancies using the nanostring nCounter technology *(Dahl et al., Lab. Invest. 2018)*. Thus, a potential for a seamless implementation of a circRNA based biomarker into clinical practice, exists.

Aims: We aimed to perform a genome-wide profiling of circRNA expression patterns in MCL and to examine the prognostic potential of selected circRNAs in MCL using diagnostic samples from patients enrolled in the MCL2 and MCL3 clinical trials, amounting to a total of 163 younger patients, all treated with chemoimmunotherapy and ASCT.

Methods: We performed RNA-sequencing and bioinformatic identification of circRNAs in an exploratory cohort of 14 newly diagnosed patients with MCL and six healthy controls. 40 circRNAs were selected for quantification with nanostring using RNA samples from diagnostic tumor tissues of patients from the MCL2/MCL3 trials. We then assessed the prognostic potential of these circRNAs with the least absolute shrinkage and selection operator (LASSO) selecting the most predictive circRNAs for time to progression (TTP) in MCL2 (n=74), which served as the training cohort. Nine circRNAs were identified, the expression levels and regression coefficients of which were used to calculate a risk score (circSCORE) for each patient, stratifying them into two groups, separated by a cut-off value. CircSCORE was also calculated for each patient in the independent validation cohort MCL3 (n=89), thereby stratifying these patients into a circSCORE high risk and a circSCORE low risk group, as well.

Results: We detected 2 962 unique circRNAs in MCL and found that expression levels were, in general, inversely correlated with the proliferation marker Ki67. In MCL2, circSCORE separated patients into a high risk group (n=29, 39%) and a low risk group (n=45, 61%) with remarkable difference in TTP. Interestingly, we confirmed the predictive impact of circSCORE for both TTP (HR 3.0;P < 0.001;Figure) and lymphoma-specific survival (LSS) (HR 3.6;P < 0.01;Figure) in the similarly treated, independent cohort MCL3. As patients in the circSCORE high risk group more frequently displayed other high risk features compared to patients in the circSCORE low risk group, we assessed whether circSCORE was an independent prognostic factor in MCL3. Even when adjusting for Ki67, blastoid morphology, MIPI and presence of *TP53* mutations, circSCORE maintained prognostic impact for both TTP (HR 3.2; P = 0.01), and LSS (HR 4.6; P = 0.02), and only MIPI high risk and presence of *TP53* mutations also had prognostic effect in these models.



Summary/Conclusion: With this study, we are the first to perform a genome-wide profiling of circRNA expression in MCL, and we show that circSCORE is a novel prognostic biomarker highly predictive of outcome in younger patients treated with chemoimmunotherapy and ASCT.

EP864 IDENTIFICATION OF M6A METHYLTRANSFERASE KIAA1429 AS A POTENTIAL TARGET IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: N^6-methyladenosine (m^{6}A) is the most abundant form of internal modifications in eukaryotic cells. m^{6}A methylation is dynamically modulated by diverse types of regulators, including methyltransferases ('writers'), RNA binding proteins ('readers'), and demethylases ('erasers'). Growing evidence has shown that m^{6}A methylation plays essential role in the development and progression of multiple cancers. However, the functions of m^{6}A methylation in diffuse large B-cell lymphoma (DLBCL) remains undefined.

Aims: In the study, we aimed to identify novel prognostic biomarker by m^{6}A methylation regulators and explore its underlying mechanism in DLBCL.

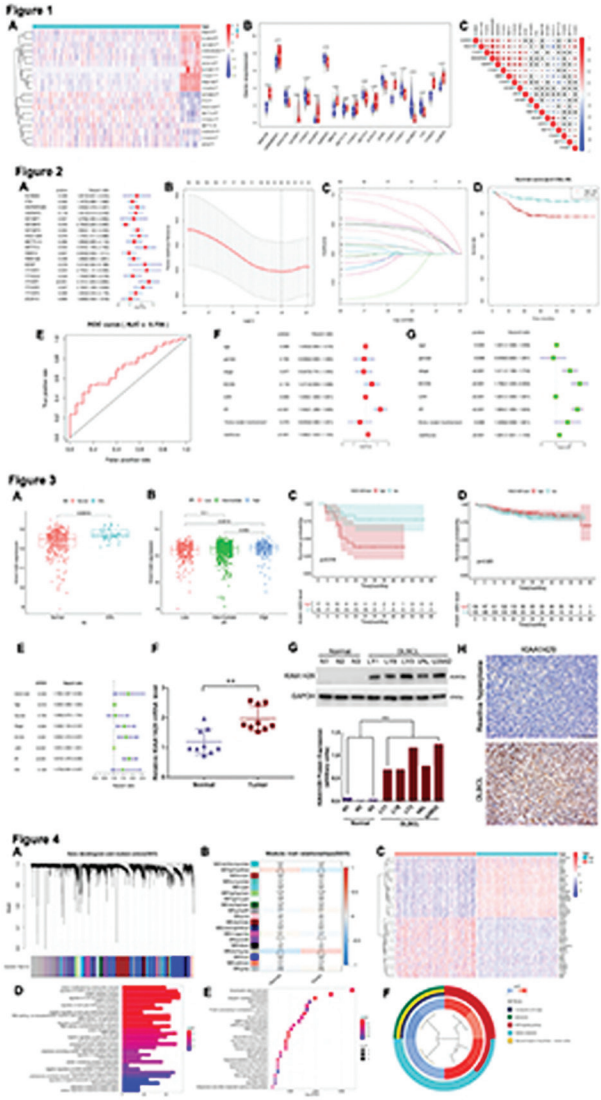
Methods: The available expression data and the clinical information of DLBCL samples and normal samples were extracted from three databases. The expression level of the m^{6}A methylation regulators was analyzed and the LASSO Cox regression was employed to calculate risk score. Kaplan-Meier survival analysis, univariate and multivariate Cox regression analyses, and ROC curve analysis were conducted. GO and KEGG enrichement were applied to explore the potential function. The lymph node biopsies of DLBCL patients and reactive hyperplasia cases were collected with informed consent to detect the expression of KIAA1429.

Results: We firstly assessed the expression of m^{6}A methylation regulators in DLBCL and found that most of them were dysregulated (p<0.001; Figure 1A-B). Subsequently, we discovered that the proportion of diverse m^{6}A RNA methylation regulators was weakly to strongly relevant (p<0.05; Figure 1C).

The univariate Cox regression analysis indicated that six genes were high-risk and were significantly associated with OS (p<0.05, HR>1; Figure 2A), including KIAA1429 (p=0.043, HR=1.743). Six genes were selected based on the minimum criteria of LASSO Cox regression to establish the risk signature (Figure 2B-C). The high-risk group had a significantly shorter OS in DLBCL patients (p<0.001; Figure 2D). Furthermore, ROC curve, univariate, and multivariate Cox regression analyses showed that high m^{6}A risk score acted as an independent indicator in DLBCL patients (p<0.001; Figure 2E-G).

KIAA1429 was found to be significantly associated with the IPI and DHL (p<0.05; Figure 3A-B). High expression of KIAA1429 resulted in a negative correlation with OS in DHL patients (p=0.018; Figure 3C). However, no significant difference was found in the OS of non-DHL patients (Figure 3D). Univariate analyses indicated that KIAA1429 was an independent indicator in DLBCL patients (p=0.04; Figure 3E). Enhanced expression levels of KIAA1429 mRNA and protein were verified in DLBCL cell lines (Figure 3F-G). Additionally, samples from DLBCL patients also showed significantly

high expression of KIAA1429 compared to the reactive hyperplasia group (Figure 3H).
WGCNA was used to investigate the underlying mechanism of KIAA1429 (Figure 4A-B). A significant association between KIAA1429 expression and its module genes was identified (Figure 4C). GO and KEGG enrichment illuminated that KIAA1429 may act as a potential prognostic biomarker by regulating the mRNA processing and MAPK signaling pathways (Figure 4D-F)



Summary/Conclusion: In summary, we identified for the first time that m^{6}A methylation regulators were dysregulated in DLBCL. More importantly, our study demonstrated the prognostic value of KIAA1429 in DHL patients. Further investigations on the mechanism of KIAA1429 in DLBCL may assist clinicians in achieving individualized treatment for this patient population.

EP865 PLK4 INHIBITION BY CFI-400945 ENHANCES DOXORUBICIN SENSITIVITY IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Polo-like kinase 4 (PLK4) has been suggested as a tumor promoter role in solid malignancies. Elevated PLK4 expression was associated with progressed grade, inferior survival and reduced chemosensitivity, highlighting as an adverse prognosis indicator and a potential target for cancer therapy. CFI-400945 was the first orally available potent PLK4 inhibitor. The antineoplastic effects of CFI-400945 have been reported in many cancers and this inhibitor has entered phase I/II clinical trials in advanced solid tumors. However, the role of PLK4 in DLBCL is still unclear. Whether CFI-400945 has therapeutic potential in DLBCL remained undefined.
Aims: We aim to investigate the biological role of PLK4 and the antitumor effects of CFI-400945 in DLBCL.
Methods: Analysis of public database and clinical specimens was used to validate PLK4 expression and evaluate its clinical significance. Cell proliferation and apoptosis was assessed by CCK8 and flow cytometry analysis. Knockdown of PLK4 with shRNA was used to evaluate the effect of PLK4 expression on CFI-400945 potency. The effectiveness of the CFI-400945 as a single agent and in combination with doxorubicin in DLBCL cells was evaluated in vitro and in vivo studies.
Results: PLK4 expression was up-regulated at both transcriptional and translational levels in DLBCL cells. High levels of PLK4 expression predicted inferior prognosis in the patients receiving CHOP-based treatment. We then evaluated the antitumor effects of PLK4 inhibition by CFI-400945. The results demonstrated that treatment of PLK4 inhibitor induced a decrease in cell proliferation, an increase in cell apoptosis and a block at the G2-M transition in a dose-dependent manner. Furthermore, we found that the antineoplastic effects of CFI-400945 in DLBCL cell lines were due to the increased DNA damage, as observed by increased accumulation of γH2AX through phosphorylation of CHK1/CHK2. Since PLK4 inhibition affects DNA damage, we next aimed to explore the effects of PLK4 expression on sensitivity of DNA damage-inducing drugs (e.g., doxorubicin). Knockdown of PLK4 improved the anti-tumor effects of doxorubicin in DLBCL cells. PLK4 inhibition resulted in increased doxorubicin-induced DNA damage. Moreover, a combined treatment of CFI-400945 and doxorubicin was associated with promising antiproliferative effects in DLBCL cells. We then investigated the synergistic anti-tumor effects of the combined treatment in vivo. Mice treated with CFI-400945 and doxorubicin had significantly lower tumor burden after 21 days compared with those treated with vehicle or doxorubicin alone.
Summary/Conclusion: The present study suggests that PLK4 is a potential therapeutic target of DLBCL. The levels of PLK4 may serve as a determinant of doxorubicin sensitivity and a predictive biomarker of the patients with DLBCL. Inhibition of PLK4 by CFI-400945 represents a promising strategy for DLBCL, with potential for combination treatment with doxorubicin-involved therapy.

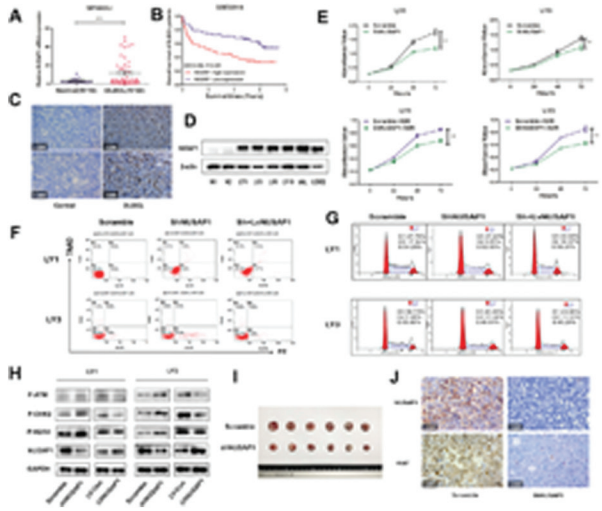
EP866 SUPPRESSION OF NUSAP1 INHIBITS CELL PROLIFERATION IN DIFFUSE LARGE B-CELL LYMPHOMA THROUGH DNA DAMAGE REPAIR PATHWAY

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Background: Diffuse large B cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) with high heterogeneity. Previous studies have identified that NUSAP1 plays an important role in the occurrence and progress of multiple tumors. Whereas, no research has been reported regarding the role of NUSAP1 in DLBCL.
Aims: Herein, we aim to further explore the expression and exact role of NUSAP1 in DLBCL development, and provide theoretical basis for new molecular markers and targeted therapy.
Methods: Peripheral blood samples from *de novo* DLBCL patients and healthy volunteers were collected with informed consents at the Department of Hematology in Shandong Provincial Hospital Affiliated to Shandong University (SPHASU). Kaplan-Meier survival curves with log-rank test of overall survival (OS) were analyzed. Immunohistochemistry staining (IHC) was performed to assess NUSAP1 expression in specimens. Expression levels of NUSAP1 mRNA and protein were detected by quantitative RT-PCR and western blotting. The DLBCL cells were transfected by lentiviral shRNA and vectors to stably silence and up-regulate NUSAP1. Effects of doxorubicin on cell viabilities were assessed by cell counting kit-8. Besides, apoptosis and cell cycle were respectively

detected by annexin V-PE/7AAD and PI/RNase staining via flow cytometry. Invasion ability was analyzed by transwell assay. ShNUSAP1 cells and Scramble cells were subcutaneously injected to SCID-Beige mice to establish xenograft models.
Results: According to clinical specimens and bioinformatics analysis, the expression level of NUSAP1 gene in samples of DLBCL patients was significantly increased than that of healthy donors (P<0.05) (Figure A). Besides, patients with high expression of NUSAP1 was related to shorter overall survival (HR=0.456, P<0.01), indicating poor prognosis (Figure B). Stronger positivity of NUSAP1 was markedly observed in DLBCL lymph nodes than reactive hyperplasia group, which was associated with Ann Arbor stage of DLBCL patients (Figure C). Compared with normal B cells, the protein level of NUSAP1 were up-regulated in DLBCL cell lines (Figure D). After transfected with lentivirus, the proliferation rate of NUSAP1 knockdown group was lower than that of the control group, while the overexpression group was faster than control (Figure E). Through flow cytometry, silencing of NUSAP1 led to increased apoptotic rates of LY1 and LY3 cells (Figure F). Along with the recovery of NUSAP1 expression level, apoptosis rates were improved again. With the addition of doxorubicin at 100nM, interference of NUSAP1 could increase the sensitivity of cells to doxorubicin (Figure E). NUSAP1 intervention induced obvious cell cycle arrest in G1 phase of LY1 and LY3 cell lines, with concomitant reduction of cell proportion in S phase (Figure G). Surppression of NUSAP1 inhibited the action of DNA damage repair pathway (Figure H). We found that tumor growth was significantly suppressed by inhibiting NUSAP1 in xenograft models (Figure I). IHC for NUSAP1 and Ki67 on tumor sections showed that tumors derived from shNUSAP1 cells exhibited significantly lower levels of Ki67 compared to control group (Figure J).



Summary/Conclusion: Collectively, NUSAP1 contributes to tumor growth both in vivo and vitro through DNA damage repair pathway, which providing a new direction for prognosis assessment and targeted therapy of DLBCL.

EP867 TIGIT EXPRESSION AND ITS SCORING SYSTEM IN CLASSIC HODGKIN LYMPHOMA: A NOVEL THERAPEUTIC TARGET?

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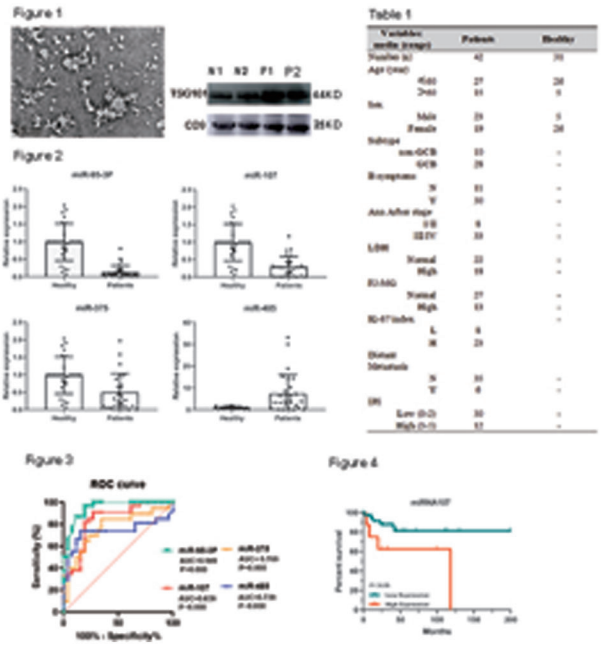
Background: Clinical use of immune-checkpoints inhibitors (anti PD-1/PD-L1) resulted very effective for the treatment of relapsed/refractory classic Hodgkin Lymphoma (CHL). Recently, T cell Ig and ITIM domains (TIGIT) has been recognized as an immune checkpoint receptor able to negatively regulate T cell functions.
Aims: Herein, we investigated the expression of TIGIT in CHL microenvironment in order to find a potential new target for inhibitor therapy.
Methods: TIGIT, PD-1 and PD-L1 expression was evaluated in 34 consecutive patients with CHL. In agreement with the evaluation model for immunohistochemical expression of PD-L1 in tumors, we proposed a scoring system for TIGIT immunohistochemistry in CHL; moreover, we compared TIGIT results with PD-1 and PD-L1 expression to obtain a complete assessment of the immunomodulation of Hodgkin lymphoma microenvironment.
Results: TIGIT expression in T lymphocytes surrounding Hodgkin Reed-Sternberg (HRS) cells was observed in 19/34 patients (56%), of which 11 (58%) had advanced stages. In 16/19 (84%) cases, TIGIT+ peritumoral T lymphocytes showed also PD-1 expression. All 15 TIGIT- patients had PD-L1 expression in HRS cells (100%) while among 19 TIGIT+ patients, 11 (58%) were PD-L1+ and 8 (42%) were PD-L1-. Using a new scoring system for TIGIT immunoreactivity, all TIGIT+ cases with higher score (4/19) were PD-L1-. Our results confirm co-expression of TIGIT and PD-1 in peritumoral T lymphocytes. Of relevance, we demonstrated a mutually exclusive expression of TIGIT and PD-L1 using new TIGIT scoring system able to identify this immunocheckpoints' modulation.
Summary/Conclusion: In conclusion, our preliminary results in Hodgkin lymphoma, demonstrated a mutually exclusive expression of TIGIT in peritumoral lymphocytes and PD-L1 in HRS cells, with an overlap in cases with low level of TIGIT reactivity. The new TIGIT scoring system is able to identify such modulation of these immunocheckpoints. These results pave the way to new therapeutic strategies for relapsed/refractory CHL

EP868 SERUM EXOSOMAL MICRORNAS AS NOVEL NON-INVASIVE BIOMARKERS FOR DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive malignant lymphoma with high heterogeneity, which bring great difficulties to precise diagnosis and prognosis. Circulation exosomal miRNAs have emerging as complementary biomarkers and exserted as new opportunities to develop non-invasive tests for early diagnosis or follow-up of disease. Accumulating evidence suggested that miR-107 played a critical role in suppressing tumorigenesis. However, the significance of exosomal miR-107 in DLBCL is still not well understood.
Aims: The aim of this study is to explore the serum exosomal microRNAs to be novel biomarkers as well as therapeutic targets for DLBCL.
Methods: Differentially expressed microRNAs (DEMs) involved in DLBCL progression were screened from Gene Expression Omnibus (GEO) database (GSE117063 and GSE29493). Serum-derived exosomes were isolated by Qiagen ExoEasy Maxi Kit. Transmission electron microscopy (TEM) and Western blot were performed to examine the exosomal characteristics. Quantitative real-time PCR (qRT-PCR) was applied to determine the serum exosomal expression levels of microRNAs from 42 DLBCL patients and 31 normal samples. Kaplan-Meier analysis, and ROC working curve analyses were performed to assess the diagnostic and prognostic values of exosomal miRNAs in DLBCL patients.
Results: A total of 14 DEMs in DLBCL were identified from the GSE117063 and GSE29493 datasets. Serum-derived exosomes were isolated from 42 patients and 31 healthy volunteers, and the characteristics of patients were subscribed in Table 1. TEM and western blot for Tsg101 and CD9 are consistent with previous description of exosomes (Figure 1). Among the identified DEMs,3 down-regulated miRNAs (miR-95-3P, miR-107, miR-375) and 1 up-regulated miRNA (miR-485) were verified to be significantly differently expressed in DLBCL patients (Figure2). ROC curve analyses revealed that these serum exosomal miRNAs, miR-95-3p, miR-107, miR-375, and miR-485, acted as potential biomarkers for DLBCL, with the AUC of were 0.94, 0.839, 0.769 and 0.739, respectively (Figure 3). In addition, Kaplan-Meier analysis of the TCGA database indicated that compared to the control group, DLBCL patients with low-expression of miR-107 presented worse prognosis (Figure 4), suggesting that miR-107 may be a prognostic factor for DLBCL.



Summary/Conclusion: In this study, we demonstrate for the first time that serum exosomal miRNAs, such as miRNA-107, could be applied as non-invasive novel diagnostic and prognostic biomarker in DLBCL. With further research we expect that miR-107 to be a promising therapeutic target for DLBCL.

EP869 DISCOVERY AND PRECLINICAL PROPERTIES OF JNJ-64264681, A POTENT AND SELECTIVE COVALENT BTK INHIBITOR FOR THE TREATMENT OF B CELL MALIGNANCIES

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Background: Bruton's tyrosine kinase (BTK), a member of the Tec family of tyrosine kinases, plays a critical role in B-cell activation and oncogenic signaling via the B cell receptor. BTK inhibitors have been widely studied in B-cell hematologic malignancies and 3 inhibitors, including the first-in-class BTK inhibitor ibrutinib, are currently approved. While BTK inhibitors have been paradigm-changing in Chronic lymphocytic leukemia, Mantle cell lymphoma, and Waldenstroms macroglobulinemia, combination therapies with other agents may be required to reach optimal response rates and cures in other histologies (eg, Diffuse large B-cell lymphoma [DLBCL]).
Aims: Describe the discovery and preclinical properties of a novel, highly selective, small-molecule covalent BTK inhibitor, JNJ-64264681, designed to enable combination therapies.
Methods: The covalent inhibitor potency was determined by k_{inact}/K_I ratios. Inhibition of B-cell activation was assessed in mouse primary cells. The proportion of free and modified BTK was determined in a covalent adduct assay. Dose response of BTK occupancy was assessed in Ramos B cells. A quantitative mechanistic model simulated and used human B cell BTK occupancy to estimate covalent binding. Target engagement and pharmacokinetics/pharmacodynamics studies were conducted in rats and tumor-bearing mice. The effect of JNJ-64264681 on cancer cell proliferation was assessed in B cell lymphoma cell lines, and tumor growth inhibition was studied in cell line and lymphoma patient-derived xenograft mouse models (OCI-Ly10, LY2298).
Results: JNJ-64264681 was developed to obtain high selectivity and ideal physicochemical properties. A series of optimizations resulted in improved microsomal stability, high pH 2 solubility, measurable pH 7 solubility, and double-digit nM potency in rat and human whole blood. Cocrystallization of JNJ-64264681 with BTK confirmed covalent bond formation with Cys481, and in line with this, the adduct was resistant to denaturation. JNJ-64264681 was highly selective against a diverse panel of receptors, enzymes, ion channels, and human kinases. BTK occupancy was dose proportional in vivo, and full occupancy was maintained even after plasma drug levels decreased. JNJ-64264681 showed potent antiproliferative activity (IC_{50} <100 nM) in CD79b-mutant activated B cell (ABC)-DLBCL cell lines, but not in cell lines which are independent of NF-κB signaling for survival, highlighting its selectivity. Treatment with JNJ-64264681 led to potent in vivo BTK occupancy, inhibition of specific cytokines and tumor growth inhibition in a CD79b-mutant ABC-DLBCL xenograft model. Furthermore, JNJ-64264681 showed significant tumor growth inhibition in the ABC-DLBCL-like LY2298 patient-derived xenograft model. Similarly, treatment with the combination of JNJ-64264681 and the MALT1 inhibitor JNJ-67856633 resulted in increased tumor growth inhibition compared with single agents and tumor regression in both CD79b mutant mouse lymphoma models.
Summary/Conclusion: The preclinical results confirm that JNJ-64264681 is a highly selective and potent BTK inhibitor and provide proof-of-concept for human trials in patients with B cell malignancies driven by the classical NF-κB pathway. JNJ-64264681 is currently in human clinical trials (NCT04210219 and NCT04657224) as single agent to establish dose and pharmacokinetics and to evaluate efficacy in combination with the first-in-class MALT1 inhibitor JNJ-67856633.

EP870 ANALYSIS OF EZH2 MUTATIONS IN SOLID AND LIQUID BIOPSY AND ITS ROLE AS PREDICTIVE MARKER FOR CHEMOTHERAPY IN PATIENTS WITH FOLLICULAR LYMPHOMA

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Background: *EZH2* encodes the catalytic subunit of Polycomb repressor complex (PCR2) and mediates methylation of Lys27 residue of histone H3 (H3K27). Missense mutations in *EZH2* lead to decreased transcriptional function of genes involved in cell cycle regulation and plasma cell differentiation, which contributes to oncogenic transformation. *EZH2* have been detected to be mutated in near 20% of follicular lymphomas (FL) and this gene is included in the risk model m7-FL International Prognostic Index (m7-FLIPI). Furthermore, *EZH2* inhibitors appear as a new treatment option in FL.
Aims: We aimed to analyse retrospectively the frequency of mutations in *EZH2* at diagnosis in tissue and circulating cell free DNA (cfDNA) in patients with FL and assess the patient's response to therapy, depending on the *EZH2* mutation status.
Methods: We included 179 consecutive patients diagnosed with FL from 2002 to 2019. Thirty-seven patients were excluded due to insufficient DNA quantity or quality. Of the 142 analysed patients, 49 had cfDNA sample at diagnosis. DNA was extracted from solid biopsies using Maxwell(R) 16 FFPE Plus LEV DNA Purification Kit (Promega). We obtained cfDNA from plasma samples, using QIAamp® Circulating Nucleic Acid (Qiagen). RT-qPCR reactions were performed in ctDNA using PrimeTime Mini LNA probe for *EZH2* Y646. Sanger sequencing were used in tumor DNA for detection of mutations in exon 16 (Y646) and 18 (A682 and A692). Clinical characteristics, therapy and outcome were collected. Data analysis including descriptive statistics and Fisher's exact test was performed using IBM SPSS Statistics 26 (IBM, USA).
Results: Of the 142 patients analysed in tissue, 41 (29%) presented mutations in *EZH2*. These mutations were found in 46% of grade 3B FL and 27% of grades 1, 2 and 3A FL (Table 1). Y646 mutations in cfDNA were detected in 5/49 (10%) with *EZH2* mutated in tumor and stage III-IV FL. Clinical and biological characteristics according to *EZH2* mutation status in tumor were compared in patients with lower-grade FL (Table 1) and high grade 3B (data not shown). No statistical differences were found in lower grade-FL. Instead, patients with grade 3B and mutated *EZH2* had statistically higher FLIPI risk (80% vs 0%; p=0.048). Overall survival (OS) of total cohort and according to therapy received and *EZH2* mutation status were compared and there were no statistically

significant differences. In terms of progression free survival (PFS), our results shown that mutated *EZH2* patients treated with R-bendamustine were significantly associated with inferior PFS (p=0.013) (Figure 1a), unlike R-CHOP treated patients (p=0.15) (Figure 1b).

Table 1. Clinical characteristics and first-line therapy in patients with grade 1, 2 and 3A FL.

	N	Total (n=129)	Mutated *EZH2* in FFPE (n=35)	Unmutated *EZH2* in FFPE (n=94)	p-value
Clinical characteristics at diagnosis, n (%)					
Age at diagnosis, mean (range)	129	62 (15-90)	64 (41-90)	62 (15-89)	0.435
Sex					
Female	129	72 (56)	22 (63)	50 (53)	0.426
Male		57 (44)	13 (37)	44 (47)	
Histology					
Grade 1, 2	123	81 (66)	25 (74)	56 (63)	0.296
Grade 3A		42 (34)	9 (26)	33 (37)	
Stage					
I-II	123	38 (30)	7 (21)	31 (33)	0.196
III-IV		90 (70)	27 (79)	63 (67)	
FLIPI risk categories					
Low-Intermediate	118	85 (72)	22 (65)	63 (75)	0.267
High		33 (28)	12 (35)	21 (25)	
First-line therapy, n (%)					
Treated	111	111 (86)	29 (83)	82 (87)	0.573
Watchful waiting	18	18 (14)	6 (17)	12 (13)	
R-bendamustine	30	30 (23)	7 (20)	23 (24)	
R-CHOP	57	57 (44)	18 (51)	39 (41)	
R-CVP, Rituximab and Radiotherapy	24	24 (20)	4 (11)	20 (21)	

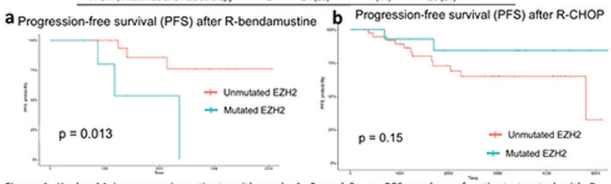


Figure 1. Kaplan-Meier curves in patients with grade 1, 2, and 3a. **a.** PFS on days of patients treated with R-bendamustine therapy; **b.** PFS on days of patients treated with R-CHOP therapy. PFS Progression-free survival.

Summary/Conclusion: The frequency of *EZH2* mutations in our total cohort is similar to previously reported. Mutations were more frequent in high grade FL patients. Low grade FL patients mutated at diagnosis, receiving R-bendamustine were associated with inferior PFS. The mutational status of these patients at diagnosis could be useful to guide treatment. In patients with stage III-IV, liquid biopsy may be used at diagnosis to guide on the selection of therapy, as *EZH2* mutations are detectable in advanced stage FL.

EP871 MELPHALAN FLUFENAMIDE IS A HIGHLY POTENT ANTI-NEOPLASTIC AGENT IN HIGH RISK DLBCL MODELS

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Background: Diffuse large B cell lymphoma (DLBCL) is a frequent aggressive lymphoid neoplasm. Standard protocol consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) has improved remission and survival rates in patients with DLBCL. Nevertheless, 30% of patients do not respond to the therapy with R-CHOP or relapse resulting in relapsed/refractory (R/R) disease. Currently, there are several protocols for the treatment of R/R-DLBCL including a combination of rituximab and bendamustine. However, survival rates in patients with R/R-DLBCL remain dismal and require improvement through introduction of novel drugs and combinations. Melphalan flufenamide (melflufen) is a novel peptide-drug conjugate that rapidly delivers cytotoxic alkylating payload inside tumor cells. This process is potentiated by aminopeptidases highly expressed in cancer cells. Therefore, prognostic significance of aminopeptidases in DLBCL and potency of melflufen were investigated in this study.
Aims: First, assess prognostic significance of aminopeptidase gene expression in DLBCL. Second, evaluate potency of melflufen in the models of high risk DLBCL.
Methods: Expression levels of aminopeptidase genes in patient samples was assessed using publicly available RNA-sequencing data (GSE125966). The prognostic significance of highly expressed aminopeptidase genes was further evaluated in R-CHOP-treated patients (N=692) with available gene expression and censored survival data (GSE31312, GSE83731). Three ABC (SU-DHL-2, U2932, NU-DUL-1) and nine GCB DLBCL (SU-DHL-4/5/8/10/16, DoHH2, DB, Toledo, RC-K8) cell lines were profiled for drug sensitivity to melflufen and standard of care (SoC) drugs doxorubicin and bendamustine using an assay quantifying living cells. The results were confirmed in vivo.
Results: Several aminopeptidase genes (*ERAP1, ERAP2, LAP3, LNPEP, LTA4H, METAP1, METAP2, NPEPPS, RNPEP, XPNPEP1, XPNPEP3*) showed high expression in DLBCL patient samples. Among these genes high expression of *LNPEP* (37.0 vs 50.4 month, HR 0.73, 95% CI 0.61-0.88, p<0.0001) and *LAP3* (37.4 vs 49.2 month, HR0.76, 95% CI 0.63-0.91, p=0.0005) conferred inferior survival of DLBCL patients. Aminopeptidase-potentiated peptide-drug conjugate melflufen showed a superior cytotoxicity to doxorubicin and bendamustine in all cell lines tested (Wilcoxon paired test p<0.0001). Interestingly, TP53 status of DLBCL cells did not significantly affect the cytotoxicity of melflufen.
Summary/Conclusion: Our results showed high expression of several aminopeptidase genes in DLBCL. Moreover, elevated expression of *LNPEP* and *LAP3* conferred significantly shorter survival in DLBCL patients. A novel peptide-drug conjugate melflufen potentiated by aminopeptidases showed a superior cytotoxicity to SoC drugs doxorubicin and bendamustine in a panel of eleven DLBCL cell lines. Low expression or mutations in *TP53* gene status of cell lines did not show a major effect on melflufen's cytotoxicity. Thus, melflufen may be suitable for treatment of high risk DLBCL.

EP872 GENOMEWIDE COPY NUMBER ANALYSIS OF GRADE 1-3A, 3B, AND COMPOSITE FOLLICULAR LYMPHOMA

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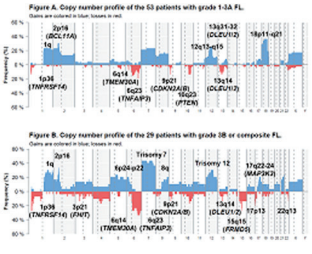
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Background: Grade 3B follicular lymphoma (FL3B) and composite FL (FL with a component of diffuse large B-cell lymphoma, DLBCL) exhibit specific biological and clinical features. Thus, gene expression profiling studies have suggested that FL3B is intimately related to FL3A, while FL3B/DLBCL would be closer to DLBCL. However, data concerning copy number alterations (CNA) of these histologies are scarce.
Aims: To characterize the copy number profile of FL3B and composite FL, and to compare it with that of FL123A.
Methods: We selected 29 patients with FL3B (n=11) or composite FL (n=18), as well as a control group of 53 patients with grades 1-3A FL. Composite cases were further subclassified into FL123A/DLBCL (C123A, n=10) and FL3B/DLBCL (C3B, n=8). All biopsies were reviewed by at least two hematopathologists. Minimal common CNA regions were defined separately for FL123A and FL3B/C123A/C3B cases. DNA was extracted from diagnostic formalin-fixed, paraffin embedded lymph node biopsies. CNA were assessed using the OncoScan CNV Assay (Thermofisher). The *BCL2* rearrangement was analyzed by FISH and/or PCR. Non-parametric statistics were used for comparisons of categorical and quantitative variables.
Results: Baseline features of the patients and CNA of the samples are detailed in the *Table*. *BCL2* rearrangement was more frequent in FL123A (87%) than in FL3B (64%) or composite FL cases (56%, *P*=0.02). We detected CNA in 78/82 samples (95%). Although no significant differences were found in the total number of CNA among groups, the number of gains was higher in FL3B (median, 5) and composite FL (median, 6) compared to FL123A cases (median, 2; *P*=0.02). The most frequent CNA among the 82 samples were 1q gain (n=22, 27%), trisomy 7 (n=21, 26%), and 1p36 copy-neutral loss of heterozygosity (n=20, 24%).
Figure A shows the CNA profile of FL123A, and *Figure B* that of FL3B and composite FL. Several CNA showed a different distribution among FL123A, FL3B, and composite FL cases. Of note, losses of 6q13-q15

Table. Baseline features and CNA data of the patients.

	FL123A (n=53)	FL3B (n=11)	Composite FL (n=18)	*P*
Age, median (range)	57 (26–79)	66 (42–82)	68 (27–89)	0.046
Female sex, n (%)	29 (55)	6 (55)	8 (44)	NS
BCL2 rearrangement, n (%)	39 (87)	7 (64)	10 (56)	0.02
Stage III-IV, n (%)	39 (74)	9 (82)	15 (83)	NS
High-risk FLIPI score, n (%)	13 (26)	3 (27)	7 (41)	NS
Overall survival, % at 10 y (95% CI)	79 (68–91)	76 (51–100)	64 (44–93)	0.02
Total CNA, median (range)	6 (0–27)	11 (1–13)	10 (0–26)	NS
Gains, median (range)	2 (0–14)	5 (2–10)	6 (0–15)	0.02
Losses, median (range)	2 (0–18)	3 (1–9)	4 (0–13)	NS
CN-LOH, median (range)	1 (0–13)	1 (0–7)	2 (0–3)	NS
6p24-p22 gain, n (%)	3 (6)	4 (36)	1 (6)	0.02
6q14 loss (TNFAIP3), n (%)	8 (15)	6 (55)	5 (6)	0.005
6q23 loss (TNFAIP3), n (%)	10 (19)	6 (55)	3 (17)	0.04
9p gain (*MYC*), n (%)	2 (4)	1 (9)	4 (22)	0.04
15q15 loss (*RMD5*), n (%)	0	2 (18)	5 (28)	<0.001
17p13 loss, n (%)	1 (2)	2 (18)	4 (22)	0.01
Trisomy 5, n (%)	1 (2)	4 (36)	1 (6)	0.002
Trisomy 7, n (%)	11 (21)	5 (46)	5 (28)	NS
Trisomy 20, n (%)	0	0	3 (17)	0.01
Trisomy 21, n (%)	3 (6)	0	5 (28)	0.03

FLIPI, Follicular Lymphoma International Prognostic Index; y, year; CI, confidence interval; CNA, copy number alterations; CN-LOH, copy-neutral loss of heterozygosity; NS, not statistically significant.



(*TMEM30A*) and 6q23-q15 (*TNFAIP3*) were more frequent in FL3B cases (n=6, 55%). We then compared composite FL cases according to the FL component (FL123A vs FL3B) and found no significant differences, with the exception of trisomy 12, which was observed in four C3B and none of the C123A cases (*P*=0.02).

Summary/Conclusion: In this CNA analysis of 29 FL3B/C123A/C3B and 53 FL123A samples, 1q gain and trisomy 7 were the most frequent abnormalities. FL123A cases had a lower number of gains, and several alterations showed a differential distribution among histological subgroups. Further studies, including targeted NGS, are under way to deepen the understanding of these specific FL subtypes.

EP873 T-CELL SUBSET COMPOSITION AND FUNCTIONALITY IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA.

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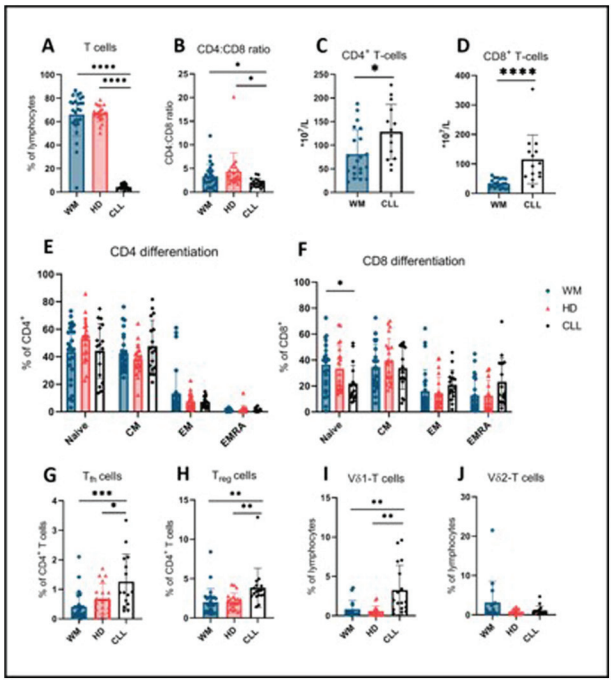
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Background: Waldenström's macroglobulinemia (WM) is an incurable low-grade B-cell Non-Hodgkin lymphoma characterized by bone marrow infiltration with lymphoplasmacytic cells, and presence of an IgM M-protein. WM resembles chronic lymphocytic leukemia (CLL) with regard to biologic and clinical characteristics. The emergence of novel autologous T-cell directed therapies has prompted deeper understanding of the immune microenvironment. In CLL, extensive abnormalities in T-cell subset distribution and function have been described. These alterations may contribute to disappointing responses to T-cell directed immunotherapies. Novel autologous T-cell directed immunotherapy may improve the outlook for WM patients. However, studies evaluating T-cell functionality in WM are lacking.

Aims: We performed a systematic evaluation of peripheral blood (PB) T-cell subset composition and function in the of WM patients.

Methods: PB samples were collected from treatment-naive, relapsed and symptomatic WM patients, HCs and treatment-naïve CLL patients. Lymphocyte phenotyping was performed and differences in functionality were assessed by determining the potential of T-cells to degranulate and produce cytokines upon stimulation for 4h with phorbol myristate acetate/ionomycin. Furthermore, cytotoxic potential of the T-cells was assessed via engagement of blinatumomab (CD3xCD19 bi-specific T-cell engager), that re-directs T-cells via CD3 to kill CD19+ tumor cells. Correlations between percentages of the various T-cell subsets, cytokine production, cytotoxic capacity and various markers of disease activity were performed for treatment-naïve WM and pretreated WM separately.

Results: A total of 16 treatment-naïve WM patients, 10 pretreated symptomatic WM patients, 21 age-matched HCs and 17 treatment-naïve CLL patients were included in this study. In WM patients, the following cell types had counts similar to HCs: T-cells (relative), CD4$^+$ T-cells (relative), absolute CD4$^+$ and CD8$^+$ T-cells, T_{fh} cells, T_{reg} cells, and Vδ1/ Vδ2 T-cells (relative). This is in contrast to CLL patients, in which T-cell numbers (relative) were decreased, absolute CD4+ and CD8+ T-cells were increased compared to HCs, T_{fh}, T_{reg}, and Vδ1 T-cell numbers were increased as expected. CD4$^+$ and CD8$^+$ T-cell differentiation was also normal in WM as opposed to CLL in which a known skewing towards terminal differentiation in the CD8$^+$ T-cell population was observed. No difference in Vδ2 T-cell count was observed between all three groups (Figure 1). No significant differences were found in cytokine production and degranulation between CD4$^+$ and CD8$^+$ T-cells from WM patients in comparison with HCs, in contrast to CLL in which decreased amounts of TNF-α and increased expression of CD107a were found. The cytotoxic potential of WM-derived T-cells was intact and similar to HC-derived cells, while CLL-derived T-cells have an impaired cytotoxic response to blinatumomab.



Summary/Conclusion: These data represent the first systematic evaluation of the T-cell compartment in WM patients. The qualitative and quantitative changes in the immune system seen in CLL are not found in WM; T-cell numbers, distribution and functionality seem mostly preserved even in pretreated patients with a high disease burden. These findings are encouraging for the application of T-cell targeted immune therapies in WM, especially for the management of relapsed/refractory WM.

EP874 BERBERINE EXERTS IMMUNOREGULATING FUNCTION IN DIFFUSE LARGE B-CELL LYMPHOMA VIA DOWNREGULATING CD47 EXPRESSION

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Background: CD47 expresses widely in human tissue and overexpresses in several malignance cells. The interaction between CD47 overexpressing on tumor cells and sSIRPα on macrophages triggers an inhibitory signal cascade that suppresses the phagocytosis function. Berberine is a quaternary amine isoquinoline alkaloid which was traditionally used in intestinal infection and found to have broad anti-tumor activities in several tumors in recent years. However, the function and mechanism of berberine in immunoregulation targeting CD47 is undefined.

Aims: To investigate the functional significance of CD47 in diffuse large B-cell lymphoma (DLBCL) progression and propose an adjuvant agent for DLBCL treatment.

Methods: Paraffin imbedding tissue sections of 55 newly diagnosed DLBCL patients and 40 reactive hyperplasia (RHL) patients were obtained after informed consents. CD47 expression was analyzed in DLBCL tissue sections and DLBCL cell lines. CD47 level was analyzed after berberine treatment, and related regulatory pathway was explored. The immunoregulating function of berberine were proved in co-culture experiment *in vitro*. A tumor bearing mice model was established to investigate the immunoregulating function of berberine *in vivo*.

Results: Firstly, we analyzed the CD47 expression in tissue sections form DLBCL and RHL patients. Compared to RHL, CD47 was overexpressed in DLBCL tissues (30/55 vs 11/40, p=0.009, **Figure 1A**). CD47 positive expression was correlation with higher DLBCL subtype (p=0.007) and Kaplan-Meier analysis showed that patients with positive CD47

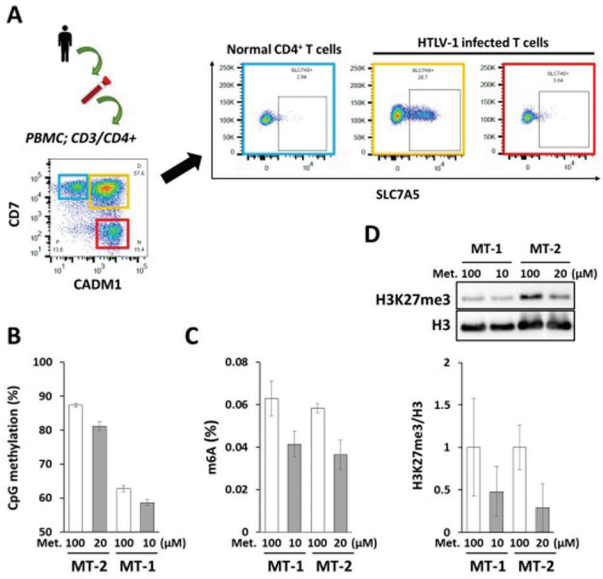
expression had a bad OS (**Figure 1B**). Furthermore, aberrantly increased expression of CD47 was also detected in some DLBCL cell lines (**Figure 1C**).
Then DLBCL cells were treated with berberine and the results revealed that CD47 was downregulated by berberine at a time-dependent manner (**Figure 2A**). In the aspect of regulatory signal pathway, CD47 was modulated by berberine at the transcriptional level (**Figure 2B**). Then, inhibitor of c-myc, a transcriptional factor of CD47, were applied to LY1 cells. The results showed that inhibition of c-myc by 10058-F4 could suppress CD47 expression (**Figure 2C, left**). The expression level of c-myc was also decreased after berberine treatment (**Figure 2C, middle**). Moreover, overexpression of c-myc resulted in the increased expression of CD47 and rescued berberine-induced downregulation of CD47 (**Figure 2C, right**). Engulfment of LY1 cells by macrophage was improved when LY1 cells were pretreated with berberine for 48 hours (**Figure 2D**). And tumor growth was inhibited by berberine in the tumor-bearing mice model with decreased expression of CD47 and increased infiltrated macrophages (**Figure 2E**). Moreover, berberine enhanced the efficacy of anti-CD47 antibody and rituximab (**Figure 2F**).
Summary/Conclusion: Our results highlighted that CD47 was a significant feature and played an anti-phagocytosis function in DLBCL progression. We provided evidence for the first time that berberine exerts immunoregulation function in DLBCL via modulating c-myc/CD47 axis and enhance the efficacy of anti-CD47 antibody and rituximab, which provided novel insights into the treatment in DLBCL.

EP875 ABERRANT EPIGENETIC REGULATION THROUGH METABOLIC REPROGRAMMING IN ATL LEUKEMOGENESIS

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Background: Adult T-cell leukemia/ lymphoma (ATL) is derived from mature T-cells transformed by human T-cell lymphotropic virus type 1 (HTLV-1). Following HTLV-1 infection, it takes decades for carriers to develop ATL. HTLV-1–infected T-cells undergo multi-step leukemogenesis, with accumulation of genetic and epigenetic abnormalities. Trimethylation at histone H3Lys27 (H3K27me3) catalyzed by polycomb-repressive complex 2 accumulates aberrantly in HTLV-1-infected T-cells and its accumulation correlates with ATL development and progression.
We recently identified common differentially hypermethylated positions that are specific to HTLV-1-infected T-cells using comprehensive DNA methylation analysis. The accumulation of DNA methylation at these sites correlated strongly with ATL development and progression (*Blood* 2020, 136: 871-884). OR-2100, which we developed as a novel decitabine prodrug with enhanced oral bioavailability, suppressed tumor cell growth and global DNA hypomethylation. Taken together, epigenetic abnormalities, especially hypermethylation of DNA and histone H3Lys27, are functionally important for ATL leukemogenesis and represent effective therapeutic targets.
Aims: Here, we aimed to understand how these epigenetic abnormalities accumulate in HTLV-1-infected cells during multi-step carcinogenesis.
Methods: HTLV-1-infected cell lines were cultured in RPMI-1640 medium containing 100 μM methionine. We also prepared modified RPMI-1640 medium with a reduced concentration of methionine. DNA methylation at long interspersed nuclear element-1 (LINE-1), which is a surrogate marker for global DNA methylation status, was determined by bisulfite pyrosequencing. N^6-methyladenosine (m6A) in mRNA (m6A RNA methylation) was quantified by ELISA.
Results: Recently, the epigenetic reprogramming that drives T cell differentiation and proliferation was shown to be regulated by the incorporation of extracellular methionine through the amino acid transporter SLC7A5, the expression of which is induced by activation of the T-cell receptor (TCR) signaling pathway. Since several negative regulators of the TCR pathway are silenced by promoter hypermethylation in HTLV-1-infected cells, we hypothesized that epigenetic abnormalities are maintained through sustained SLC7A5-mediated incorporation of methionine in ATL cells.
As expected, we found that *SLC7A5* gene expression was higher in HTLV-1-infected T-cells than in normal T-cells using the gene expression datasets GSE55851 and GSE33615. Flow cytometric analysis of SLC7A5 protein expression in peripheral blood mononuclear cells from ATL patients revealed SLC7A5 expression in HTLV-1-infected cells from one of 10 ATL patients (Fig. A). Two HTLV-1-infected cell lines, MT-2 and MT-4, also expressed high levels of SLC7A5 protein. Methionine restriction suppressed the growth of HTLV-1-infected cell lines. As expected, DNA and RNA hypomethylation was induced by methionine restriction (Fig. B, C). A decrease in H3K27me3 and protein arginine methylation was also confirmed by western blot analysis (Fig. D). To understand better the epigenetic responses to methionine restriction, we are performing multi-omics analysis using transcriptome, DNA methylome, histone methylome and metabolome data.



Summary/Conclusion: Based on these results, we think that the epigenetic state of some HTLV-1-infected cells is regulated by methionine metabolism. Targeting methionine incorporation or metabolism to change epigenetic reprogramming could constitute a novel therapeutic strategy for the treatment of ATL.

EP876 XENOGRAFT MODELLING OF DRIVING MOLECULAR EVENTS IN BURKITT LYMPHOMA

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Background: The genomic landscape of Burkitt lymphoma has largely been defined, but the clonal complexity and key molecular events driving disease development and/or relapse remain to be determined. In part this relates to the relative lack of patient samples, especially following relapse, and the limited number of representative experimental models.
Aims: To develop a novel approach to the modelling and study of sporadic Burkitt lymphoma biology we developed orthotopic patient-derived xenograft models. The aim is that such models can be used both to study the molecular drivers of disease development/relapse and for pre-clinical testing of new treatment approaches.
Methods: Samples from newly presenting or relapsed patients were collected and cryopreserved with informed consent for animal research. Thawed cells were injected into NSG (NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ, Jackson Laboratory) or Rag2$^{-/-}$γc$^{-/-}$ (C;129S4-Rag2$^{tm1.1Flv}$ Il2rg$^{tm1.1Flv}$/J, Jackson Laboratory). Tumour bearing animals were killed and serial

transplantation performed. Parallel samples were taken for cytogenetic and molecular analysis.
Immunohistochemistry and cytogenetic analysis were performed within an NHS diagnostic laboratory setting. RNA and DNA were isolated and subjected to mRNA or exome sequencing using Illumina Novoseq or NextSeq platforms. Species specific transcripts were identified and murine reads removed using Disambiguate before further analysis. Exome data were analysed using GATK4.
Results: Viable cells from multiple sources (tumour, pleural effusion, bone marrow) were successfully cryopreserved and showed good viability. Patient material from all samples engrafted within 30-48 days. Serial transplantation across three (n=3) or four (n=1) generations was successful in all samples.
Immunohistochemical/cytogenetic analysis were consistent with the original pathological diagnoses. Transcriptomic analysis identified a metagene expression pattern consistent with published Burkitt lymphoma patient data, as distinct from diffuse large B cell lymphoma, confirming the representative nature of the models at this level.
Exome sequencing identified several mutations previously described to be recurrent in sporadic Burkitt lymphoma, including in the genes *MYC*, *TP53*, *ARID1A*, *RHOA* and *ID3*. Multiple pathogenic mutations in *ID3* were identified in each of three seperate patient samples and analysis of variant allelic frequency across sequential xenograft generations demonstrated differential fitness within the subclonal populations.
Summary/Conclusion: Patient-derived xenograft models of Burkitt lymphoma are feasible and representative of the original disease, despite cryopreservation. Molecular analysis of these models provides an alternative approach to the study of drivers of disease progression and may be used to track clonal evolution in response to therapy.

EP877 CHN1 IS A NOVEL PROGNOSTIC MARKER FOR DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common B-cell malignancy. Thirty to forty percent of DLBCL patients still experience relapse or develop refractory disease even with standard immunochemotherapy, leading to a poor prognosis. Currently, although several gene-based classification methods can be used to predict the prognosis of DLBCL, some patients are still unable to be classified.
Aims: This study was performed to identify a novel prognostic biomarker for DLBCL.
Methods: A total of 1,850 B-cell non-Hodgkin lymphoma (B-NHL) patients in 8 independent datasets with microarray gene expression profiles were retrieved from the Gene Expression Omnibus (GEO) database and Lymphoma/Leukemia Molecular Profiling Project (LLMPP). The candidate genes were selected through three filters in a strict pipeline. Survival analysis was performed in two independent datasets of patients with both gene expression data and clinical information. Gene set enrichment analysis (GSEA) and the CIBERSORT algorithm were used to explore the biological functions of the genes.
Results: We identified 6 candidate genes associated with the clinical outcome of DLBCL patients: *CHN1*, *CD3D*, *CLU*, *ICOS*, *KLRB1* and *LAT*. Unlike the other five genes, *CHN1* has not been previously reported to be implicated in lymphoma. We also observed that *CHN1* had prognostic significance in important clinical subgroups; in particular, high *CHN1* expression was significantly related to good outcomes in DLBCL patients with the germinal center B-cell-like (GCB) subtype, stage III-IV, or an International Prognostic Index (IPI) score > 2. Multivariate Cox regression analysis of the two datasets showed that *CHN1* was an independent prognostic factor for DLBCL. Additionally, GSEA and CIBERSORT indicated that *CHN1* was correlated with cell adhesion and T cell immune infiltration.
Summary/Conclusion: Our data indicate for the first time that *CHN1* is associated with the prognosis of DLBCL and suggest its potential utility as a prognostic marker in DLBCL.

EP878 CCL2-CCR2 AXIS SIGNALING PROMOTES DIFFUSE LARGE B-CELL LYMPHOMA CELL SURVIVAL AND INVASION

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Background: Diffuse large B cell lymphoma (DLBCL) incidence rates have increased year by year, a part of them have poor clinical outcomes, but the underlying mechanism involved is still unclear. Chemokines have been thought to play an important role in occurrence and development of tumors, but they are poorly studied in DLBCL. CC-Chemokine Ligand 2 (CCL2), the most representative of the CC chemokine family members, through binding to its high affinity receptor, CC chemokine receptor 2 (CCR2), has be regarded to involve in tumor growth, angiogenesis, epithelial mesenchymal transition, metastasis and immune escape etc. in recent years, but the role and mechanism in DLBCL has not been reported yet. Our preliminary study showed high expression of CCL2 or CCR2 was correlated with clinicopathological characteristics, and an adverse prognostic factor for overall survival (OS) and progression-free survival (PFS) of DLBCL patients.
Aims: The purpose of this study is to investigate the role of CCL2-CCR2 axis signaling in DLBCL by in vitro experiment.
Methods: CCL2 and CCR2 expression were analyzed in human DLBCL cell lines and normal B lymphocytes by Western blot (WB) and qPCR. CCL2 and CCR2 genes were silenced by lentivirus infection. The proliferation, migration, apoptosis and signaling pathway were detected by CCK8, transwell, flow cytometry (FC) and WB, respectively.
Results: CCL2 and CCR2 were expressed in all human DLBCL cell lines (SUDHL-2, SUDHL-4, SUDHL-6, OCI-Ly8 and OCI-Ly10). Blockade of CCL2-CCR2 axis signaling with lentivirus infection, CCL2 neutralizing antibody or CCR2 antagonist inhibited tumor cell proliferation, migration and anti-apoptosis ability. The CCL2-CCR2 axis involved in the proliferation and migration of DLBCL cells by activating PI3K/Akt signaling pathway, and induced apoptosis through activation of P38MARK signaling pathway.
Summary/Conclusion: Our study demonstrates that CCL2/CCR2 axis signaling plays an important role in the development of DLBCL by stimulating cell proliferation, migration and anti-apoptosis. The inhibition of CCL2 or CCR2 may, therefore, be a potential target for anticancer therapy in DLBCL.

EP879 LENALIDOMIDE-INDUCED EFFECTS ON CELL SURFACE EXPRESSION OF CD19 AND CD20 IN DLBCL CELL LINES AND FUNCTIONAL IMPACT ON ANTIBODY-MEDIATED CYTOTOXICITY

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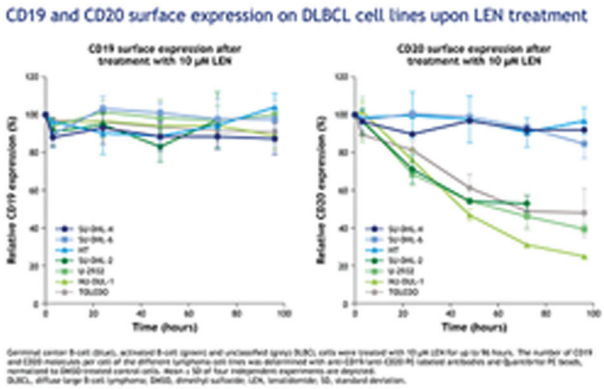
Background: Lenalidomide (LEN) is an immunomodulatory drug with direct cytotoxic effects on tumor cells and stimulating effects on T and natural killer (NK) cells, making it an attractive combination partner for antibody therapies. However, clinical studies evaluating the addition of LEN to anti-CD20 based therapies compared to the current first-line standard of care (R-CHOP) for patients with diffuse large B-cell lymphoma (DLBCL) showed discordant results (ECOG-ACRIN trial 1412; ROBUST study). Recently, the combination of LEN with the anti-CD19 antibody tafasitamab has shown clinically meaningful efficacy in patients with relapsed or refractory DLBCL (L-MIND study).
Aims: We aimed to investigate whether LEN treatment affects antigen levels of CD19 and CD20 on DLBCL cell lines from different subtypes and whether potential target antigen modulation has an influence on antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP).
Methods: CD19 and CD20 surface expression was analyzed in 7 DLBCL cell lines (3 activated B-cell, ABC; 3 germinal center B-cell, GCB; 1 unclassified) after incubation with 1/10 µM LEN for 24–96 hours (h). For ADCP assays, DLBCL target cells were pretreated with 10 µM LEN or dimethyl sulfoxide (DMSO) for 96 h and then incubated with macrophages at an effector to target (E:T) ratio of 2:1 and 10 nM tafasitamab or rituximab (RTX) for 3 h. For ADCC assays,

DLBCL target cells were pretreated with 10 µM LEN or DMSO for 72 h and then incubated with NK cells at E:T ratios of 0.3:1 or 1:1 for 2 h in the presence of 1 nM tafasitamab, RTX or obinutuzumab (OBI). Antigen expression, ADCC activity, and ADCP activity were assessed by flow cytometry.

Results: While CD19 expression on lymphoma cells was unaffected by LEN treatment, CD20 expression was significantly reduced by 47–75% in all cell lines from the ABC and unclassified DLBCL subtype (SU-DHL-2, U-2932, NU-DUL-1 and TOLEDO; Figure). CD20 surface expression of the tested GCB lines was not affected by LEN treatment.

In ADCP assays, decreased CD20 levels were associated with significantly diminished phagocytosis rates mediated by RTX in 3/7 cell lines (% relative reduction in phagocytosis: 37, 23, and 21 in SU-DHL-2, U-2932, and TOLEDO cells, respectively). In contrast, no or negligible reduction of RTX-mediated phagocytosis by LEN was observed in the remaining 4/7 cell lines. ADCP activity of the CD19-targeting antibody tafasitamab remained unchanged in all tested cell lines.

Significant reductions in target cell killing were also observed in ADCC assays with 2/3 LEN-treated lymphoma cell lines for RTX (% relative reduction in ADCC: 14 and 16 in SU-DHL-2 and U-2932 cells, respectively) and for the glyco-engineered antibody OBI (% relative reduction in ADCC: 13 and 22 in SU-DHL-2 and U-2932 cells respectively). By contrast, RTX-/OBI-mediated cytotoxicity was not reduced by LEN in the GCB cell line SU-DHL-4. ADCC activity of tafasitamab against all 3 tumor cell lines was not decreased by LEN pretreatment.



Summary/Conclusion: LEN treatment decreased surface expression of CD20 but not CD19 in all tested ABC and unclassified DLBCL cell lines. Rates of ADCC and ADCP with CD20 antibodies were reduced in 3/4 of these cell lines, but this was not observed with tafasitamab. These findings suggest that antigen expression levels could have an impact on combination therapies with LEN in certain DLBCL subtypes and support the rationale for combining tafasitamab with LEN, independent of cell of origin.

EP880 LOW PERCENTAGE OF T-LYMPHOCYTES IN FOLLICULAR LYMPHOMA LYMPH NODE BIOPSIES, MEASURED BY FLOW CYTOMETRY, IS ASSOCIATED WITH INFERIOR PROGRESSION FREE SURVIVAL.

L. Korin [1,*], S. Cranco [1], M. L. Fuente [1], E. Babuin [1], A. Vitriu [1], P. Ochoa [1], A. Vijnovich Baron [2], F. Diaz Couselo [3], A. Novoa [4], M. B. Venegas [4], P. Tempra [4], N. Tartas [1], M. D. R. Custidiano [1], M. C. Foncuberta [1], J. C. Sanchez Avalos [1]

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Lymph node TL % was able to further stratify clinical outcome in pts with low risk FLIPI-2. 75th percentile PFS for the low risk subgroup was estimated at 55.3 months but could improve to up to 97.4 months if normal TL % was detected, p:0.032. The same trend was observed in FLIPI-1 low risk pts (estimated 75th percentile of 55.3 months for the whole low risk category and of 29.6 and 97.4 months for the low and normal TL % subgroups, respectively; p:0.064).

Background: Several studies have suggested that tumor microenvironment (TME) could play an important role in lymphomagenesis and tumor progression in non-Hodgkin lymphoma. Gene-expression signatures derived from nonmalignant cells in the tumors, that predict survival, were identified in follicular lymphoma (FL). However, these molecular tools are not widely available and TME variables that could be easily translated into clinically relevant prognostic biomarkers are still missing in FL.

Aims: To determine the prognostic impact on survival of the percentage (%) of T lymphocytes (TL), measured by flow cytometry (FC), in tissue biopsies of FL patients (pts) at diagnosis and to evaluate whether these variables can provide additional information when superimposed on the FLIPI.

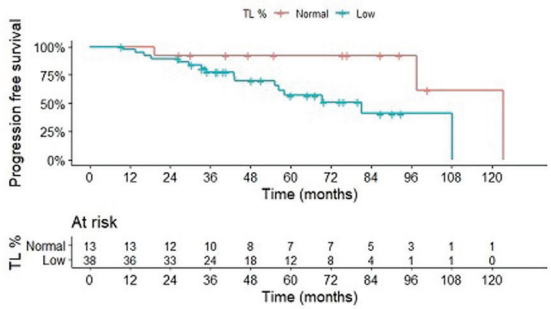
Methods: We selected pts with grade I-IIIa FL and available tissue biopsy FC data at the time of diagnosis who received treatment at our institution between 2007 and 2018. Clinical information was collected from medical records.

FC analysis was performed with 8-color FC panels according to international Euroflow protocols. % of lymph node TL by FC was compared to the normal values determined by Battaglia et al (Immunology 2003), and analyzed as an ordinal variable in 3 categories: low, normal and high. Progression free survival (PFS) was estimated with Kaplan-Meier method. The comparison between variables was performed with log-rank test and Cox proportional hazards model.

Results: 60 pts were included in this retrospective study. Median age was 57.5 years. 75% had stage III-IV disease. 28.3% of pts were stratified as high risk according to FLIPI-1 and only 13.3% with FLIPI-2 and PRIMA-PI. 23.3% were treated with Rituximab monotherapy and the remaining with Rituximab + CHOP, CVP or bendamustine. Complete response rate was 91.7%. 46 pts (76.6%) received Rituximab maintenance. POD24 was observed in 5 pts. Median PFS was estimated in 97.4 months. Only 3 pts died in our cohort with a median follow up time of 5.7 years.

A low % of TL in lymph nodes was associated with inferior PFS (hazard ratio 4.66, 95% confidence interval 1.02-21.21, p:0.046, figure 1). Median PFS in pts with normal lymph node TL % was 123.3 months compared to only 81 months in the low TL risk subgroup (p:0.05). There was also a trend towards worse outcomes in pts with high lymph node TL although not statistically significant (hazard ratio 11.17, 95% confidence interval 0.91-136, p:0.058).

Figure 1: Kaplan-Meier estimates of progression free survival in follicular lymphoma according to normal vs low T-lymphocyte percentage in lymph node biopsies



Summary/Conclusion: Low TL percentage in lymph nodes of pts with FL was associated with inferior outcomes in our cohort. First line therapies including an immunomodulatory agent such as lenalidomide could constitute an interesting strategy to restore a favorable immune microenvironment in this setting. Furthermore, the percentage of TL was able to provide additional prognostic information when combined with low risk FLIPI, identifying a subgroup with truly indolent behavior with 75% showing no evidence of relapse in more than 8 years. Data obtained from FC is easily acquired and should be taken into consideration when studying TME in FL.

EP881 PROGNOSTIC ROLE OF CD30 FROM A RETROSPECTIVE REVIEW OF 295 PATIENTS WITH ANGIOIMMUNOBLASTIC T CELL LYMPHOMA

J. Parrish [1,*], S. Premji [1], M. Khan [2], A. Elias [2], L. Malpica [2], R. Nair [2], D. Chihara [2], R. Miranda [3], J. Xu [3], F. Vega [2], S. Srour [4], S. Iyer [2]

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Background: Angioimmunoblastic T cell lymphoma (AITL) is an aggressive malignancy with poor response to conventional chemotherapy. AITL is a subcategory of peripheral T cell lymphomas. Despite the approval of CD30 directed antibody drug conjugate- Brentuximab vedotin (BV), the prognostic role of CD30 in AITL is unknown.
Aims: The main aim of this study was to study the prognostic significance of CD30 expression in AITLThe main aim of the single institution retrospective study was to elucidate the prognostic implications of CD30 in AITL.
Methods: We analyzed patients newly diagnosed with AITL at our institution between 2000 and 2020. Along with CD30 receptor testing, variables such as date of diagnosis included age, gender, stage, LDH level, platelets, hemoglobin, bone marrow involvement, and EBV receptor positivity were collected. Treatment and progression data including response to frontline therapy, presence of consolidation stem cell transplant (SCT), and usage of brentuximab-based treatment. Endpoints were progression free survival (PFS) and OS; Univariate (UVA) and multivariate (MVA) Cox proportional hazard models were used to determine the significance of variables at diagnosis on PFS and OS.
Results: Out of the 295 individuals diagnosed with AITL,129 patients with CD30 testing who had response and survival data were included. This group had a median age of 65 (range 29-83) years and male predominance (51%) were identified. Table 1 summarizes patient and disease characteristics. Median follow up time was 40 (range 2-137) months, with three-year PFS and OS of 48% and 23% respectively. Sixty-seven individuals died within the first three years of the study. The 3-year OS is 46% in CD30+ individuals, and 55% in those who are CD30- (p=0.578). PFS is 20% in CD30+ individuals, and 29% in those who are CD30- (p-0.675). The variables included in Table 1 were assessed using UVA. Achieving Complete remission (CR) following frontline therapy (p=<0.0001) and consolidation with SCT (p=0.0428) were significantly associated with improved PFS. For OS, age <65 (p=0.0129), female gender (p=0.0437), and SCT (p=0.0003) were statistically associated with improved survival. CD30 and variables with p-value <0.15 were included in MVA. For PFS, achieving CR to frontline therapy (reference, complete remission), (HR 2.987, 95% CI: 1.524-5.855, p=0.0014) and consolidation with SCT (reference, SCT) (HR 2.036, 95% CI: 1.208-3.432, p=0.0076) were associated with better PFS. For OS, age >65 (HR 3.131, 95%CI: 1.545-6.344, p=0.0015), BM involvement (HR 2.134, 95% CI: 1.151-3.956, p=0.0161), incomplete remission (HR 2.208, 95% CI: 1-4.876, p=0.0499), male gender (HR 0.367, 95% CI: 0.199-0.678, p=0.0014), no SCT (HR 4.085, 95% CI: 2.119-7.872, p=<0.0001) and positive CD30 (reference, positive CD30) (HR 0.322, 95% CI: 0.158-0.656, p=0.0018) were associated with inferior OS.

Table 1		
Demographics	CD30 Positive (n=97)	CD30 Negative (n=32)
Median Age (range in years)	63 (29-83)	67 (42-83)
<65	53 (55%)	12 (38%)
>65	44 (45%)	20 (62%)
Gender (n=129)		
Female	53 (55%)	10 (31%)
Male	44 (45%)	22 (69%)
Stage (n=109)		
I-II	2 (2%)	3 (11%)
III-IV	79 (98%)	25 (89%)
LDH (n=72)		
Normal	25 (42%)	5 (38%)
High	34 (58%)	8 (62%)
Platelets (n=75)		
>=150 k	48 (80%)	9 (60%)
< 150 k	12 (20%)	6 (40%)
Anemia (n=76)		
Yes	31 (51%)	10 (67%)
No	30 (49%)	5 (33%)
Bone marrow involvement (n=117)		
Yes	31 (35%)	13 (46%)
No	58 (65%)	15 (54%)
EBER (n=122)		
Positive	71 (78%)	20 (65%)
Negative	20 (22%)	11 (35%)
Disease status (n=78)		
Complete response	75 (82%)	24 (83%)
Not in remission	17 (18%)	5 (17%)
Consolidation Stem cell transplant (n=115)		
Yes	48 (56%)	14 (48%)
No	38 (44%)	15 (52%)
Brentuximab-based treatment		
Yes	16 (20%)	0
No	64 (80%)	0

Summary/Conclusion: Age <65, achieving CR to induction treatment, and upfront SCT proved to be strong predictors of improved OS. In our cohort, only 20% of our patients received BV; nevertheless, unlike previous studies, individuals with CD30 positivity did not trend towards better OS. Therefore, additional work on CD30 biology in AITL is warranted.

EP882 EXPRESSION AND CLINICAL SIGNIFICANCE OF STING IN T- AND NK-CELL NON HODGKIN LYMPHOMAS

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Background: The mechanisms of anti-tumor immune responses are currently under intense investigation in the era of immunotherapy. Cytosolic DNA of either endogenous or exogenous origin is sensed by the cGAS-STING pathway. Cyclic GMP-AMP (cGAMP) synthase (cGAS) is a cytosolic DNA sensor that activates anti-tumor immune responses through production of the second messenger cGAMP, which activates the adaptor protein STING. The latter then activates the transcription factors IRF3 and NF-κB via TBK1 and IKK kinases, respectively, inducing the expression of certain interferons (IFNs), such as IFN-alpha and IFN-beta, along with cytokines, which lead to cytotoxic T-cell mediated tumor cell killing. The expression patterns of STING protein in neoplastic cells of non Hodgkin lymphomas (NHL) is unknown to date.
Aims: To investigate the expression patterns and clinical significance of STING in T- and NK-cell lymphomas.
Methods: In the present study, we investigated STING expression and activation in 15 lymphoma cell lines by Western blot analysis using whole cell lysates and by immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded cell blocks. The *in vitro* panel included four cell lines of ALK+ anaplastic large cell lymphoma (ALK+ ALCL) (Karpas 299, DEL, SUPM2, L-82), two of ALK- anaplastic large cell lymphoma (ALK- ALCL) (Mac1, Mac2a), one of Sezary syndrome (Hut78), and one of T-acute lymphoblastic leukemia (Jurkat), as well as eight B-cell lymphoma cell lines for comparison. In addition, STING protein expression was assessed in well-characterized cohorts of patients with T-cell NHLs using diagnostic biopsies obtained prior to treatment, immunohistochemical methods and a well validated monoclonal antibody. The T-cell NHL group (n=126) included 38 ALK+ ALCL, 36 ALK- ALCL, 17 other peripheral T-cell lymphomas (PTCLs) and 35 extranodal NK/ T-cell lymphomas of nasal type (NK/T-Nasal).
Results: High STING expression and activation assessed by Western blot analysis was found in all ALK+ and ALK- ALCL cell lines, as compared to Hut78 and Jurkat cells. Mac2a cells derived from a later stage of ALK- ALCL expressed higher levels of STING than Mac1 cells, which are derived from the same patient as Mac2a but at an earlier stage of disease. By contrast, the B-cell lymphoma cell lines were all negative or expressed very low levels of STING protein. Using a 10% cut-off for positivity, STING was differentially expressed among T-cell NHLs (Table 1, p<0.01, chi-square test) with ALK+ ALCL showing the highest frequency of STING-positive tumors. STING expression did not correlate with any clinical parameters including age, gender, Ann Arbor

stage, IPI score, LDH levels, B-symptoms, anemia, and others. STING expression in the lymphoma cells showed a statistical trend towards inferior overall survival in the ALK- ALCL group but not in other PTCL subtypes.

Table 1. STING expression in T- and NK-cell non Hodgkin lymphomas

Lymphoma type	Number of patients	STING-positive (n, %)	P-value
T-cell NHL	126	87 (69)	p<0.01
ALK+ ALCL	38	36 (95)	
ALK- ALCL	36	24 (67)	
Other PTCL	17	8 (47)	
T/NK nasal type	35	19 (54)	

Summary/Conclusion: STING is commonly and differentially expressed among T- and NK-cell NHL types and, therefore, pharmacologic modulation of cGAS-STING pathway activity may have therapeutic implications in T-cell malignancies.

EP883 SERUM MIR-22 AS NOVEL NON-INVASIVE PREDICTOR OF CLINICAL OUTCOME AND RESPONSE TO THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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[1]IRCCS Regina Elena National Cancer Institute, Rome, Italy, [2]Institute of Oncology Research, Faculty of Biomedical Sciences, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland, [3]Tor Vergata University, [4]Campus Bio-Medico University, Rome, Italy

Background: Diffuse large B-cell lymphoma (DLBCL) is a clinically and genetically heterogeneous neoplasm with aggressive clinical course. The first-line treatment is chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), however up to 40% of patients are refractory to treatment and have a poor clinical outcome. The available prognostic tools are not able to identify all the patients refractory to R-CHOP. Liquid biopsies, introduced with the benefit of being non-invasive, facilitate serial sampling and dynamic patients monitoring. MiRNAs, small non-coding RNAs frequently deregulated in cancer, are present in body fluids in a highly stable form, making them interesting candidates as biomarkers. In this regard, we have previously performed a pilot study on serum miRNAs profile in DLBCL patients, and found that serum miR-22-3p was significantly correlated with PFS.
Aims: In order to validate the value of circulating miR-22 as reliable non-invasive biomarker and investigate is biological function in DLBCL, we pursued the following aims: a) to analyze serum miR-22 in an independent validation cohort of DLBCL patients; b) to compare miR-22 expression in serum and matched tumor samples and c) to asses its functional role in DLBCL pathogenesis and response to R-CHOP treatment.
Methods: Multicentre prospective study on de novo DLBCL patients (n=42) uniformly treated with R-CHOP. miR-22 expression profile was evaluated by qRT-PCR in serum samples and in matched tissue samples. Survival analysis was performed by Kaplan–Meier method. miR-22 levels were further analysed by qRT-PCR in six DLBCL cell lines and related conditioned culture medium. Sensitivity to R-CHOP treatment for each cell line was evaluated determining R-CHOP IC50 by cytotoxicity MTT assays after 72h hours of treatment. HBL1 DLBCL cell line was transfected with miR-22 mimic by electroporation, 24h hours post transfection cells were plated and vital cells were counted at 24h, 48h and 72h hours.
Results: a). Our data show that patients with baseline higher serum miR-22 levels had a significant worse clinical outcome in terms of 2-year progression free survival (p = 0.015). When considering all enrolled patients (training + validation cohorts: 78 patients) serum miR-22 was differentially expressed in refractory patients compared to responders (p=0.047). b) The comparison results of miR-22 expression in serum and paired tumour samples indicate a significant and inverse correlation (Spearman's Rho= -0.469, p=0.010). c) Assessing miR-22 expression in extracellular (conditioned medium) and intracellular fraction of DLBCL cell lines we observe that the value of extracellular to intracellular ratio of miR-22 levels is directly correlated with the cell resistance (IC50 of R-CHOP) to R-CHOP treatment (Spearman's Rho = 0.928; value = 0.008). Moreover, a decreased proliferation rate was found upon miR-22 overexpression in HBL1 cells (a cell line with low miR-22 basal expression).
Summary/Conclusion: Altogether the results of our study suggest that miR-22 may represent a prognostic and predictive biomarker in DLBCL, and may be involved in lymphoma pathogenesis and in mechanisms of response to treatment.

EP884 TUMOR MICROSATELLITE ANALYSIS IN B-CELL LYMPHOMAS

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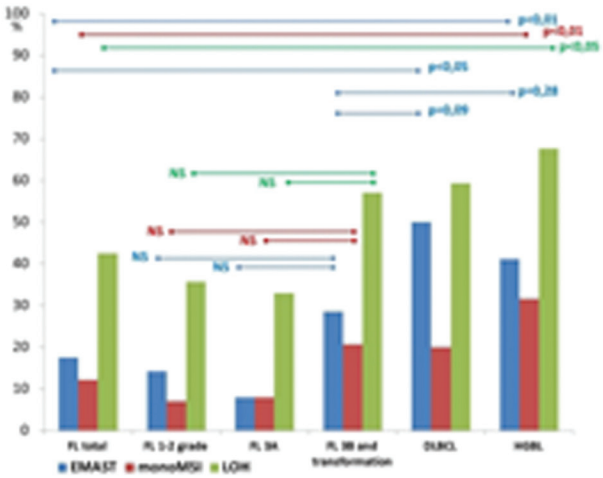
[1]National Research Center for Hematology, Moscow, Russian Federation (Russia), Moscow, Russian Federation

Background: Identification of patients with an unfavorable course of B-cell lymphomas could be difficult at the disease onset. The existing risk stratification models are based mainly on the patient somatic status and disease clinical features. The evidence suggests that it is necessary to search for new markers that would reflect the pathogenesis and behavior of the particular tumor.
DNA repair system functions to preserve the original sequence. The role of mismatch repair system (MMR) deficiency and the resulting microsatellite repeats instability (MSI) has been proven for solid tumors, in particular, colorectal cancer. As B-cell tumors are characterized by high genetic plasticity we suggest that their pathogenesis may also involve changes in the repair system.
Aims: To analyze microsatellite changes associated with repair system deficiency in patients with aggressive and indolent B-cell lymphomas.
Methods: Thirty-five diffuse large B-cell lymphoma (DLBCL) patients, 38 high-grade B-cell lymphoma (HGBL) patients, and 84 follicular lymphoma (FL) patients were included. There were 28 1-2 grade FL patients,

Figure1. The frequency of EMAST, monoMSI, and LOH in B-cell lymphoma groups and the results of pairwise comparison in the χ^2 test.

	FL total	FL 1-2 grade	FL 3A grade	FL 3B and transform ation	DLBCL	HGBL
EMAST	14*/80** (17,5%)	4/28 (14,3%)	2/24 (8%)	8/28 (28,6%)	16/32 (50%)	13/31 (41,2%)
monoMSI	10/82 (12,2%)	2/28 (7,1%)	2/25 (8%)	6/29 (20,7%)	7/35 (20%)	12/38 (31,6%)
LOH	34/80 (42,5%)	10/28 (35,7%)	2/24 (33%)	16/28 (57,1%)	19/32 (59,4%)	21/31 (67,7%)

*number of positive cases
**number of cases with a valid study result



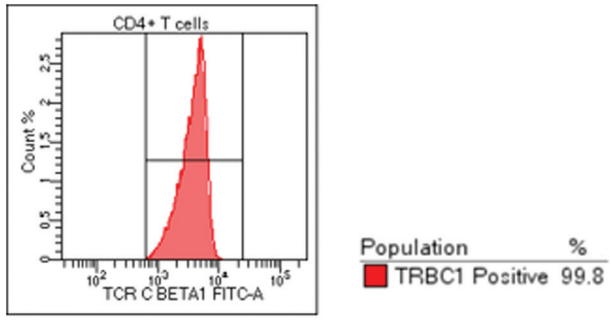
25 3A grade FL patients, and 31 patients with type 3B FL and the transformation of FL into large-cell lymphoma in the latter group. All patients gave their voluntary consent to participate in the study. Microsatellite instability was studied using COrDIS Plus and COrDIS MSI kits (Gordiz Ltd, Russia) in tumor tissue and in peripheral blood cells as a control sample. Amplification was performed using thermal cycler DNAEngine (BioRad, USA). The subsequent fragment analysis was performed on the genetic analyzer Nanofor-05 (Sintol Ltd, Russia).
Results: The detected changes in the microsatellite profile were classified as follows: EMAST (elevated microsatellite alterations at selected tetranucleotide repeats) – the appearance of a new allele of tetranucleotide loci; LOH (loss of heterozygosity) – allelic imbalance; monoMSI – aberrations of mononucleotide markers that could not be differentiated between LOH and instability. Data on these genetic alterations frequencies and results of $\chi 2$ test are shown in Figure 1.
In general, DLBCL and HGBL are more likely to have microsatellite aberrations, especially EMAST, than FL. Microsatellite aberrations frequencies in DLBCL and HGBL groups were comparative. Within the general group of FL, differences were observed between indolent (1-2 and 3A grades) and aggressive FL (3B and FL transformation), but they did not reach statistical significance. However, EMAST, monoMSI, and LOH frequencies in transformed FL are seemed higher than in indolent FL.
The aggressive FL group is intermediate between DLBCL and HGBL and indolent FL. It is important to note that the histological transformation of FL does not accumulate a significant number of microsatellite aberrations in the genome, not like aggressive B-cell lymphomas de novo. This indicates that microsatellite repeats instability is mostly the tumor feature at its early development stages and is not acquired during tumor progression.
Summary/Conclusion: Microsatellite instability is common in B-cell lymphomas. EMAST, monoMSI, and LOH distribution have no nosological specificity. These genetic alterations are more peculiar to aggressive lymphomas de novo. The lack of statistical significance in pairwise comparison does not allow considering microsatellite analysis as a differential diagnosis tool. However, the probable prognostic significance of EMAST, monoMSI, or LOH could be reached while expanding the cohort of patients and conducting additional survival analysis.

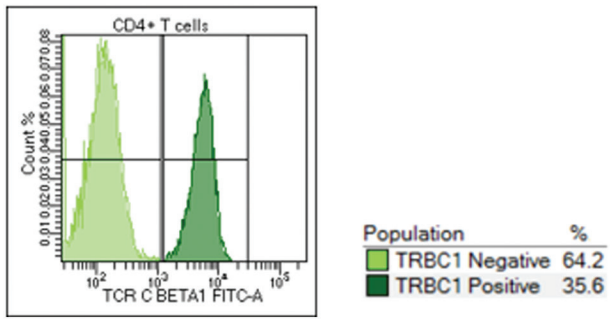
EP885 RELIABLE DETECTION OF T-CELL CLONALITY BY FLOW CYTOMETRY IN MATURE T-CELL NEOPLASMS USING TCR B CONSTANT REGION 1 (TRBC1): A COMPARISON WITH PCR BASED CLONALITY TESTING.

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Background: T-cell lymphomas are a pathologically and clinically complex group of heterogenous disorders. Often the interpretation of flow cytometry patterns may present challenges. Identification of an antibody specific for the TCR β constant region 1 (TRBC1) proposes to identify T-cell clonality and distinguish pathological T cells from normal T cells.
Aims: The aim of this project was to validate the diagnostic abilities of TRBCB1 antibody when used in conjunction with an existing T-cell antibody panel.
Our aim was to use a control group of patient samples and assess TRBC1 expression on both CD4+ and CD8+ T cells separately, and calculate the ratio of TRBC1 positive and negative αβ T cells.
30 cases submitted for an investigation of a T -cell lymphoproliferative disorder were then assessed for TCBC1 expression.
We report here on our experience with the TRBC1 antibody, from validation to real-life experience by direct comparison of TRBC1 expression with molecular clonality testing.
Methods: 10 normal peripheral blood samples were utilised to determine the normal biological range of TRBC1 on T cells. 30 consecutive patient samples submitted for investigation of a lymphoproliferative disorder were evaluated in a blind fashion independent of molecular analysis findings. Assessment of T-cell antigens including CD2/CD3/CD4/CD5/CD7/CD8/CD16/CD26/CD45/CD56/TCR αβ/TCR γδ along with TRBC1 were completed. Results were then compared to TCR gene rearrangement patterns by PCR.
Results: All normal control cases displayed a polytypic pattern of TRBC1 expression, with an average ratio of TRBC1 positive to TRBC1 negative expression of 1:2. Of the 30 consecutive cases evaluated, 7 cases were polytypic for TRBC1 and 22 cases were monotypic for TRBC1 expression. Direct comparison with molecular analysis demonstrated that no sample identified with monotypic (restricted) expression of TRBC1 was reported as polyclonal by PCR. A concordance rate of 95% (21/22 cases) between a clonal TCR gene rearrangement PCR result and a monotypic TRBC1 expression was calculated.





Summary/Conclusion: We have found the anti-TCR C Beta 1 antibody to be of high diagnostic value for assessment of clonality in patients with a suspected T cell neoplasm when used in conjunction with our existing diagnostic panel.
Incorporation of the TRBC1 antibody as part of the evaluation of a suspected T-cell neoplasm improves the identification of clonal T cells by flow cytometry and correlates well with molecular methods.
The importance of implementing a gating strategy directed at the abnormal population of T cells cannot be overstated.
This antibody is designed to detect clonal abnormalities in the constant region of the Beta chain of the TCR, therefore, it is not applicable for the assessment of normal γδ T cells or γδ T cell neoplasms.
To conclude, our results prove that this antibody improves the identification of clonal T cells by flow cytometry and is amenable to integration into a busy flow cytometry laboratory. By recognising the pitfalls and remaining mindful of the importance of gating strategies in the execution of this assay we find the TRBC1 antibody represents an excellent addition to the investigation of T-lymphoproliferative disorders by flow cytometry.

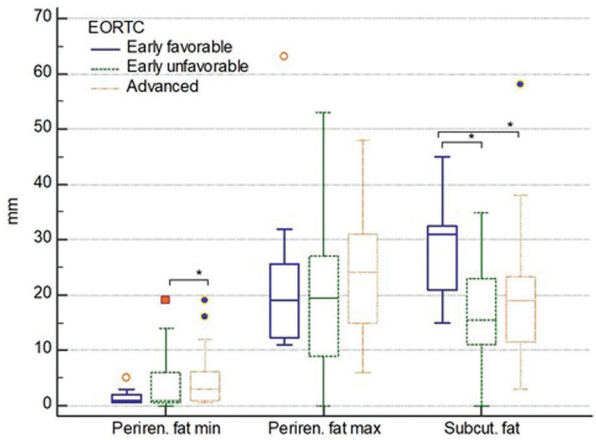
EP886 DIFFERENT ABDOMINAL FAT COMPARTMENTS DIFFERENTLY REFLECT ON PROGNOSIS IN CLASSICAL HODGKIN LYMPHOMA PATIENTS

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Background: There are conflicting data how obesity might affect outcomes in patients with classical Hodgkin lymphoma (cHL). Computed tomography (CT) scans done at the time of cHL staging offer a unique opportunity to assess different body fat compartments and their potential prognostic associations without exposing these patients to additional unnecessary procedures.
Aims: We aimed to assess subcutaneous and visceral abdominal fat measurements in patients with cHL at the time of diagnosis and to investigate their clinical associations.
Methods: We retrospectively analyzed 82 newly diagnosed cHL patients from our center with available CT scans prior to receiving specific therapy and with available clinical data. Patients were treated with either

ABVD or eBEACOPP chemotherapy regimens and subsequent radiotherapy per physicians' decision. Perirenal fat was chosen as a measurement of visceral fat and its thickness was assessed as the largest and the smallest distance from kidney outline to the inner limit of abdominal wall at the transversal level of the renal vein. Subcutaneous fat thickness was assessed as the largest distance between the skin and outer limit of the muscular abdominal wall at the transversal level of the umbilicus.
Results: Median age was 36 years, majority of patients were males [46/82 (56.1%)]. The most common histological subtype was nodular sclerosis [61/82 (74.4%)]. A total of 11/82 (13.4%) patients were classified as early favorable, 38/82 (46.3%) as early unfavorable and 33/82 (40.2%) as advanced disease by EORTC system. All three abdominal fat thickness measurements (minimal and maximal perirenal and subcutaneous fat thickness) correlated positively together, showed moderate positive correlation with BMI (Rho 0.54 to 0.57; P<0.05) and weak positive correlation with total psoas muscle area at the L3 level (Rho 0.24 to 0.33; P<0.05).
Patients with more advanced EORTC disease stage were significantly more likely to have higher minimal perirenal fat thickness but lower subcutaneous fat thickness (P<0.05 for both analyses) as shown in Figure 1. Similarly, minimal perirenal fat thickness was significantly positively correlated with the IPS (Rho=0.34, P=0.002), whereas subcutaneous fat thickness was significantly negatively correlated with the IPS (Rho=-0.27, P=0.013). No significant associations of BMI with EORTC stages nor IPS were present (P>0.05).
Higher minimal (HR=8.4; P<0.001) and maximal perirenal fat thickness (HR=3.15; P=0.049), but lower subcutaneous fat thickness (HR=3.57; P=0.033) were associated with inferior overall survival in univariate analyses. In addition, lower subcutaneous fat thickness (HR=4.45; P=0.005) was also associated with shorter time to disease progression. There was no association of BMI with neither survival nor time to progression.
Associations of perirenal and subcutaneous fat thickness were further analyzed in the multivariate models adjusted for age, gender, Ann Arbor stage and IPS. Both minimal perirenal fat thickness >2 mm (HR=49.2; P=0.019), subcutaneous fat thickness ≤22 mm (HR=45.7; P=0.038) and IPS (HR=2.44; P=0.025) remained significantly associated with inferior overall survival. Subcutaneous fat ≤22 mm (HR=14.4; P=0.013) and older age (HR=1.04; P=0.043) remained independently associated with shorter time to disease progression.



Summary/Conclusion: Excess body fat might differently affect outcomes in patients with cHL depending on its distribution. Distinction between different abdominal adipose tissue compartments is necessary to better understand relationship between obesity, cachexia and prognosis in patients with cHL.

EP887 TRITON X-114 AND AMINE-BASED WASH STRATEGY REDUCES LPS TO FDA-LIMIT AND ACHIEVES PURER, MORE POTENT RECOMBINANT IMMUNOTOXIN.

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Background: Recombinant immunotoxins (rIT) are fusion proteins of a targeting moiety and pseudomonas exotoxin (PE). They arrest protein synthesis in eukaryotes by ADP-ribosylation of elongation factor 2 (eEF2) leading to target cell death. The CD22 targeted immunotoxin Moxetumomab pasudotox (Moxe) was approved for the treatment of relapsed/refractory hairy cell leukemia. Because immunotoxins stop eukaryotic protein expression, they are expressed in *E. coli*. However, proteins expressed in *E. coli* are contaminated by endotoxin (also called lipopolysaccharides (LPS)). LPS binds to toll-like receptors, inducing up to life-threatening systemic inflammation in mammals. Therefore, FDA-approved LPS-limit for therapeutics as well as for substances used in immunological studies in animals are as low as 0.05 EU/mg.
Aims: We aimed to establish a broadly applicable protein purification method to reduce LPS below FDA approved limits without altering stability or function of the protein.
Methods: Immunotoxins were expressed in *E. coli*, refolded, and purified using standard protocol by three column chromatography. To reduce LPS, an on column Triton X-114 wash, amine based spin columns, or the combination of the two was tested. LPS levels were measured by LAL-assay, protein quality control was done by SDS-PAGE analysis. Immunotoxins were tested extensively *in vitro* for ADP-ribosylation, cytotoxicity, thermal stability, and binding affinity. *In vivo* efficacy was determined in a systemic xenograft model.
Results: Moxe produced by standard method was contaminated by 2.7 EU/mg LPS. The on column Triton X-114 wash did not reduce LPS contamination by itself and spin-columns reduced LPS to 0.40 EU/mg. When combined, LPS was reduced by 120-fold to 0.02 EU/mg compared to standard method. Immunotoxins purified by the combination were purer by 9% which we found to be a result of the Triton X-114 on-column wash. Furthermore, *in vitro* cytotoxicity was enhanced up to 2.4-fold which was not explained by increased enzymatic ADP-ribosylation activity or improved protein stability, but by an enhanced binding affinity to CD22 on the cell surface. LPS-reduced protein maintained *in vivo* efficacy. Additionally, LPS was reduced below FDA-limits for other antibody formats (dsFv and Fab), for distinct PE variants and for antibodies against distinct targets.
Summary/Conclusion: Only Triton X-114 on-column wash combined with amine-residue-based spin columns reliably reduced LPS contamination below FDA-approved limits. Resulting immunotoxins were purer and more potent. With some modifications, the method may be applicable for any chromatography-based purification processes and may be run entirely on column.

Myelodysplastic syndromes - Biology & Translational Research

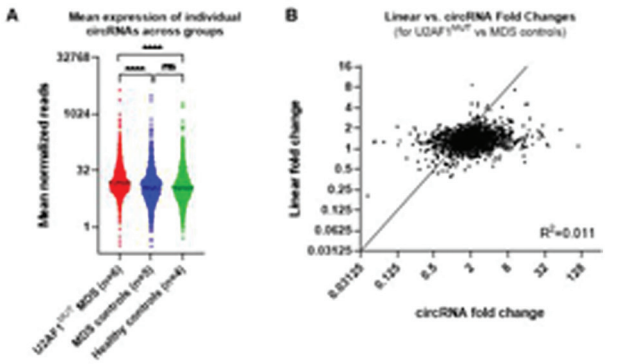
EP888 IMPLICATIONS OF THE SPLICEOSOME MUTATION U2AF1 FOR THE EXPRESSION OF CIRCULAR RNA

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Background: Spliceosome mutations are common in myelodysplastic syndromes (MDS), but their role in cancer biogenesis and progression is not fully understood. *U2AF1* mutation is associated with a poor prognosis. This splicing factor is responsible for recognition of the 3' splice site, a process which is altered by the two commonly found hotspot mutations at residues S34 and Q157. Circular RNAs are produced when backsplicing events occur, in competition with linear mRNA splicing. CircRNAs have been implicated in numerous cancers and immune processes.
Aims: To explore the impact of *U2AF1* mutation on circRNA expression in MDS.
Methods: We analyzed RNAseq data from a transgenic mouse model with doxycycline-inducible $U2AF1^{S34F}$/$U2AF1^{WT}$ expression.[1] In addition, we generated total RNAseq data from FACS sorted CD34+ bone marrow cells from patients with MDS with *U2AF1* mutation (3 S34 mutations, 3 Q157 mutations), along with 5 matched MDS controls without spliceosome mutations and 4 healthy controls. CircRNAs were identified using the pipelines CIRI2 and find_circ, with detection by both pipelines required. CircRNA counts were normalized using DESeq2 including linear mRNA expression. DESeq2 was also used to generate adjusted p values.

Results: CircRNA expression was predominantly upregulated with the induction of *U2AF1*^{S34F} mutation in mice (p<0.0001, Wilcoxon test). The correlation between fold changes in circular and linear RNA expression (from corresponding splice sites) was low (R^2 =0.005) indicating that altered circRNA expression was independent to changes in linear expression. In MDS patients, circRNA expression was significantly higher in those with *U2AF1* mutations than matched controls (Figure A, p<0.0001, Wilcoxon test), whilst there was no significant difference between the MDS controls and the healthy controls. Again, changes in circRNA expression were independent to changes in linear expression (Figure B, R^2=0.011). Seven specific circRNAs were significantly upregulated (p_{adj}<0.05 and fold change >2) in patients with *U2AF1* mutation vs MDS controls. Literature searching revealed that two of these circRNAs (circZNF609 and circCSNK1G3) have previously been linked to cancer (hepatic cell carcinoma and renal cell carcinoma, respectively).[2,3] Global circRNA expression levels did not differ between patients with S34 and those with Q157 mutations (p=0.374, Wilcoxon test), but the patterns of expression were found to be distinct, indicated by separation of the two mutations on unsupervised cluster analysis.



Summary/Conclusion: We found both in a murine model and in MDS patients that *U2AF1* mutations lead to an increase in circRNA expression. Furthermore, distinct circRNA expression profiles were seen for mutations at the S34 and Q157 loci. Further investigation of the biological mechanism by which *U2AF1* mutation supports backsplicing, and profiling of a larger cohort of MDS patients, is merited.

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3. Li, W. *et al.* CircCSNK1G3 up-regulates miR-181b to promote growth and metastasis via TIMP3-mediated epithelial to mesenchymal transitions in renal cell carcinoma. *J. Cell. Mol. Med.* (2021).

EP889 MYELODYSPLASTIC SYNDROME IN YOUNG ADULT WITHOUT PREVIOUS ORGANIC DISFUNCTION: PREDOMINANCE OF GERMLINE VARIANTS IN GENES OF DNA REPAIR PATHWAY AND THEIR CLINICAL IMPACT

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Background: In myelodysplastic syndromes(MDS) in young adults without previous organic dysfunction, the role that germline variants play in its pathogenesis remains to be defined. In fact, the WHO 2017 classification only includes alterations in a single gene, *DDX41*, in this subgroup of patients. In order to provide knowledge in this group of patients, where these findings could impact allogeneic hematopoietic stem cell transplantation (allo-HSCT) strategies.
Aims: We proposed an exhaustive clinical analysis, favoured by the prospective nature of the study in a Spanish multicentre cohort of patients with data from paired tumor-germinal exome sequencing.
Methods: Prospective cohort study (2014-2020) of 168 patients from 20 Spanish Group of Myelodysplastic Syndrome (GESMD) centers with a *de novo* diagnosis of MDS between 16-60 years old, without prior organ dysfunction. Collection of 107 clinical variables in relation to family and personal history, diagnosis, treatment, HSCT and disease evolution. Whole exome sequencing(WES) was performed in paired tumor-germline samples with 100x average depth, 150 million reads per sample, and >95% Q30[a]. WES libraries were prepared using SureSelectXT Target Enrichment System for Illumina Version B.2 and sequenced on a HiSeq4000-NovaSeq6000-Illumina platform. The analysis of the variants was carried out by means of an in-house pipeline: filtering out intronic, synonymous and those variants with MAF>1%. The germline variants were categorized according to ACMG criteria.
Results: The median age at diagnosis was 49 years old(16-60) with the following WHO 2017 diagnoses: 13.6% MDS-unilineage dysplasia(UD), 11.1% MDS-ring sideroblasts(RS), 32.1% MDS-multilineage dysplasia(MD), 27,1% MDS-excess blasts(EB), 5.6% MDS-isolated deletion-5q(del-5q), 2.5% MDS-unclassifiable(U), 8% chronic myelomonocytic leukemia(CMML). We found germline variants which categorized as pathogenic(P), likely pathogenic(LP) or uncertain significance(VUS) in 82%(n=139) of 168 patients. The frequency of patients with germline variants according to the gene function/pathway were 36%(n=62) DNA damage response, 2%(n=4) telomere function maintenance, 10%(n=18) hematopoiesis regulators, 4.8%(n=8) ribosome function, 11.9%(n=20) immune response,and 32.7%(n=55)others. *DDX41*(n=3) and *SAMD9L*(n=1), recurrently implicated in the predisposition to myeloid neoplasia without extra-hemopoietic clinical features, were only present in 4 cases in our cohort. Patients with germline

TABLE 1. Clinical-genetic characteristics of the study cohort and comparisons between different groups based on the presence or absence of germline variants (VUS + LP + P according to ACMG).

VARIABLE	GLOBAL COHORT (N=168)	(A) With germline variant (GV) (n=139)	(B) With GV of DNA damage response (n=62)	(C) Without GV (n=29)	(D) Without GV of DNA damage response (n=106)	P (A vs C)	P (B vs C)	P (B vs D)
Age at diagnosis,y.o., median (range)	49 (16-60)	48.7(26-60)	49 (16-60)	53 (16-60)	49 (16-60)	0.042	0.032	0.289
Genre (F/M), %	55/45	58/42	31/31	41/59	58.1 /41.9	0.102	0.443	0.310
Family history of hematological disease, %	11.3	7.8	11.5	26.9	11.1	0.005	0.086	0.938
Family history of MDS/AML, %	8.5	4.3	7.7	26.9	8.9	<0.001	0.021	0.805
Family history of oncologic neoplasia, %	16.7	18.6	24	8	12.5	0.199	0.094	0.081
Bone marrow cellularity, % (hipo vs normo/hiper)	25.5 vs 74.5	26.4 vs 73.6	27.8 vs 72.2	21.4 vs 78.6	24.2 vs 75.8	0.585	0.532	0.632
Blasts in bone marrow, %, median(range)	3 (0-16)	3 (0-16)	4 (0-16)	2 (0-15)	3 (0-16)	0.179	0.233	0.621
Number of lineage dysplasia, 1 vs 2/3, %	18.1 vs 81.9	19.3 vs 80.7	18.9 vs 81.1	12 vs 88	17.6 vs 82.4	0.387	0.448	0.847
Abnormal Karyotype and/or FISH, %	32.7	31.8	32.1	37	33	0.598	0.659	0.911
Myelofibrosis, %	10.1	19.8	6.5	24.1	12.3	0.013	0.016	0.132
IPSS-R (≤3.5 vs >3.5), %	59 vs 41	57.4 vs 42.6	61.4 vs 38.6	66.7 vs 33.3	57.6 vs 42.4	0.372	0.641	0.640
Allo-HSCT,%	31.4	30.5	29.8	35.7	32.4	0.592	0.584	0.742
OS, median(range)	38.4 (0-483)	38.5(0-483)	29 (0-313)	32.8 (1-384)	39,9(1-483)	0.993	0.397	0.089
Time to AMLt, median(range)	33.1(0-483)	33.3(0-483)	24 (0-312)	32.8 (1-483)	38.8(0.9-483)	0.853	0.289	0.052
AMLt,%	13.7	13.5	21.1	14.3	9.6	0.916	0.453	0.043
Deceased, %	23.8	24.5	27.4	20.7	21.7	0.665	0.491	0.401

variants(P and/or LP and/or VUS) in DNA repair genes(Table1) showed a lower age(49 vs 53 years old; p=0.032), a higher frequency of family history of MDS/acute myeloid leukemia(AML), and less probability of concomitant myelofibrosis; together with a statistical tendency to present family history of oncologic neoplasia, when compared with those cases without germline alteration. In the overall cohort, the presence of germline variants in DNA repair genes was correlated with superior risk to progression to AML and worse survival. These findings remain statistically significant even when applying a multivariate analysis with IPSS-R dichotomized (≤3.5 vs >3.5).

Summary/Conclusion: Young adult patients diagnosed with MDS *de novo*, without having presented any previous organ dysfunction, show a germline profile enriched in variants affecting genes of the DNA repair pathways. This subgroup presents subtle but relevant clinical differences that would support its specific pathogenicity, adding clinical information to the prediction data *in silico*.

EP890 MOLECULAR AND CYTOGENETIC CHARACTERIZATION OF MYELODYSPLASTIC SYNDROMES IN CELL-FREE DNA

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Background: Molecular studies and conventional cytogenetics are essential for patients with myelodysplastic syndromes (MDS) to establish a correct diagnosis and to optimize their prognosis and management. Routinely, these analyses are performed in bone marrow (BM) samples, especially cytogenetics as it is difficult to obtain metaphases in peripheral blood (PB) samples. Analysis of cell-free DNA (cfDNA), also known as liquid biopsy, has been reported as a reliable approach for detecting molecular abnormalities in MDS. However, there is limited information about cytogenetic alteration analysis in cfDNA from MDS patients.

Aims: To analyze the molecular and cytogenetic abnormalities of cfDNA using next generation sequencing (NGS) in patients with MDS.

Methods: BM aspirates and PB samples were collected from 57 newly diagnosed or treatment-naïve patients with MDS: 1 MDS-SLD, 33 MDS-MLD, 3 MDS-RS-SLD, 10 MDS-RS-MLD, 2 MDS-del(5q), 5 MDS-BE-1, 1 MDS-BE-2 and 2 MDS-U. PB samples from 33 healthy controls were also studied. Molecular characterization was performed in paired samples of BM DNA and cfDNA by NGS in all patients. Libraries were prepared using a custom panel including 48 myeloid-associated genes and genomic regions localized at the most frequently altered chromosomes in MDS (QIAseq Custom DNA Panels, Qiagen) and sequenced using Illumina technology with a 3000x minimum coverage. 14/57 (24.6%) presented cytogenetic/FISH alterations at the time of diagnosis, 2 of them with alterations not covered by the panel (+14, del(9q)). Copy number variant (CNV) analysis was performed by NGS to detect cytogenetic alterations in both cfDNA and BM, and confirmed by chromosomal microarrays (CMA) in BM DNA (CytoScan/OncoScan, ThermoFisher).

Results: We obtained a median amount of total cfDNA of 60.1 ng/ml in MDS patients that was significantly higher than that obtained from healthy controls (median 5.16 ng/ml) (p<0.001, Mann-Whitney). Sequencing of BM DNA and cfDNA showed a comparable mutational profile (153/161 mutations, 95.0% concordance). The most frequently mutated genes were *TET2* (47.4%), *SF3B1* (29.8%), *ASXL1* (21.1%), *SRSF2* (19.3%), *DNMT3A* (15.8%), *ZRSR2* (14.0%) and *U2AF1* (12.3%). A strong correlation was observed between the VAF of BM and cfDNA (r=0.787, p<0.001, Spearman). There were 7 discordant mutations: 3 were only detected in cfDNA and 4 were only detected in BM. These 7 discordant mutations presented a lower variant allele frequency (VAF) (median 7.41%, range 2.86–25.53%) when compared to the VAF observed in cfDNA in the whole cohort (median 31.44%, range 0.74–98.28%).

CNV analysis by NGS showed cytogenetic alterations in 9/57 MDS patients in both BM DNA and cfDNA. 8/12 (73%) cases with altered karyotype/FISH were detected by NGS, and the remaining were identified in few metaphases (2 cases presented +8 and 1 case +4) and in one case a del(5q) only detected by FISH. Interestingly, in a patient without analyzable metaphases in the karyotype, del(20q) was found by NGS and was confirmed by CMA. Overall, CMA and NGS were highly concordant to detect chromosomal aberrations although they do not reach the detection achieved by karyotype/FISH. However, all the cytogenetic aberrations detected by NGS in BM DNA were also detected in cfDNA (100% concordance).

Summary/Conclusion: The analysis of cfDNA allows the characterization of the molecular abnormalities in patients with MDS. Cytogenetic alterations were detectable in most cases by NGS in both BM DNA and cfDNA although with a lower detection rate than karyotype/FISH.

EP891 ALL-TRANS RETINOIC ACID ENHANCES THE CYTOTOXIC EFFECT OF DECITABINE ON MYELODYSPLASTIC SYNDROMES VIA ACTIVATING RARA-NRF2 COMPLEX

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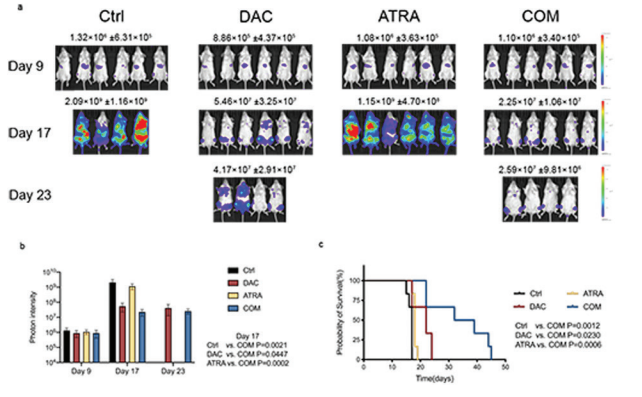
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Background: Decitabine (DAC) is used as first-line therapy in patients with higher-risk (HR) myelodysplastic syndromes (MDS). However, the clinical outcomes of patients treated with DAC as monotherapy were far from satisfactory with overall response rate (ORR) of 33%>55.4% and overall survival (OS) of 17.7-22 months. Some clinical researches reported that the addition of ATRA to DAC increased response rate and prolonged survival of MDS and elderly acute myeloid leukemia (AML) patients. Therefore, the effect and mechanisms of combination therapy with DAC and ATRA have been studied.

Aims: Conducting the study to investigate the efficacy and mechanisms of DAC combined with ATRA on HR MDS both *in vitro* and *in vivo*.

Methods: The combination effects of DAC and ATRA were studied via MDS cell lines and primary cells from newly diagnosed MDS and AML patients. The underlying molecular mechanisms were investigated through MDS cell lines. The MOLM-13-luciferase xenograft murine model was used to verify the enhanced cytotoxic effect of combined drugs.

Results: The current study indicated that the strategy combining DAC and ATRA synergistically induced apoptosis of MDS-L and MOLM-13 cells *in vitro*, and inhibited the viability of primary cells from MDS and AML patients. The combination treatment significantly decreased leukemia burden and prolonged survival of the MOLM-13-luciferase xenograft murine model. Mechanistically, treatment on MDS-L and MOLM-13 cells with DAC as a single agent activated nuclear factor erythroid-2 related factor 2 (Nrf2) signaling pathway. Nrf2 pathway, the master regulator of cellular redox equilibrium, is widely reported to mediate resistance to chemotherapy, demethylation therapy, and target therapy in various tumors. Once activated, Nrf2 leads to the downstream antioxidant response, restrains cellular reactive oxygen species (ROS) accumulation, attenuates ROS-dependent cytotoxicity, thus conferring resistance to DAC. In the current study, the apoptosis of MDS-L and MOLM-13 cells induced by single DAC and combined with ATRA can be reversed by pretreatment with the ROS scavenger N-acetylcysteine (NAC), indicating that the cytotoxicity induced by both monotherapy and combination therapy were ROS dependent. Co-treatment with DAC and ATRA activated the RARα-Nrf2 complex in the nucleus, and reduced binding of HDAC1 to the functional complex, which prevented Nrf2 from being activated by DAC alone, promoted ROS accumulation and enhanced ROS-dependent cytotoxicity, thus overcoming the resistance of MDS cells to DAC.



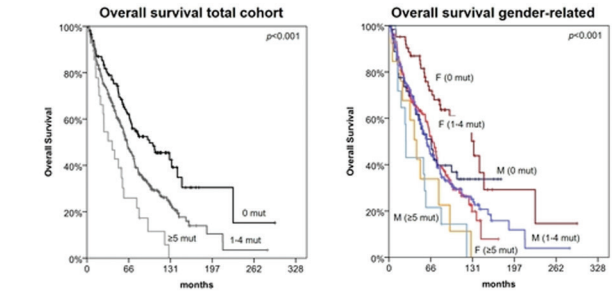
Summary/Conclusion: The interaction between DAC and ARTA exerts collaborative cytotoxicity in MDS cells. Therefore, the regimen combining DAC and ATRA in higher-risk MDS holds potential for clinical application and deserves further explorations.

EP892 LESS CAN BE MORE – GENDER-RELATED MUTATIONAL LANDSCAPE AND OUTCOME IN MYELODYSPLASTIC SYNDROME

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Background: Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell neoplasms associated with cytopenias. Diagnosis is based on peripheral blood count, bone marrow morphology and cytogenetics. In addition to cytogenetics, which allows risk stratification of patients, multiple recurrent mutations have been identified in recent years. For some diseases, a gender-dependent prevalence of mutations and their impact on outcome have been described, but a systematic evaluation of the mutational landscape and its impact on the prognosis of patients in relation to their gender in MDS is still lacking.
Aims: To compare the molecular genetic landscape and identify potential different outcomes between female and male patients with MDS.
Methods: The cohort comprised 588 patients (234 female and 354 male) with a median age of 72, diagnosed as MDS by cytomorphology and cytogenetics following WHO classification. All patients were previously investigated by next generation deep sequencing (Haferlach et al, Leukemia 2014) and WGS. All data were analyzed for 4 virtual gene panels, the 12 genes as given in the MDS NCCN guidelines with a incidence >5% (Version 2.2020), the 34 gene panel summarized in McClure et al. (J Mol Diag 2018), the 723 cosmic cancer gene census (CCGC, v91) panel and finally the exome.
Results: A gender-specific analysis of the MDS subtypes confirmed the already known female predominance in MDS with isolated del(5q) (73% vs 27%; p<0.001), while all other MDS subtypes showed no gender differences. Additionally, female patients showed higher platelet counts than their male counterparts (mean 227,229/µl vs. 180,950/µl; p=0.001). There were no gender-related differences in age, karyotype or IPSS-R score. However, in non del(5q) subtypes female showed predominantly a normal karyotype (79% vs. 67%; p=0.002). Addressing individual gene mutations showed that female patients were more often mutated in *DNMT3A* (40/234, 17% vs. 24/354, 7%; p<0.001), while males were more often mutated in *TET2* (119/354, 34% vs. 58/234, 25%; p=0.027). Interestingly, *ZRSR2* mutations (on chr. X) occurred nearly exclusively in male patients (39/354, 11% in male vs. 1/234, 0% in female; p<0.001). Overall the median number of mutations was slightly higher in male patients and the absence of mutations in the myeloid specific gene panels was more pronounced in female patients (NCCN gene panel: 63/234, 27% vs. 55/354, 16%; p=0.001; McClure gene panel: 52/234, 22% vs. 44/354, 12%; p=0.002). The differences in mutation detection rates disappeared with the larger CCGC panel and the exome. In the following, we aimed to investigate whether the higher number of mutations in males also had an impact on patient outcome. While age and karyotype showed prognostic impact in both groups, gender *per se* did not affect the outcome. However, looking at gender-dependent survival, a prognostic impact becomes apparent by subdividing the myeloid gene panels into groups with no, 1-4, and ≥5 mutations per patient. Surprisingly, men showed no difference in survival between the two groups with no and less than 5 mutations, whereas this was statistically significant in women (figure, NCCN gene panel). This difference decreases with increasing panel size and number of mutations.**Summary/Conclusion:** Between female and male MDS patients differences in prevalence and mutational landscape occur. The number of mutations within a small panel of 12 recurrently mutated genes show prognostic impact that is predominant in female patients and should therefore be considered for risk stratification.



	months (n, cases)
0 mutation	98 months (n=117)
1-4 mutations	63 months (n=442)
≥5 mutations	40 months (n=28)

Female (F) months (n, cases)	Male (M) months (n, cases)
133 months (n=62)	66 months (n=55)
68 months (n=158)	60 months (n=284)
43 months (n=13)	27 months (n=15)

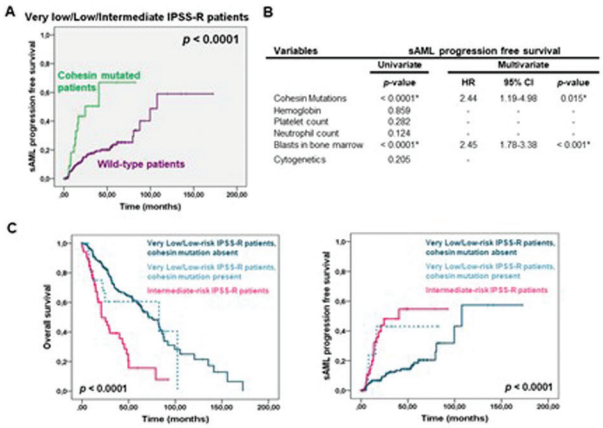
EP893 COHESIN MUTATIONS ARE ASSOCIATED WITH A POOR PROGNOSIS PHENOTYPE AND A WORSE CLINICAL OUTCOME IN LOW-RISK MYELODYSPLASTIC SYNDROMES PATIENTS

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Background: Mutations in cohesin genes have been described as novel mutations occurring in 10-15% of myelodysplastic syndromes (MDS), suggesting that the cohesin complex presents an important pathway in the MDS pathogenesis. However, the clinical impact of cohesin mutations is still undetermined.
Aims: Molecular and clinical characterization of MDS patients harboring cohesin mutations: genetic background, disease phenotype, clinical outcome and prognostic impact of integration of these mutations with conventional risk factors.
Methods: A cohort of 421 patients diagnosed with MDS was analyzed by targeted deep sequencing using an Illumina® custom panel of 117 myeloid-related genes, including cohesin genes: *STAG1*, *STAG2*, *SMC1A*, *SMC3*, *RAD21* and *CTCF*.
Results: The median age at diagnosis was 74.7 years (range 29.4-92.2); 59% were male. According to the WHO 2017 classification most of the patients had MDS with multilineage dysplasia with or without ring sideroblasts (MDS-RS-MLD and MDS-MLD, 45.5%), followed by MDS with excess blasts (MDS-EB2, 16% and MDS-EB1, 14.6%). Regarding IPSS-R, the majority of patients had very low (27%) and low (44%) risk, with 85% of the series having normal karyotype or clonal alterations of very good or good risk. The median follow-up was 2.3 years (range 0.01-15.6) and during this time 49% of patients died and 30% progressed to acute myeloid leukemia (AML).
The NGS study identified 54 mutations in cohesin genes in 50 patients (11.9%), being most of them loss of function type and *STAG2* (36/50) and *SMC3* (7/50) the most frequently mutated genes. Regarding the molecular landscape of patients with cohesin mutations: mutated patients presented a significantly higher number of mutations (p<0.0001) and displayed a specific mutational profile with a strong co-occurrence between cohesin and splicing mutations (p<0.0001) and Ras pathway alterations (p=0.001).
Regarding the clinical characterization, mutations in cohesin genes were associated with **MDS-EB-1/2** subtypes (p<0.0001), **intermediate and high-risk IPSS-R** categories (p=0.001) and **intermediate cytogenetic risk** (p=0.001), especially with trisomy 8 (p<0.0001). Moreover, patients with cohesin mutations displayed a **poor prognosis disease phenotype**, characterized by lower platelet, neutrophil and leucocyte count in blood (p=0.004, p=0.003 and p=0.037, respectively), a higher number of blasts in bone marrow (p=0.0003) and a **higher rate of progression** to sAML (p<0.0001).
Regarding the influence on clinical outcome, cohesin-mutated patients showed a **shorter overall survival** (OS: 3.1 *vs.* 5.2 years, p=0.052) and **a shorter time to sAML progression** (LFS: 1.4 *vs.* 8.3 years, p<0.0001). Noteworthy, this adverse impact was observed mainly in very low, low and intermediate-risk IPSS-R patients regarding LFS (multivariate analysis: HR 2.4, 95% CI 1.2-5.0; p=0.015).

To further study the negative impact of cohesin mutations, we assessed their **prognostic value on the IPSS-R stratification**. Of note, the OS and LFS of very low/low-risk patients who harbored cohesin mutations were statistically significant shorter than those without these mutations, but nearly identical to intermediate-risk patients.



Summary/Conclusion: Patients harboring cohesin mutations displayed a specific mutational profile, a poor prognosis disease phenotype and a worse clinical outcome, characterized by a higher rate and a shorter time to sAML progression. In addition, the incorporation of cohesin mutational data into current IPSS-R classification improved the prognostic stratification of very low and low-risk patients.

EP894 SINGLE-CELL RNA SEQUENCING TO EXPLORE THE ABNORMAL DIFFERENTIATION OF HEMATOPOIETIC STEM AND PROGENITOR CELLS IN MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKEMIA

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Background: Myelodysplastic syndrome (MDS) and acute myeloid leukemia(AML) are both myeloid neoplasms with obvious heterogeneity. The biological mechanisms of clonal proliferation, abnormal differentiation of hematopoietic stem and progenitor cells(HSPC)are largely unknown. Single-cell RNA sequencing (scRNA-seq) can reveal the specific information of individual cells, which is of great significance for revealing the heterogeneity and exploring the mechanism of MDS and AML.
Aims: To explore the mechanism of clonal proliferation and delayed differentiation of HSPC in patients with MDS and AML at single-cell level.
Methods: 5 MDS patients (2 with low-risk MDS[LR-MDS] and 3 with high-risk MDS[HR-MDS]), 2 AML patients were recruited. All the patients have signed the informed consent. Lineage-negative (Lin^-) hematopoietic cells from bone marrow(BM) were sorted by immunomagnetic beads, then scRNA-seq and bioinformatics analysis were given. The scRNA-seq data of BM mononuclear cells from 17 healthy donors (HDs) were downloaded from Gene Expression Omnibus (GEO) database, and the data of Lin^- cells were selected manually as control. According to the gene-set enrichment analysis, ribosomal genes and mitochondrial genes were selected for further confirmation by Quantitative Real-time polymerase chain reaction (qPCR) in $CD34^+$ cells from BM, and the correlations between gene expression and clinical characteristics were analyzed.
Results: The gene expression patterns in patients with MDS and AML were significantly different from HDs, and they were also significantly heterogeneous among patients. The proportion of hematopoietic stem cells(HSC) and multipotent progenitors(MPP) in MDS and AML was higher than that in HDs, while the proportion of erythroid precursors and lymphoid progenitors was significantly lower than that in HDs(Figure A,B).
Further analysis of HSC and MPP showed that the differential expression genes of MDS compared to HDs were similar to those of AML compared to HDs, so MDS and AML were put together to compare with HDs. Down-regulation of ribosomal genes and the up-regulation of mitochondrial genes were the most significant. Enriched up-regulated gene sets included abnormal mitochondrial metabolism, oxidative respiratory chain defects and neutrophil degranulation in HSC and MPP of MDS and AML patients, while down-regulated gene sets were enriched in ribosome, translation, metabolism of proteins(Figure C,D).

The mRNA expression of ribosomal and mitochondrial genes in BM $CD34^+$ cells by qPCR was consistent with the data of scRNA-seq. The expression of MT-CYB mRNA in LR-MDS(n=10), HR-MDS(n=14), AML(n=26) was significantly higher than that in the control group(patients with iron-deficiency anemia[IDA], n=16) ($P<0.05$), and the expression of MT-CO1 mRNA got similar results ($P<0.05$). (Figure E,F). The expression of RPL31 mRNA in LR-MDS(n=14), HR-MDS(n=24), AML(n=25) was lower than that in the control group(patients with IDA, n=22) ($P<0.01$), and positively correlated with hemoglobin (HB) ($r=0.377$, $P=0.020$)and platelet (PLT) ($r=0.367$, $P=0.023$). (Figure G-I).

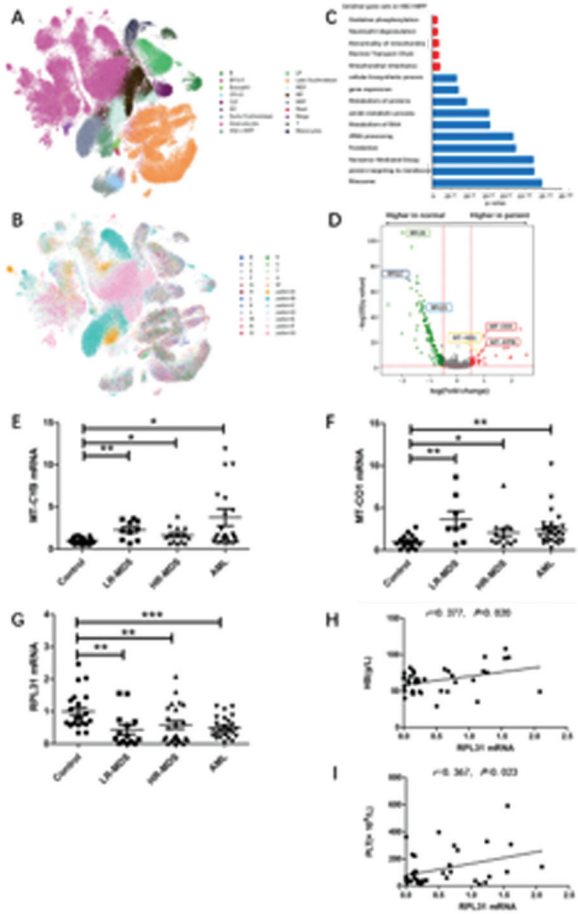


Figure A,B. UMAP of scRNA-seq data displaying Lin^- hematopoietic cells from 17 healthy donors(HDs) , 5 MDS and 2 AML patients. **A.** Display of clusters. **B.** Display of samples. **C.** Enriched gene sets in HSC and MPP. Red: up-regulated in MDS and AML, blue: down-regulated in MDS and AML. **D.** Volcano map of differential expression genes of HSC and MPP. **E,F.** MT-CYB, MT-CO1 mRNA in BM $CD34^+$ cells by qPCR in control, LR-MDS, HR-MDS, AML. **G-I.** RPL31 mRNA in BM $CD34^+$ cells by qPCR in control, LR-MDS, HR-MDS, AML and its correlation with HB and PLT in MDS patients. HSC: hematopoietic stem cells; MPP: multipotent progenitors; BM: bone marrow; LR-MDS: low-risk MDS; HR-MDS: high-risk MDS.

Summary/Conclusion: In patients with MDS and AML, dysfunction of ribosome and translation, abnormal mitochondrial metabolism and oxidative respiratory chain in HSPC, may be related to the incidence and development of MDS and AML.

EP895 LNCRNA PCSK1N-202 PROMOTES CD34+CELL PROLIFERATION VIA PIM2/HIF-1A IN MYELODYSPLASTIC SYNDROMES

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Background: Myelodysplastic syndromes (MDS) are characterized by malignant clonal hematopoietic stem cells with high-risk of progression to acute myeloid leukemia (AML). Pim-2 is a serine/threonine protein kinase that is elevated in various types of cancer and plays essential roles in the regulation of signal transduction cascades, which promote cell survival and cell proliferation. Our previous study revealed that pim-2 was highly expressed in CD34+ cells derived from the bone marrow of patients with MDS/AML. The expression of Pim-2 induces elevated expression of HIF1-α by decreasing the expression of IDH1, resulting in acceleration of CD34+ cell proliferation.
Long non-coding RNAs (lncRNAs) represent the majority of cellular transcripts and play pivotal roles in hematopoiesis. However, the functions of lncRNA on hematopoietic stem cells malignant clone remains largely unknown.
Aims: Here we investigate the profile of lncRNA derived from the bone marrow $CD34^{+}$cells in MDS patients and AML secondary to MDS (sAML) patients. And we focused on the lncRNA which could regulate pim2
Methods: The profile of lncRNAs in bone marrow CD34+ cells from MDS patients and sAML patients was detected by high throughput RNA-seq technology. The biological function and signal pathway of the target genes of differentially lncRNAs were analyzed by GO and KEGG cluster analysis. RT-PCR were used to detected the lncRNA and pim2. The SKM-1cell line was used in the study. The lentiviral vector(sh-RNA) were transfected into SKM-1 to interfere the lncRNA. CCK8 was performed to measure the proliferation rate of SKM-1 transfected with the lentiviral vector. 7-AAD/PI was used to analyze the apoptosis of SKM-1.
Results: In sAML, we found 1173 lncRNAs (648 upregulated/525 downregulated) and 326 mRNAs (125 upregulated/201 downregulated) significantly deregulated compared to those in MDS patients (|logFC| > 1, p value < 0.05). Overall, the KEGG enriched processes were mainly related to four mechanisms: metabolic pathways, phagosome, metabolism of xenobiotics by cytochrome P450, glycine, serine and threonine metabolism, glycosphingolipid biosynthesis - lacto and neolacto series, fatty acid degradation, cGMP-PKG signaling pathway. GO term analysis showed the mainly related lncRNAs function on cellular metabolic process, organic cyclic compound metabolic process, nucleobase-containing compound metabolic process and etc. Of these, lncRNA PCSK1N-202 may targeted-regulate the pim2 mRNA. RT-PCR showed that PCSK1N-202 was upregulated in AML and MDA patients. And PCSK1N-202 was positive related with pim2. The SKM-1 transfected with LV-sh- PCSK1N-202 induced the decline of pim2 followed with decreased cell proliferation rate, and increased cell apoptosis.

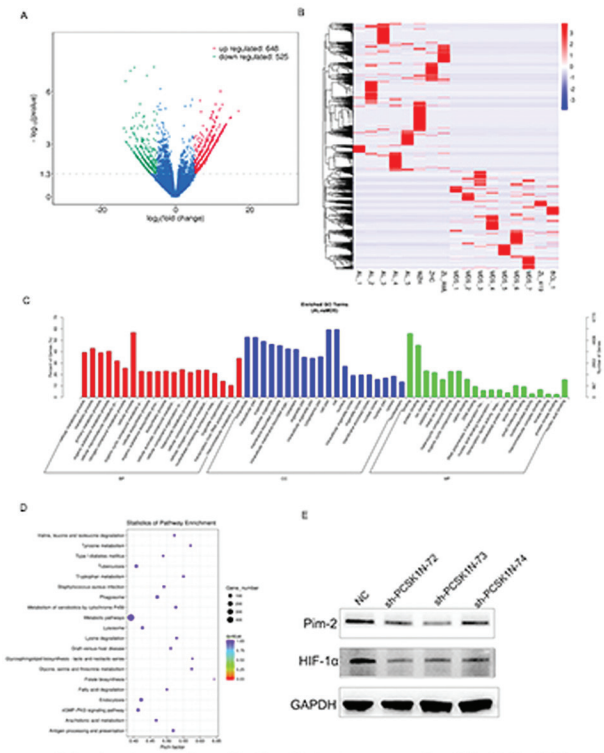


Fig A and B The volcanoplot and heatCluster of the differential lncRNAs in sAML, compared to MDS. Cand D. GO and KEGG terms of the differential lncRNAs. E. The interference of PCSK1N induced the downregulation of pim2 and HIF-1α

Summary/Conclusion: We reported novel information on specific lncRNAs contributing to AML transformation of MDS, and proposed cellular processes associated with these lncRNAs. Of the lncRNAs, the upregulation of PCSK1N-202 transcript might promotes CD34+cell proliferation via pim2/HIF-1α in myelodysplastic syndromes.

EP896 CLONAL HEMATOPOIESIS IS COMMON IN HIP ARTHROPLASTY PATIENTS AND ASSOCIATES WITH AUTOIMMUNE DISEASE AND LOWER HEMOGLOBIN LEVELS

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Background: Clonal hematopoiesis (CH) is a common age-related condition predisposing to blood cancer and cardiovascular disease (CVD). Murine models demonstrate CH-mediated altered immune function and proinflammation. Low-grade inflammation has been implicated in the pathogenesis of osteoarthritis (OA), the main indication for total hip arthroplasty (THA). THA-derived hip bones serve as a major source of 'healthy' hematopoietic cells in experimental hematology.
Aims: We prospectively investigated frequency and clinical associations of CH in 200 patients without known hematologic disease undergoing THA for OA.
Methods: BM samples were collected from 200 patients without known hematologic disease undergoing THA for OA between 07/2017 and 08/2020 after written informed consent. The study was approved by the respective ethics committees in accordance with the Declaration of Helsinki. Targeted sequencing of 68 genes recurrently mutated in hematologic malignancies identified variants with a VAF threshold of ≥1%. For correlative analyses of clinical parameters, only variants fulfilling the current CHIP definition (clonal hematopoiesis of indeterminate potential, defined as somatic variants with allele frequencies [VAF] ≥2%) were included. Statistical analysis was performed with GraphPad Prism v6.0 and R v3.6.3.
Results: Prevalence of CH was 50.0%, including 77 patients with CHIP, and 23 patients harboring CH with lower mutation burden (VAF 1-2%). CH became progressively more frequent with age (Figure 1A). Most commonly mutated genes were *DNMT3A* (29.5%), *TET2* (15.0%) and *ASXL1* (3.5%). Most patients (n=56) had 1 mutation, 32 harbored 2 variants, and 10 carried 3 mutations, while two patients harbored 4 or 5 mutations, respectively. Number of variants per individual correlated with age (p=0.031), whereas VAF (median 2.7%, range 1.0-32.7%) did not (p=0.73). CHIP significantly correlated with older age (median, 74.0 years [y] with CHIP *vs.* 68.5 y without, respectively; p<0.00010), lower hemoglobin levels (median, 12.7 g/dL *vs.* 13.7 g/dL; p=0.0020) and higher MCV (median, 91.8 fl *vs.* 89.0 fl; p=0.0076). Of note, 66.7% of the patients with anemia had detectable mutations with VAF≥2% (who would thus be classified as clonal cytopenia of uncertain significance [CCUS]), whereas prevalence of CHIP was lower in patients with normal hemoglobin levels (32.7%, p=0.0014). Furthermore, we observed an enrichment of *SF3B1* and *TP53* mutations in anemic patients compared to those with normal blood counts (p=0.020). CHIP carriers were more likely to have CVD (p=0.0080), as previously reported, and present/prior malignancy (p=0.029). Strikingly, CHIP also associated with presence of autoimmune disease (AID, p=0.034), comprising diverse autoimmune disorders. Multivariate analysis with adjustment for age and sex confirmed significant associations between CHIP and older age (p=0.025), lower hemoglobin levels (p=0.0078), and AID (p=0.0081), but not with CVD or malignancy (Figure 1B).

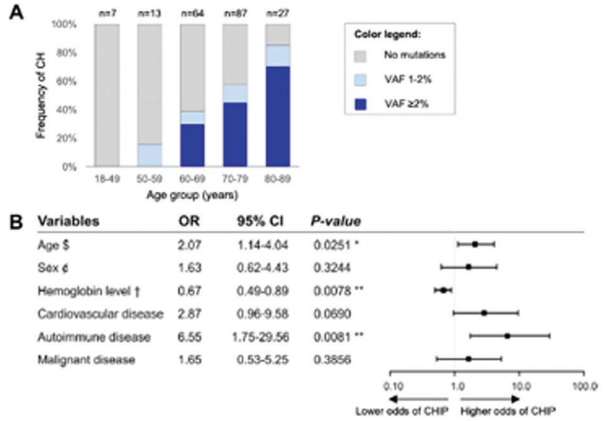


Figure 1. Frequency and clinical correlates of CH/CHIP in patients undergoing THA.
(A) Frequency of CH among different age groups.
(B) Multivariate analysis. $ per 10 years increase. ¢ fermale versus male. † per 1g/dL increase.

Summary/Conclusion: Prevalence of CH in our prospectively enrolled cohort of older adults undergoing THA for OA is considerably higher than previously reported in healthy individuals or specific patient groups, such as those with ischemic heart failure or CVD. Together, these findings underscore the association between CH and inflammatory diseases. Our results have considerable relevance for management of patients with OA, AID and anemia, and question the use of hip bone-derived cells as 'healthy' experimental controls.

EP897 THE CAR VIRUS RECEPTOR MEDIATES MATURATION AND MIGRATION IN ERYTHROID PRECURSOR CELLS AND IS DOWNREGULATED IN MDS

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Background: Myelodysplastic syndromes (MDS) are myeloid neoplasms presenting with dysplasia in the bone marrow (BM) and peripheral cytopenia. Most patients present with erythroid hyperplasia in the BM and anemia.
Aims: We screened for genes that are expressed abnormally in erythroid progenitor cells (EryPC) and contribute to the pathogenesis of MDS.
Methods: In mRNA array- and flow cytometry staining experiments, we found that the Coxsackie-Adenovirus receptor (CAR) is markedly downregulated in $CD45^{low}/CD105^{+}$ EryPC in MDS patients compared to control EryPC.
Results: CAR was also down-regulated in EryPC in patients with acute myeloid leukemia with BM dysplasia. Correspondingly, the erythroblast cell lines HEL, K562, and KU812 stained negative for CAR. Lentiviral transduction of the full-length *CAR* gene into these cells resulted in an increased expression of early erythroid antigens, including CD36, CD71, and glycophorin A. In addition, *CAR*-transduction resulted in an increased migration against a serum protein gradient, whereas transfection of truncated *CAR*-variants did not induce erythroid antigens or migration. Furthermore, we found that conditional knock-out of *Car* in hematopoietic cells in C57BL/6 mice results in anemia, an accumulation of erythroid cells in the BM, erythroid dysplasia and impaired migration of murine EryPC against a serum protein gradient. Decreased CAR expression on EryPC was found to correlate with high-risk MDS and decreased survival.
Summary/Conclusion: Together, CAR is a functionally relevant marker that is down-regulated on EryPC in MDS and is of prognostic significance. Decreased CAR expression may contribute to the maturation defect and altered migration of EryPC and thus their pathologic accumulation in the BM in MDS.

EP898 UNCLASSIFIABLE MYELODYSPLASTIC SYNDROME DEFINED BY A CYTOGENETIC ABNORMALITY: A REAL-LIFE STUDY.

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Background: Unclassifiable myelodysplastic syndrome defined by a cytogenetic abnormality (MDS-U-C) is a rare, poorly characterized entity that encompasses patients with at least one cytopenia, no marked dysplasia and a karyotype with one or more abnormalities considered to be presumptive criteria for MDS. Many cytopenia are still referred to as idiopathic cytopenia of undetermined significance (ICUS) because the cytological and cytogenetic diagnostic criteria for MDS are not met. Thanks to next generation sequencing (NGS) techniques, the discovery of somatic mutations in over 30% of patients with ICUS has prompted the definition of the entity "clonal cytopenia of undetermined significance"(CCUS). At present, these somatic abnormalities are not included in the WHO's diagnostic classification of MDS.
Aims: The aim of this study was to determine the clinical, laboratory and genetic characteristics of patients with cytopenia and cytogenetic abnormalities (regardless of whether or not the latter are listed by the WHO as presumptive) but no significant dysplasia. The ultimate objective was therefore to diagnose MDS-U-C more reliably in real life.
Methods: We performed a retrospective study of 64 patients diagnosed between 2011 and 2019 in nine French centres. The main inclusion criteria were cytopenia, at least one cytogenetic abnormality and the absence of marked dysplasia. Bone marrow smears were examined independently by three cytologists. Karyotypes were reviewed by members of the *Groupe Francophone de Cytogénétique Hématologique*. NGS was used to screen patients for a targeted panel of 58 genes frequently altered in MDS.

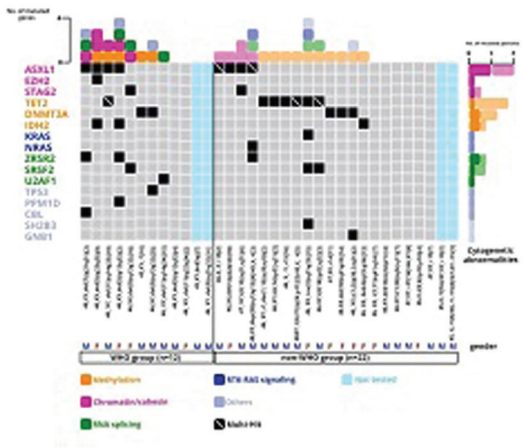


Figure 1: The genetic spectrum of cases of cytopenia with cytogenetic abnormalities

Each column represents a patient having had a molecular analysis (left: WHO-group, n =12; right: non-WHO group, n=22), and each row corresponds to a particular gene. Black and grey squares indicate mutated and non-mutated genes, respectively. Genes labelled as "multi-hit" contain more than one mutation. The plot at the top shows the number of mutated genes in each patient. The mutations are color-coded according to the legend below the grid. The plot on the right shows the number of patients with a mutation for each gene, by group (high opacity: WHO-group; low opacity: non-WHO group). The sex of each patient is specified below the grid.

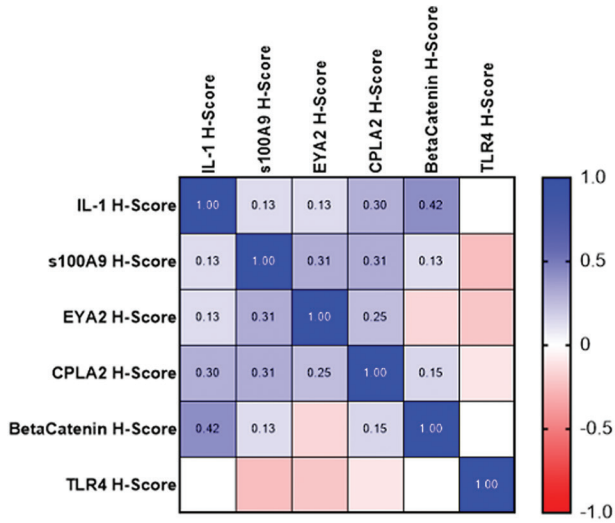
Results: The centralized cytology review led to 30 of the 64 patients being reclassified as having MDS; this relatively high proportion reflects the poor specificity of dysplastic features. We then divided the remaining 34 dysplasia-free patients into two groups: the "WHO group" comprising 12 individuals with a presumptive cytogenetic abnormality (including del(5q) (n=4), del(11q) (n=3), del(9q) (n=3), del(7q) (n=1) and -7 (n=1); median age: 74.3) and the "non-WHO group" comprising 22 individuals with non-recurrent abnormalities (except for trisomy 15 (n=5); median age: 76.7). The proportion of patients with one or more somatic mutations was 80% in the WHO group (mean number per patient: 2.4) and 70% in the non-WHO group (mean: 1.4) (p=0.11). The frequency of *ASXL1* mutations was higher in the WHO group (40% vs. 20 % in the non-WHO group; p=0.38), whereas the frequency of *TET2* mutations was higher in the non-WHO group (30% vs 10% in the WHO group; p=0.37) (Figure 1). The number and type of mutations in the WHO group were similar to those seen in patients with MDS, who harboured a median of 2 or 3 driver mutations (predominantly in *TET2, DNMT3A* and *ASXL1*). Although the same genes were involved in the non-WHO group, the mutation burden was lower than in MDS but higher than in clonal haematopoiesis of indeterminate potential (CHIP). With a median follow-up time of 10.4 months, the WHO group appeared to have a worse prognosis: 25% of these patients progressed to high-grade MDS (vs.4.5% in the non-WHO group; p=0.11).
Summary/Conclusion: Our present results confirmed that MDS-U-C is rare and is difficult to diagnose. Even though patients meeting all the criteria for MDS-U-C (i.e. the WHO group) seemed to progress more often to high-risk MDS and harboured a greater number of deleterious mutations (e.g. mutations in *ASXL1*), "non-WHO" patients must not be neglected; the latter require close monitoring and should perhaps be classified as cases of CCUS.

EP899 USING TISSUE MICROARRAY TO DETECT INFLAMMASOME SIGNALING COMPONENTS THAT CONTRIBUTE TO THE PATHOGENESIS OF MYELODYSPLASTIC SYNDROME

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Background: Myelodysplastic syndromes (MDS) are characterized by aberrant maturation, ineffective hematopoiesis, cytopenia, and progression to acute myeloid leukemia. MDS pathogenesis is multifactorial and potentially linked to constitutive innate immune stimulation converging upon the NLRP3 inflammasome to induce pyroptosis, a caspase-1 dependent cell death. lnflammasome assembly is initiated by both cell-extrinsic stimuli including S100A9, the TLR4 and CD33 ligand, and cell-intrinsic danger signals licensing caspase-1 which activates IL-1b and beta-catenin resulting in cell death and cellular proliferation leading to maturation and differentiation blocks. Further, EYA2 has been suggested to be an inflammasome activator, whereas cPLA2 has been suggested to be an inhibitor.
Aims: The purpose of this study is to determine whether immunohistochemistry (IHC) may be utilized to assess expression of inflammasome components.
Methods: An IRB protocol was approved prior to initiating this study. We retrospectively identified 43 low risk MDS patients. A tissue microarray (TMA) was constructed utilizing MDS bone marrow biopsy samples (2-3 representative cores per sample). IL-1, S100A9, EYA2, cPLA2, beta-catenin, and TLR4 expression were assessed by IHC after validation of each antibody. IHC expression was scored independently by two hematopathologists by calculating scores (product of staining intensity x percent expression). IHC expression was compared using Spearman correlation estimate. Demographic and clinical data were collected and correlated with IHC expression using Kruskal-Wallis test, Spearman correlation, and Logrank test.
Results: Patients were median 72 years of age, 67% men and included 47% MDS-MLD, 35% MDS-RS, 14% MDS-SLD, 2% MDS del5q and 2% MDS-U. IL-1 expression correlated with beta-catenin expression, r = 0.42, 95% Cl 0.115 to 0.658 (p = 0.007). There was a trend towards significance between IL-1 and cPLA2, r = 0.30 (p = 0.067); S100A9 and CPLA2, r = 0.31 (p = 0.052); and S100A9 and EYA2, r = 0.31 (p = 0.057). See figure for correlation between antigen expression scores. Percentage EYA2 expression correlated with blast count, r = 0.425 (p = 0.008). The IHC expression of these antigens did not correlate with WHO MDS subclassification, IPSS, R-IPSS, disease progression, or survival ($p < 0.05$).



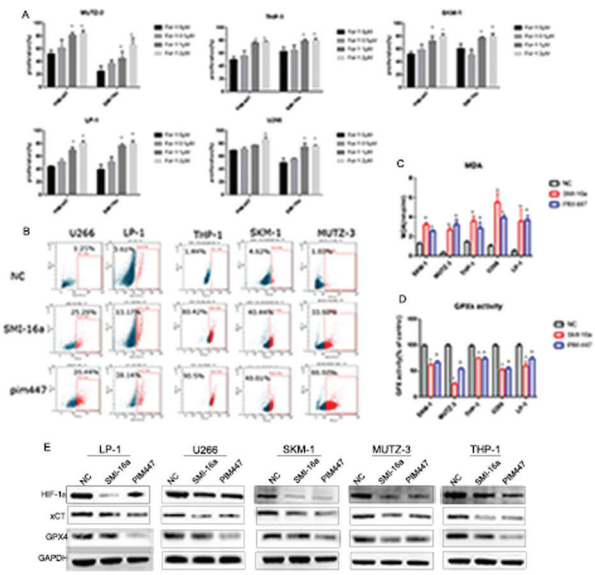
Summary/Conclusion: IHC staining of inflammasome activators using TMA may allow better characterization of molecular pathways contributing the MDS pathogenesis. A correlation was seen between expression of antigens known to be increased downstream of NLRP3 inflammasome activation. Furthermore, increased expression of EYA2 correlated with blast count. A future study will compare expression patterns between normal, low risk MDS and high risk MDS samples and correlate these findings with clinical outcome data to further elucidate the pathogenesis of MDS and identify potential targetable markers for novel therapeutic strategies.

EP900 PIM INHIBITORS INDUCE THE FERROPTOSIS VIA HIF1A/GPX4 PATHWAY IN HEMATOLOGICAL MALIGNANT CELLS

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Background: Ferroptosis, a form of regulated cell death (RCD) that involves iron accumulation and lipid peroxidation, is remarkably distinguishable from other forms of RCD, including necroptosis, apoptosis, and unregulated necrosis, in terms of its biochemistry, morphology, and genetics. Ferroptosis has been declared to be involved in many diseases, especially kinds of cancers. These studies provide useful evidence for the treatment of cancers. The Proviral Integration site for Moloney murine leukemia virus (PIM) kinases were reported to increased in several cancers, such as AML (acute myeloid leukemia) and MM (multiple myeloma). Nowadays the pim inhibitors are undergoing clinical trials. However, the mechanism of the pim inhibitors on tumor cells is still unclear.
Aims: The study aims to investigate whether the pim inhibitors can induce the ferroptosis in hematological malignant cells and what the mechanism is.
Methods: The cell lines SKM-1, MUTZ-3, THP-1, U266 and LP-1 treated with pim inhibitors (SMI-16a and Pim-447). CCK-8 assay was used to examine the cell proliferation following treated with drugs. The MDA (malondialdehyde) and GPXs were detected with biochemical method. FCM (flow cytometry method)was used to detected the ROS(reactive oxygen species). RT-qPCR was used to detected the relative expression level of mRNA involved. The related proteins were detected by western blot.
Results: The two pim inhibitors could decrease the proliferation of these cell lines significantly (Fig.1). And the inhibition effect treated for 48h was more obvious than 24h.The growth-inhibitory effect of pim inhibitors could be partially reversed by ferrostatin-1(ferroptosis inhibitors) (Fig.2). Then we analyzed the intracellular ROS level of the cells treated with SMI-16a and Pim-447 (Fig.2). SMI -16a and Pim-447 could increase the ROS level. The MDA level increased and the GPXs activity decreased following the treatment of SMI-16a and Pim-447(Fig.2). These results revealed that SMI-16a and Pim-447 induce ferroptosis in these cell lines. In order to investigate what the mechanism is, we preformed the western blot to examine the related proteins. The results showed that HIF-1αand xCT declined, which induced the GPX4 decreased(Fig.3).



Summary/Conclusion: Our study provides significant evidence to confirm the occurrence of ferroptosis in hematological malignant cells treated with pim inhibitors, and demonstrates that inhibition of ferroptosis was through HIF-1α/GPX4 pathway. These findings reveal a new form of cell death in the treatment of pim inhibitors.

EP901 BMSCS REGULATE THE FUNCTION OF NK CELL BY CD155/TIGIT/CD226 PATHWAY IN MDS PATIENTS

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Background: Myelodysplastic syndromes (MDS) are characterized by dysplastic bone marrow, ineffective hematopoiesis and high-risk transformation to acute myeloid leukemia (AML).It has been clearly addressed that the BM microenvironment plays an important role in malignant hematopoiesis, but the mechanism leading to MDS-associated immune is still unknown.
Aims: To analyzed the immune status of MDS patients, evaluated its impact on prognosis, and tried to study the specific mechanism of how mesenchymal stromal cells (MSCs) affecting immunity.
Methods: The study included 84 healthy controls and 84 inpatients with primary MDS, 22 patients with AML.We collected flow cytometry(FCM) reports and clinical data, including patient's sex, age, peripheral blood trilineage at initial diagnosis, number of bone marrow blast cells, karyotype analysis, etc. All MDS patients were stratified by IPSS-R for disease risk. 1. Statistical analysis of lymphocyte subset counts and cytokines in peripheral blood of different types of patients and healthy controls. 2. Correlation analysis between hemoglobin, platelets,neutrophil, blast cells, cytogenetics and lymphocyte counts was performed.3.We generated MSCs in BM samples from MDS patients and HCs.The expression of CD155 in MSCs and TIGIT/CD226 in lymphocytes were detected by FCM.
Results: 1.Percentage counts of NK cells in the HC group(19.94,95%CI 17.86-22.02, P<0.001)were significantly higher than other groups.The higher-risk group of MDS(11.51,95%CI 9.34-13.68) was obviously lower than the lower-risk group(16.91,95%CI 13.85-19,97)(P=0.006),close to the AML group(9.77,95%CI 6.33-13.20).Meanwhile, the level of IFN-Y in serum which is secreted mainly by NK cells was also the highest in the HC group(5.50,95%CI 3.74-7.26), followed by the MDS group and the lowest in the AML group(2.64,95%CI 1.91-3.37).Moerover,the higher-risk group(3.26,95%CI 2.45-4.07) was significantly lower than the lower-risk group(4.80,95%CI 3.66-5.95).In addition, CD8+ T cells and CD19+ cells had similar results as NK cells, but there was no significant difference with CD3+ cells and CD4+ T cells.2.Significantly higher level of NK cells percentage counts were found in patients with hemoglobin ≥ 100 ×1012/L compared to patients with lower hemoglobin(23.23,95%CI 17.26-29.21 and 15.77,95%CI 13.00-18.55,P=0.010). While the levels of NK cells were higher in patients with blast cells≤5% than in those with higher blast cells. (19.51,95%CI 16.09-22.93 and 14.65,95%CI 11.55-17.74,P=0.027). Patients with better karyotypes also had higher NK levels than those with poorer karyotypes(22.75,95%CI 19.47-22.03 and16.26,95%CI 11.36-21.15,P=0.060).No significant difference was found between NK cell levels with regard to platelet and neutrophil counts.CD8+ T cells behaved similarly to NK cells. 3.The expression of CD155 on the surface of BMSCs was significantly higher in the MDS group than that in the HC group(P=0.001, Figure1). Moreover,MDS patients had higher expression of TIGIT(P=0.012) and lower expression of CD226(P=0.001,Figure2B) on the surface of NK cells in bone marrow than that in HCs.And CD8+ T cells also have similar results as NK cells.We analyzed the correlation between TIGIT of NK cells and CD155 of BMSCs, and found that they were negatively correlated (P=0.0297), while CD226 was positively correlated with CD155 (P=0.0706, Figure 2C).

Figure 1

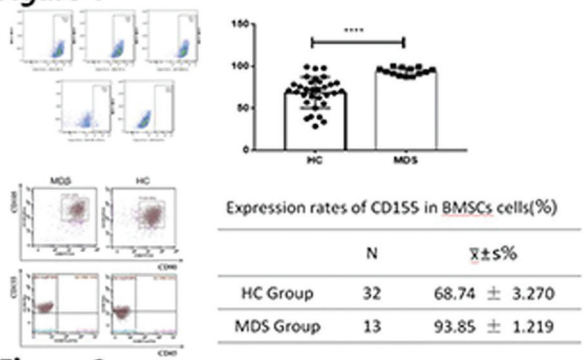
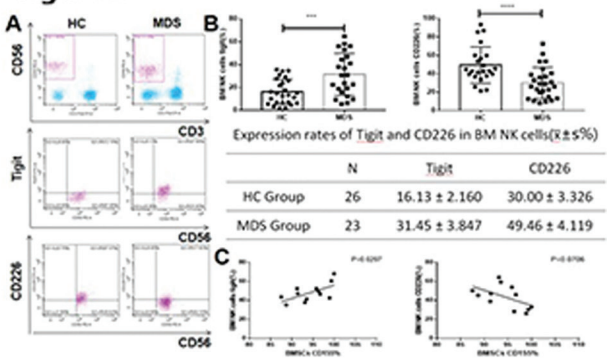


Figure 2



Summary/Conclusion: The decreased immune function in MDS patients is associated with prognosis.BMSCs are responsible for inducing an immune-suppressive microenvironment in MDS through CD155/TIGIT/CD226 pathway, the underlying mechanism remains to be further study.

EP902 PHARMACOLOGIC INHIBITORS OF CDK4/CDK6 EXERT ANTI-NEOPLASTIC EFFECTS ON CMML CELLS AND SYNERGIZE WITH THE MULTI-KINASE INHIBITOR PONATINIB IN NEOPLASTIC MONOCYTES

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Background: In chronic myelomonocytic leukemia (CMML), therapeutic options include hematopoietic stem cell transplantation, chemotherapy, demethylating agents and hydroxyurea (HU), which is used for palliative cytoreduction. Despite these approaches, progression to secondary acute myeloid leukemia (sAML) is frequently seen and the prognosis is poor. No targeted therapies are available in CMML. CDK4 and CDK6 serve as major drug targets in applied oncology. However, the effects of CDK4/CDK6 inhibitors have not been analyzed in CMML contexts so far.
Aims: We examined the anti-neoplastic effects of HU, which has been described to counteract CDK4/CDK6-expression in leukemic cells, and the specific CDK4/CDK6 inhibitors palbociclib, ribociclib and abemaciclib on primary CMML cells and various monoblastic cell lines. We also aimed to define cooperative anti-neoplastic effects of CDK4/CDK6-targeting drugs and the multi-kinase inhibitor ponatinib.

Methods: Primary leukemic cells of the bone marrow were obtained from 11 patients: 8 with CMML, 3 with sAML following CMML. We also analyzed the monoblastic cell lines THP-1, MONO-MAC-6 (MM6) and U937. Cell proliferation was determined by ^{3}H-thymidine uptake. Apoptosis and cell cycle distribution were quantified by flow cytometry. CDK4 and CDK6 mRNA were quantified by qPCR and protein expression and phosphorylation by Western blot analysis.
Results: Both HU and the CDK4/CDK6 inhibitors tested were found to disrupt the CDK4/CDK6-pathway in THP-1 and MM6 cells. Whereas HU decreased CDK4 and CDK6 mRNA- and protein expression, palbociclib, ribociclib and abemaciclib suppressed the expression and phosphorylation of RB1, the main target of CDK4/CDK6. HU was found to inhibit proliferation in all cell lines (IC_{50}: THP-1: 25-50 µM; MM6: 100-150 µM; U937: 500-750 µM) and in all primary cell samples tested (IC_{50}: 50-250 µM). Moreover, the CDK4/CDK6 inhibitors palbociclib, ribociclib and abemaciclib blocked cell proliferation in all cell lines (IC_{50}: 0.5–10 µM) and all primary cell samples examined (IC_{50}: 0.01–0.5 µM). Antiproliferative effects were accompanied by cell cycle arrest and induction of apoptosis. We next searched for suitable combination partners for CDK4/CDK6 inhibitors and identified ponatinib, a broad-spectrum multi-kinase inhibitor. Ponatinib was found to inhibit proliferation in all monoblastic cell lines (IC_{50}: 0.05-2.5 µM) and in primary leukemic cells (IC_{50}: 0.01-2.5 µM). The drug combinations HU+ponatinib, palbociclib+ponatinib, ribociclib+ponatinib and abemaciclib+ponatinib resulted in strong synergistic anti-proliferative effects in THP-1, MM6 and primary cells isolated from 2 CMML patients. Interestingly, the combinations HU+palbociclib, HU+ribociclib, and HU+abemaciclib also resulted in synergistic growth inhibition, a phenomenon, that can be best explained by different drug target interaction profiles. Finally, we were able to demonstrate, that the triple combination `HU+palbociclib+ponatinib´ exerts superior growth-inhibitory effects in THP-1 cells compared to all 2-drug combinations tested.
Summary/Conclusion: HU and specific CDK4/CDK6-targeting drugs inhibit the proliferation of CMML cells and synergize with ponatinib in producing growth-arrest. Targeting CDK4/CDK6 may be an interesting therapeutic approach in CMML. The clinical value of this observation remains to be tested in forthcoming studies.

EP903 THE PIVOTAL ROLE OF WEE1 AND PARP-1 IN MYELODYSPLASTIC SYNDROME (MDS): A NEW STRATEGY FOR THE TARGETED THERAPY OF MDS

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Background: Myelodysplastic syndrome (MDS) is the clonal myeloid neoplasm which is characterized by blood cytopenia and an increased risk of transformation to acute myelogenous leukemia (AML). About 30 to 40% of MDS patients develop AML and these patients are chemoresistance. Moreover, iron overload (IOL) often begins to develop in patients with MDS through repeated blood transfusion. Because the outcome of MDS is poor, alternative therapeutic strategies are required to improve the survival of MDS patients.
Aims: The inhibition of the DNA damage response pathway including Poly (ADP-ribose) polymerase 1 (PARP-1) in the treatment of cancer has recently approved in clinically. Wee1 is also an oncogenic nuclear kinase, which regulate the cell cycle as a crucial G2/M checkpoint. Because overexpression of Wee1 can be observed in various cancer types, Wee1 inhibitor could suppress MDS and AML cells in combination with PARP-1 inhibitor.
Methods: In this study, we investigated whether Wee1 was involved in MDS progress. We also investigated the efficacy of Wee1 inhibitor, MK-1775 and PARP1 inhibitor, talazoparib by using MDS and AML cell line, SKM-1, MDS-L, U937, THP-1, MV4;11 and osteoblastic cell line, MC3T3-E1.
Results: We first investigated the relationship between Wee1 expression and MDS patients by microarray gene expression data from the online Gene Expression Omnibus (GEO). Wee1 expression was increased in AML transformed cells and AML cells compared to refractory anemia with excess blasts cells (GSE14468). In contrast, PARP-1 expression was not changed. We next evaluated the effect of MK-1775 or talazoparib on proliferation of MDS and AML cell lines. 72 h treatment of MDS and AML cells were inhibited by MK-1775 or talazoparib in a dose dependent manner. Cellular cytotoxicity and caspase 3/7 activity was also increased. We next investigated the relationship between MK-1775 and talazoparib. We found that cotreatment with MK-1775 and talazoparib showed superior effect than single drug treatment. We found that cellular cytotoxicity, caspase 3/7 activity, intracellular reactive oxygen species (ROS) and beta-galactosidase staining positive cells were also increased after MK-1775 and talazoparib treatment. Cotreatment with MK-1775 and talazoparib reduced colony formation. Cell cycle analysis showed significant cell population in sub G1 and induced apoptosis. The study of gene expression profiling of cells revealed that the expression of anti-apoptotic genes such as *BCL11A* and *BCL2* were reduced. We also found γ-H2AX was increased and BCL2 was reduced after MK-1775 and talazoparib treatment by immunoblot analysis. The change of mitochondrial transmembrane potential is one of the early intracellular events to occur following induction of apoptosis. Mitochondrial membrane potential was changed after MK-1775 and talazoparib treatment. Wee1 shRNA transfected cells reduced cellular proliferation. Cell cycle analysis showed G2/M arrest. We found that sensitivity of talazoparib was increased and induced apoptosis in Wee1 shRNA transfected cells. We next examined IOL by using osteoblastic cell line, MC3T3-E1. The cellular proliferation was reduced by ferric ammonium citrate (FAC) in a dose dependent manner. Intracellular ROS was increased. Talazoparib treatment protected FAC mediated cell death.
Summary/Conclusion: Targeting a combination of DNA damage and cell cycle checkpoints enhances therapeutic efficacy, and is proposed as a novel strategy for high-risk MDS and AML. It also provides promising clinical relevance as a therapeutic candidate for MDS patients.

EP904 AZACITIDINE SEQUENCED WITH RIGOSERTIB DOWNREGULATES NEGATIVE REGULATORS OF HEMATOPOIESIS INCLUDING MULTIPLE MAPK PATHWAYS IMPACTING STEMNESS/DIFFERENTIATION OF MDS-L CELLS WITH CLINICAL IMPLICATIONS

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Background: Myelodysplastic Syndrome (MDS) is characterized by ineffective clonal hematopoiesis and bone marrow failure (BMF). Azacitidine (AZA), a hypomethylating agent is the standard of care for treatment of higher-risk MDS patients either alone or in combination with newer therapeutic options [Silverman LR, Cancer Medicine 2017]. Responses to AZA alone occur in 50% of pts with significant improvement in hematopoiesis [Fenaux et al Lancet Oncol 2009]. AZA improves overall survival of pts, yet despite this, 100% of pts ultimately fail treatment. AZA combined with Rigosertib (RIGO), a novel agent that downregulates the Ras pathway inhibits Ras/Raf signaling [Athuluri-Divakar SK, *et al.* Cell, 2016], yields a response rate of 54% in pts who were HMA failures [Navada SC, *et al.* EHA 2019]. Chronic activation of the MAPK pathway can activate inflammatory pathways suppressing hematopoietic function (Ramalingham Nat Comm 2020). Thus, understanding the mechanism of resistance and identification of targets which can reverse HMA failure and improve hematopoiesis in MDS pts is critical.
Aims: To assess the effects of modulation of the Ras pathway combined with a hypomethylating agent specifically on MAPK signaling, the stemness and differentiation of the MDS-L cell line.
Methods: We investigated the differential protein expression in response to different treatment (AZA, RIGO alone and sequential combinations RIGO/AZA; AZA/RIGO) *in vitro* in MDS-L cell line by Reverse Phase Protein Array (RPPA). Further, we also studied the functional role of these treatments on differentiation in MDS cells by growing cells on semi-solid media as well as by flow cytometry using various stem cell and differentiation markers (CD34, CD38, CD45, CD123).
Results: RPPA analysis indicated discrete responses to treatment in MDS-L cells. The response was prominent with differential expression of 43 proteins specifically in MDS-L cells treated with the sequenced combination of RIGO/AZA that include PIK3R1, AKT1, mTOR, p38 MAPK, PTEN, RPS6KA1 (Fold change (FC) < -2). All of these proteins are downregulated which suggests inhibition of PI3K, mTOR and MAPK signaling. Proteins belonging to metabolic pathways, including ACC1 and ACLY, were found to be downregulated, whereas proteins related to mitochondrial function and oxidative phosphorylation (OXPHOS) were upregulated (FC > 1.5/< -1.5) in cells treated with RIGO/AZA.In addition, we found that MDS-L cells represented both CD34+CD38+ and CD34+CD38- populations. AZA increases the percentage of CD34+CD38+, indicative of differentiation, whereas RIGO alone increased the percentage of CD34+CD38- cells, representing a primitive stem cell population. Based on the combination of differentiation markers, we observed that RIGO alone, and sequenced combination RIGO/AZA, impacts different progenitors such as granulocyte-macrophage progenitor (GMP), megakaryocyte erythroid progenitor (MEP), and multipotent progenitor (MPP). RIGO/AZA treatment showed a decrease in GMP, while the % of MEP was increased, as compared to other treatments.

Summary/Conclusion: In addition to inhibition of the PI3/AKT/mTOR and MAPK pathway, the RIGO/AZA combination impacts metabolic and differentiation pathways of MDS-L cells. RIGO alone appears to promote maintenance of a primitive stem cell population in a less differentiated state, while the RIGO/AZA sequenced combination appears to encourage cells to enter a cycling stage. Further studies are underway to determine the effect of metabolic changes on differentiation and maintenance of hematopoietic stem cells.

EP905 PHENOTYPIC AND GENETIC FEATURES OF MYELODYSPLASTIC SYNDROME (MDS) BONE MARROW (BM) DERIVED MESENCHYMAL STROMAL CELLS (MSC) FOR DISEASE PROGNOSIS AND THERAPY

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Background: Current strategies for MDS prognosis and therapy are primarily based on features of the hematopoietic system, but there is also a growing appreciation for the role that MDS-MSCs play in the development of the disease. The mechanisms by which MSCs contribute to different stages of MDS are not well understood but it is clear that there is a change in MSC biology during the course of MDS that may reflect the extent of progression or offer therapeutic opportunities for targeting the microenvironment.
To study this possibility, we retrospectively analyzed MSC samples from patients, focusing on how their characteristics change with risk classification and more importantly, with time to disease transformation. Our analysis identified gene cluster expression changes in patients that rapidly progressed to secondary leukemia and suggests targetable elements in MDS-MSCs that may help with slowing progression.
Aims: We aim to demonstrate that MDS-MSCs provide meaningful information that helps with disease prognosis and also highlight potential opportunities for targeting these MDS microenvironmental cells for therapy.
Methods: We investigated 34 MDS-BM samples with defined clinical outcomes. MSCs were derived from MDS-BM and cultured up to passage 3 for experiments. RNAseq, karyotyping, differentiation, immunophenotyping, secretome, co-culture LTC-IC assays were performed, and their results compared to discover changes related to disease progression. We also investigated the use of hypomethylating agents and MSC differentiation modulators as potential therapy for the MDS microenvironment *in vitro* or with pre-clinical animal models.
Results: RNAseq, secretome and functional assays show that certain unique characteristics group MDS-MSCs from patients with rapidly transforming disease better than other donor samples. These include gene and protein expression associated with changes in metabolism, hematopoietic support, angiogenesis, inflammation and ECM remodeling. Specifically, MDS-MSCs from rapidly transforming disease secreted elevated levels of macrophage inhibitory factor (MIF), pentraxin-3 (PTX3), VEGFa and reduced levels of SDF-1a. RNAseq analysis showed a cluster of >3000 genes separating samples from patients that transformed <2 years vs >5 years and implicated pathways in metabolism, ECM remodeling and angiogenesis. Finally, functional assays conducted on MDS-MSCs showed that >5 year survivors were more responsive to hypomethylating therapy and differentiation modulators as potential treatment for these stroma cells in reversing their dysplastic phenotype.
Summary/Conclusion: Analysis of MDS-MSCs may complement existing hematopoietic-based approaches for improving disease prognosis and may offer synergistic ways to slow disease progression.

EP906 PREVALENCE OF UBA1 MUTATIONS IN MDS/CMML PATIENTS WITH SYSTEMIC INFLAMMATORY AND AUTO-IMMUNE DISEASE

L.-P. Zhao [1,*], B. Schell [2], M. Sébert [1], M. Boy [3], P. Lemaire [2], S. Matis [2], L. Larcher [2], C. Chauvel [2], M. B. Dhouaieb [2], V. Bisio [3], C. Preudhomme [4], A. Marceau-Renaut [4], R. Itzykson [1], A. Mekinian [5], O. Fain [5], A. Toubert [3], P. Fenaux [1], N. Dulphy [3], E. Clappier [2], L. Adès [1]

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Background: Systemic inflammatory and auto-immune diseases (SIAD), often including relapsing polychondritis (RP), are observed in 25% of patients with MDS or CMML, although the causal relationship is unclear. We previously reported in 85 MDS/CMML patients with SIAD (Zhao *et al*, Leukemia 2021) that *TET2*, *IDH1/2* and *SRSF2* mutations were more frequent in those patients compared to a control cohort of MDS/CMML patients without SIAD, and correlated with naïve/memory T cell imbalance and defects in immune checkpoint receptors expression. Recently, somatic mutations in the *UBA1* gene were described, defining a novel disease called VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (Beck *et al*, NEJM 2020). 24% of the patients with VEXAS syndrome were reported to have MDS, and 60% had a previous diagnosis of RP.
Aims: To explore the prevalence of *UBA1* mutations in patients diagnosed with MDS/CMML and SIAD
Methods: From our cohort of 85 patients with MDS/CMML and SIAD, all male patients (n=45) for whom material was available (n=33) were analyzed for the presence of *UBA1* mutations. DNA was obtained from peripheral blood or bone marrow mononuclear cells and Sanger sequencing of exons 2 and 3 as well as exon-intron junctions was performed.
Results: The 33 patients with SIAD included 6 MDS with excess blasts, 21 MDS without excess blasts and 6 CMML. 3 of them had *UBA1* mutations. All 3 patients had MDS without excess of blasts, and no CMML patient had *UBA1* mutation. Review of their bone marrow smears showed numerous vacuoles in myeloid and erythroid precursors, which were however not specific of *UBA1* mutated cases of MDS. Patients #1 and #2 had normal karyotype while patient #3 had 9q deletion (**Table 1**). Mutations in *UBA1* affected methionine-41 in patient #2 and patient #3 as reported by Beck *et al*, while patient #1 had a newly described mutation of a splice site predicted to have similar consequence on UBA1 protein (Bourbon *et al*. Blood 2021). Patient #3 had also somatic mutations in *DNMT3A* and *TP53* (VAF 11% and 2%, respectively), while no other mutation was detected in patients #1 and #2 in our next-generation sequencing panel including 80 genes involved in myeloid malignancies.

3 patients in our MDS/CMML SIAD cohort had relapsing polychondritis, and 2 of them (patients #1 and #2) had *UBA1* mutations. The last patient with *UBA1* mutation (#3) had giant cell arteritis (GCA) (out of 7 GCA diagnosis in our SIAD cohort). All 3 patients with *UBA1* mutation had steroid refractory SIAD and were heavily treated with other immunosuppressive therapies including methotrexate, azathioprine or cytokine targeting agents. Patients #1 and #3 received azacytidine (AZA) for their SIAD, based on our previous experience (Fraison *et al*. Leukemia Research

Table 1: Patients main SIAD and hematological characteristics

Variables	Patient #1	Patient #2	Patient #3
Age at MDS/CMML diagnosis	74	78	66
Sexe	Male	Male	Male
SIAD features	relapsing polychondritis, Sweet syndrome	relapsing polychondritis, Hashimoto	giant cell arteritis
Hematological diagnosis	MDS SLD	MDS MLD	MDS SLD
Karyotype	normal	normal	Del 9q
Mutations in myeloid genes NGS	none	none	*DNMT3A* (VAF 11%), *TP53* (VAF 2%)
***UBA1* mutation**	c.118-1G>C	c.T122C:p.Met41 Thr	c.A121G:p.Met41Val
IPSS-R category	low	high	high

Values are presented as median [interquartile range] or number (%). MDS: Myelodysplastic Syndromes; CMML: Chronic Myelomonocytic Leukemia; SIAD: Systemic and Inflammatory Autoimmune Disease; SLD: Single Lineage Dysplasia; MLD: Multilineage Dysplasia; IPSS-R: Revised International Prognosis Scoring System;

2016), with a partial response allowing dose reduction of steroids. At last follow up, none of the 3 patients with *UBA1* mutation had MDS progression, and patient #2 died from a stroke 2.4 years after MDS diagnosis.

Summary/Conclusion: Our retrospective study represents the first assessment of *UBA1* mutation among patients with myeloid malignancies associated with SIAD. The low prevalence of *UBA1* mutations in our cohort suggests that other pathophysiological mechanisms may drive inflammation in a majority of MDS/CMML patients with associated SIAD, including mutations in epigenetic regulators *TET2/IDH* and *SRSF2* as we previously proposed.

EP907 MESENCHYMAL STROMAL CELLS AS A POTENTIAL THERAPEUTIC TOOL IN ENHANCING RESIDUAL HEALTHY HAEMATOPOIESIS IN LOW-RISK MDS PATIENTS

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Background: Mesenchymal stromal cells (MSC) play a key role in the pathophysiology of MDS. Thus, MSC in MDS patients are abnormal and characterised by poor hematopoietic support capacity and their dysfunction contributes to the expansion of the malignant clone.
Aims: Considering the involvement of MSC in the pathophysiology of MDS, we aimed to study whether healthy MSC might have therapeutic potential in the positive regulation of residual healthy hematopoiesis in low-risk MDS patients.
Methods: Bone marrow (BM) samples from MDS patients (n=21), all from the low-risk MDS-DM category [WHO 2017] (IPSS: low/int-1 risk and IPSS-R: very low to intermediate) of new diagnosis and not exposed to haematological treatment, as well as from healthy donors (HD) (n=13), were analysed. Mononuclear cells (MNC) and MSC were isolated and expanded according to standard methodology up to 3rd-4th pass.
A short-term co-culture model was established in transwell (MNC:MSC ratio of 3:1, for 48h) with different cell combinations:
- Control MDS-MNC (basal MNC, not co-cultured).
- Control HD-MNC (basal MNC, not co-cultured)
- Group 1.1 - MDS-MSC co-cultured MDS-MNC
- Group 1.2 - MDS-MSC co-cultured HD-MNC
- Group 2.1 - HD-MSC co-cultured MDS-MNC
- Group 2.2 - HD-MSC co-cultured HD-MNC
- Group 3 - MDS-MSC co-cultured Mix-MNC (MDS+HD)
- Group 4 - HD-MSC co-cultured Mix-MNC (MDS+HD)

After 48h of culture, MNC from each group were collected and clonogenic assays were performed, from 5000 MNC seeded on semi-solid methylcellulose medium with EPO, at 37°C and 5% CO_2. After 14 days of incubation, CFU-erythroid (CFU-E) and CFU-granulomonocytic (CFU-GM) were counted (CFU/5000 MNC).
Results: In basal state (without co-culture with MSC) MDS-MNC showed a deficient formation of CFU-E and CFU-GM compared to HD-MNC, as well as an imbalance between the number of CFU and clusters, which translates into defective hematopoiesis in MDS patients (not shown).
To determine the effect of the addition of MSC on MNC of MDS patients (groups 1.1 and 2.1), we analysed the ratio between CFU formed by MDS-MNC co-cultured with MSC (MDS or HD) versus basal MDS-MNC (not co-cultured). We observed that the addition of HD-MSC trends to increase erythroid colony formation (Fig. 1-A) and that CFU-granulomonocytic were significantly enhanced by addition of MSC (Fig. 1-B).
In an environment simulating the diseased condition (groups 3 and 4), with mixed MDS and HD MNC (residual hematopoiesis), a significant recovery of hematopoietic capacity occurs with the addition of MSC,
Summary/Conclusion: Taken together, our results suggest that HD-MSC enhances MNC clonogenic capacity, especially when co-cultured with mixed MDS and HD MNC. Considering that this situation mimics what happens in lower-risk MDS patients, where often normal and dysplastic hemopoiesis coexists, HD-MSC could be a potential therapy to rescue residual healthy hematopoiesis and improve hematopoietic potential in these patients.

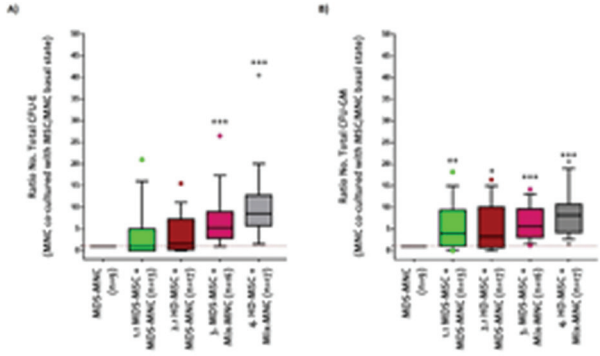


Figure 1. Ratio between CFU formed from MDS-MNC co-cultured with MDS-MSC or HD-MSC (as indicated in each study group) and CFU formed from basal state MNC-SMD (not co-cultured), in methylcellulose medium supplemented with EPO. **A)** CFU-E ratio, **B)** CFU-GM ratio. Data expressed as median ± range of the n indicated in each case. Mann-Whitney U test: * = p < 0.05; ** = p < 0.01; *** = p < 0.001; ns = not significant.

EP908 SIMPLE FLOW CYTOMETRY IMMUNOPHENOTYPING APPROACH PREDICTS THE DEVELOPMENT OF MYELOID NEOPLASMS IN PATIENTS WITH CCUS

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Background: Myeloid neoplasms (MN) are diagnosed by a combination of clinical, morphologic and genetic findings. Aberrant immunophenotype of myeloid cells by flow cytometry immunophenotyping (FCIP) is frequently associated with MN. However, by itself FCIP is insufficient for establishing the diagnosis of MN due to (I) lack of specificity and (II) marked variability in appraches by different laboratories. We have previously shown that abnormalities of CD13/HLA-DR expression on CD34-positive blasts could be a sensitive and specific method for a simple assessment of myeloid dysmaturation.
Aims: To determine whether a simple immunophenotyping approach using aberrant expression of CD2, CD7 and CD56 on myeloid blasts, and qualitatively abnormal FCIP patterns on CD13/HLA-DR and CD13/CD16 plots could predict development of MN in a subpopulation of patients with clonal cytopenia of undetermined significance (CCUS).
Methods: Bone marrow aspirates were analyzed using 2 8-color FCIP tubes (see table below). A total of 500,000 events were collected per tube, using BD Canto II instruments. The data were analyzed using Kaluza software. CD34+CD45dim blasts were evaluated for the aberrant expression of CD2, CD7 and CD56 (cut-offs 10%, 30%, and 10%, respectively, were established previously by adding 2 SD to the mean of the expression in the normal cohort. In addition, CD34-positive blasts were evaluated for the aberrant expression pattern of CD13/HLA-DR, as previously described [AJCP (2014) 142:292]. Aberrancies of granulocyte maturation were evaluated on the CD13/CD16 plot.
Relevant clinical and laboratory data, including CBC and the presence of genetic abnormalities, were extracted from the electronic medical record. Statistical analysis was done using R statistical software.
Results: Out of 86 patients with CCUS, 21 developed MN over the follow-up time period (median follow-up 28 months). FCIP abnormalities detected at diagnosis of CCUS were predictive of the future developmen of MN, with the most significant abnormalities being: (I) aberrant expression of CD7 on CD34-positive myeloid blasts (p=0.014, HR 3.74), (II) aberrant pattern of CD13/HLA-DR expression on CD34-positive myeloid blasts (p=0.019, HR 2.59), and (III) presence of multiple (>1) FCIP abnormalities (p=0.003, HR 1.90).

	FITC	PE	PercP Cy5.5	Pe-Cy7	APC	APC-H7	V450	V500
Tube 1	HLA-DR	CD13	CD34	CD33	CD117	CD16	CD15	CD45
Tube 2	CD2	CD7	CD34	CD56	CD36	CD64	CD38	CD45

Summary/Conclusion: A simple FCIP approach, which includes assessment of CD13/HLA-DR pattern on CD34-positive myeloid blasts, can be useful in predicting the development of MN in CCUS patients.

Myelodysplastic syndromes - Clinical

EP909 VENETOCLAX AND AZACITIDINE COMBINATION IN CHEMOTHERAPY INELIGIBLE PATIENTS WITH THERAPY-RELATED MYELOID NEOPLASMS, ANTECEDENT MYELODYSPLASTIC SYNDROMES OR MYELODYSPLASTIC/ MYELOPROLIFERATIVE NEOPLASMS

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Background: Patients (pts) with therapy-related myeloid neoplasms (tMN), antecedent myelodysplastic syndrome, or antecedent myelodysplastic/myeloproliferative neoplasms (A-MDS/MPN) may have poor outcomes due to age and adverse genetic/karyotypic features. In the VIALE-A study, pts with tMN and A-MDS/MPN unfit for intensive chemotherapy treated with venetoclax (Ven) and azacitidine (Aza) demonstrated superior response rates and overall survival (OS) than Aza alone.
Aims: We describe the efficacy and safety of Ven+Aza among pts with tMN and A-MDS/MPN.
Methods: Data were pooled from pts enrolled in VIALE-A (NCT02993523) comparing pts who received Ven+Aza or placebo (Pbo)+Aza and a prior phase 1b study (NCT02203773) where pts received Ven+Aza. Enrolled pts were ≥18 years, treatment-naïve with no prior exposure to hypomethylating agents, and ineligible for intensive chemotherapy. Pts on Ven+Aza received Ven 400 mg orally (days 1–28) and Aza (75 mg/m^2; days 1-7/28-day cycle). Composite complete remission rate (CRc; complete remission [CR] + CR with incomplete hematologic recovery [CRi]), duration of response (DoR), and OS were assessed. Disease assessments were per modified International Working Group response criteria for AML.
Results: In this pooled analysis, tMN was observed in (Ven+Aza/Pbo+Aza) 31/9 and A-MDS/MPN in 59/26 pts. Poor-risk cytogenetics were observed in 18 (58%)/6 (67%) with tMN (5 or 5q deletion [del]: 4/1; 7 or 7q del: 6/1; complex [≥ 3 clonal abnormalities]: 10/ 4), and 19 (32%)/13 (50%) with A-MDS/MPN (5 or 5q del: 10/ 5; 7 or 7q del: 6/ 1; complex: 14/ 9). *TP53* mutation was observed in 5 /3 pts with tMN and 8/0 pts with A-MDS/MPN. Pts with tMN received a median (Ven+Aza/Pbo+Aza) of 5/4 cycles of treatment. CRc was achieved in19 (61%)/1 (11%). The mDoR was not reached (NR) (95% CI: 17.8, NR)/8.5 (NR, NR) months. The mOS was 16.4 (95% CI: 4.1, NR)/11.3 (0.6, 17.5) months. Pts with A-MDS/MPN received a median (Ven+Aza/Pbo+Aza) of 9/5 cycles of treatment. CRc was achieved by 39 (66%)/7 (27%) pts with mDoR of 17.3 (95% CI: 9.6, NR)/5.8 (1.1, NR) mos. The mOS was 15.9 (95% CI: 11.5, NR)/10.1 (4.7, 14.5) mos. Common grade≥3 adverse events (Ven+Aza/Pbo+Aza) were febrile neutropenia (tMN: 39%/11% and A-MDS/MPN: 36%/12%) neutropenia (tMN: 29%/33%; A-MDS/MPN: 39%31%), and thrombocytopenia (tMN: 32%/33%; A-MDS/MPN: 39%/62%).
Summary/Conclusion: Ven+Aza compared to Aza monotherapy resulted in higher CRc rates with longer DoR and median OS among treatment-naïve pts with tMN and A-MDS/MPN ineligible for intensive chemotherapy. The safety profile was similar to overall pts with the Ven+Aza combination. Outcomes by cytogenetic and molecular risk-groups will be presented.

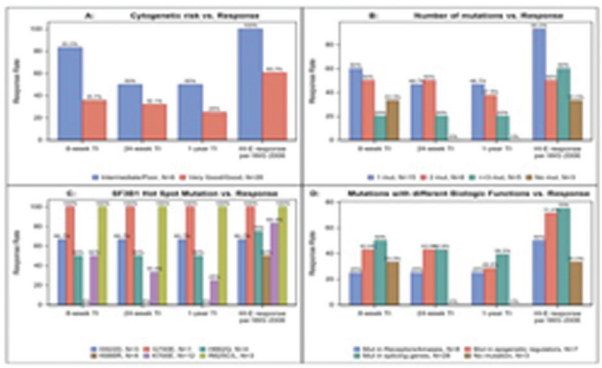
EP910 EFFICACY OF IMETELSTAT IS INDEPENDENT OF MOLECULAR SUBTYPES IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESA)

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Background: IMerge (MDS3001, NCT02598661) is a Phase 2/3 global study of imetelstat, a first-in-class telomerase inhibitor, for red blood cell (RBC) transfusion dependent (TD) non-del(5q) patients (pts) with ESA-R/R LR-MDS. Phase 2 results indicated that imetelstat achieved durable transfusion independence (TI) with a manageable safety profile (Steensma ASH 2018; Fenaux EHA 2019; Steensma JCO 2020). With a median follow-up of 24 months for Phase 2, 42%, 32% and 29% of 38 pts achieved ≥8-week (w), ≥24-w and 1-year (y) TI, respectively (Platzbecker EHA 2020).
Aims: To evaluate clinical efficacy of imetelstat in molecularly defined subtypes based on cytogenetic and mutation profiles.
Methods: At screening, bone marrow aspirates were used for cytogenetic analysis by karyotyping. Peripheral blood samples were collected to analyze mutations by next-generation sequencing using the Illumina TruSight Myeloid Panel of 54 genes. Correlation analyses between molecular profiles and clinical efficacy, including TI ≥8-w, ≥24-w, ≥1-y, and hematologic improvement-erythroid (HI-E) response per International Working Group 2006 guidelines, were performed for pts in the Phase 2 part of IMerge study.
Results: Of 34/38 pts with baseline cytogenetic results, 28 (82.4%) pts had very good/good and 6 (17.6%) pts had intermediate (int)/poor cytogenetic risk (n=3 trisomy 8, n=1 for del(7q), inv(3)/t(3q) and complex karyotype). Though pts with int/poor risk had higher TI and HI-E response rates compared with pts with very good/good risk pts, no statistically significant difference was observed: 83.3% (5/6) vs 35.7% (10/28) had ≥8-w TI; 50% (3/6) vs 32.1% (9/28) had ≥24-w TI; and 50% (3/6) vs 25% (7/28) had ≥1-y TI; 100% (6/6) of pts with int/poor risk group vs 60.7% (17/28) achieved HI-E response (Fig. A).
Of 31/38 pts with baseline mutation data, 28 (90.3%) pts had at least one mutation, among which 15 (53.6%), 8 (28.6%) and 5 (17.9%) pts had 1, 2 and ≥3 mutations, respectively. The ≥8-w TI rate was 60%, 50% and 20% respectively, ≥1-y TI rate was 46.7%, 37.5% and 20% respectively, and HI-E response rate was 93.3%, 50% and 60%, respectively (Fig. B). Three pts (9.7%) had no mutation detected, of which 1 pt had 8-w TI and HI-E response. The most frequently mutated gene was SF3B1 (87.1%, n=27), consistent with the predominance of ring sideroblast phenotypes (n=23); followed by DNMT3A (19.4%), KIT (16.1%) and RUNX1 (6.4%), all coexisting with SF3B1 mutation. Among pts with SF3B1 mutation, hot spot mutations were detected: 3 (11.1%) E622D, 3 (11.1%) R625C/L, 4 (14.8%) H662Q, 4 (14.8%) K666R, 12 (44.4%) K700E and 1 (3.7%%) G740E, respectively. Durable TI was observed in pts with these hot spot mutations except K666R, and HI-E response was seen in pts with all hot spot mutations (Fig. C). Analysis of clinical responses across the mutation defined subgroups on genes involved in different biological functions, including splicing process, epigenetic regulation, or receptors/kinases, were performed and ≥8-w TI was 50.0%, 42.9% and 25.0%; ≥24-w TI was 42.9%, 42.9% and 25.0%; ≥1-y TI was 39.3%, 28.6% and 25.0%, and HI-E responses were 75.0%, 71.4% and 50.0%, respectively (Fig. D).
Summary/Conclusion: Imetelstat demonstrated clinical efficacy across different molecularly defined subgroups including in pts with poor prognosis in heavily transfused LR-MDS ESA-R/R, who have limited treatment options. Phase 3 of IMerge, a placebo-controlled trial of imetelstat, is ongoing to further confirm the efficacy, safety, and biomarker results.

Figure: Response rate across different molecular defined subgroups

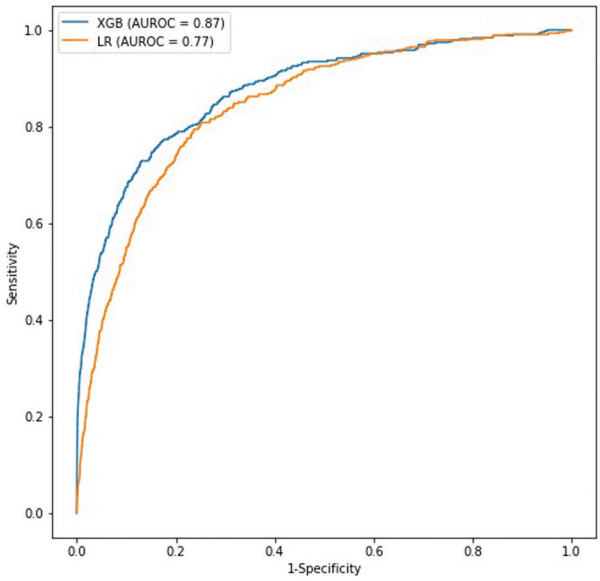


EP911 A MACHINE LEARNING APPROACH TO PREDICTING RISK OF MYELODYSPLASTIC SYNDROME

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Background: Myelodysplastic syndrome (MDS) is an underdiagnosed preleukemic condition mainly affecting patients over the age of sixty. In approximately one-third of patients, MDS evolves into acute myeloid leukemia (AML), which is highly aggressive and can be fatal. Accurate and early MDS diagnosis can allow physicians to monitor patients and provide early treatment, which may delay advancement of MDS and improve quality of life in many patient populations. However, MDS is often unrecognized by primary care physicians and is difficult to distinguish from other causes of bone marrow failures, cytopenias, and other clonal stem cell disorders.
Aims: The purpose of this study is to develop a machine learning algorithm (MLA) for the prediction of MDS one year prior to clinical diagnosis of the disease.
Methods: Retrospective analysis was performed on 790,470 patients over the age of 45 using electronic health records (EHR) drawn from over 700 healthcare sites across the US between 2001 and 2019. Two models, including a gradient boosted decision tree model (XGBoost) and a logistic regression model, were trained to predict onset of MDS using vital signs, lab results and demographics information from up to 2 years of patient EHR data. The models did not require blast percentage and cytogenetics as inputs. Retrospective predictions were made 1 year prior to MDS diagnosis as determined by International Classification of Diseases (ICD) codes. Performance was assessed with regard to area under the receiver operating characteristic curve (AUROC) and a SHAPley analysis of feature importance.
Results: On a hold-out test set, the XGBoost model achieved an AUROC value of 0.87 when tested for prediction of MDS one year prior to MDS diagnosis, at a sensitivity of 0.70, and specificity of 0.88. Age, hematocrit, red blood cell count, and peripheral oxygen saturation were found to be the most important features for MDS prediction. The XGBoost model was compared against a logistic regression model. The logistic regression achieved an AUROC of 0.77, at a sensitivity of 0.75 and specificity of 0.79. Receiver operating characteristic (ROC) curves and comparison of AUROC of the XGBoost (XGB) and logistic regression (LR) models are shown in figure below.



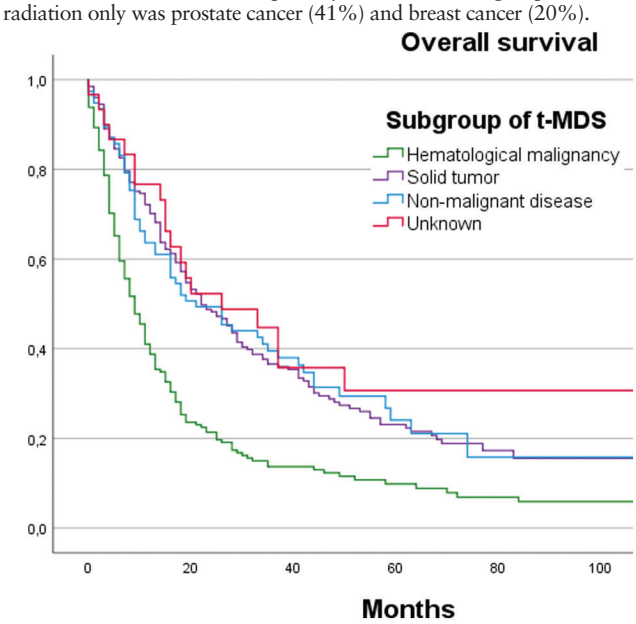
Summary/Conclusion: Machine learning methods can be used to accurately predict MDS one year prior to diagnosis using current standard procedures. The algorithm only utilized readily available EHR data, without requiring blast percentages or cytogenetics. In clinical practice, use of such a tool may allow for early diagnosis of MDS and more appropriate treatment admini stration.

EP912 THERAPY-RELATED MDS; A WIDE DEFINITION THAT NEEDS NARROWING

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Background: MDS patients with a history of chemotherapy and/or radiation therapy for a malignant or non-malignant disease are considered to have therapy-related MDS (t-MDS). This group is generally described to constitute 15-20% of all MDS cases and to have more adverse prognostic factors such as transfusion dependency and high risk cytogenetics. They also have shorter survival and are often treated aggressively if possible. For t-MDS patients only treated with radiation, the data is conflicting
Aims: The aims of this study were to characterize t-MDS in a population-based setting, to compare clinical characteristics and outcomes between t-MDS and de novo MDS (d-MDS), and between subgroups of t-MDS.
Methods: All patients aged 16 years or older diagnosed with MDS and MDS/MPN 2009-2017 and reported to the nationwide Swedish MDS-register were included (n= 3379). All patients treated with chemotherapy and/or radiation prior to the diagnosis of MDS were considered to have t-MDS.
Data on previous cancer diagnoses was obtained from the Swedish Cancer Registry and data on non-malignant diseases from the National Patient Register. In cases with multiple malignant diseases preceding MDS, the most likely one was chosen based on latency time and treatment traditions. Information was obtained from the Swedish Cause of Death Register up to November 20, 2019 to calculate overall survival (OS).
To assess the distribution of baseline patient characteristics, chi-squared test and Wilcoxon rank sum test was used. OS was analysed using the Kaplan–Meier approach with log-rank test used to compare OS.
Results: The median survival of the 14% (n=486) of patients classified as t-MDS was shorter compared to d-MDS, 16 vs 28 months (p=0.000). As a group, patients with t-MDS had more high risk cytogenetics, more transfusion dependency and a higher IPSS-R score compared to d-MDS. Patients previously treated with both chemotherapy and radiation and chemotherapy alone had a shorter median survival as compared to those treated with radiation only, 10 and 14 vs 32 months, respectively (p=0.000). Patients with a previous non-malignant disease or a previous solid tumour had a longer survival compared to patients with a previous hematological malignancy, 21 and 22 vs 9 months, respectively (p=0.000). To have the primary malignancy as an underlying cause of death was more common in patients with a previous hematological malignancy (43%) compared to patients with a previous solid malignancy (17%).
In the group of t-MDS patients previously treated with radiation only, known prognostic factors such as IPSS-R score, cytogenetics and transfusion dependency had a significantly lower risk profile compared to other groups of t-MDS. The most common primary condition in the group treated with radiation only was prostate cancer (41%) and breast cancer (20%).



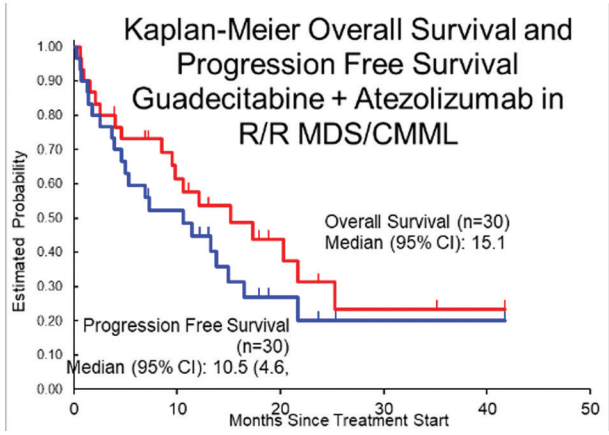
Summary/Conclusion: Using Swedish register data we have characterized a large cohort of t-MDS. These patients have a significantly shorter survival as compared to d-MDS, but the survival difference is highly heterogeneous among subgroups. Patients previously treated with radiation only, have clinical characteristics and survival comparable to d-MDS and we question if these should be considered t-MDS. Patients with a previous hematological malignancy have a dismal prognosis, in part because of mortality associated with the primary condition.

EP913 RESULTS OF A PHASE I/II CLINICAL TRIAL COMBINING GUADECITABINE WITH ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY MYELODYSPLASTIC SYNDROME (MDS) OR CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

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Background: Median overall survival after failure of hypomethylating agents (HMAs) for patients with myelodysplastic syndrome (MDS) is 5-6 months. Preclinical and clinical data suggest that myeloblasts express PDL-1 and that HMAs induce T-cell PD-1 expression, which may promote resistance or relapse despite effective demethylation.
Aims: To determine the safety profile, efficacy and impact on overall survival of atezolizumab (atezo), a PDL-1 inhibitor, in combination with the decitabine and deoxyguanosine dinucleotide guadecitabine (guaD), for patients with MDS and CMML treated after failure of an approved HMA.
Methods: We conducted a Phase I/II clinical trial for adult patients with relapsed or refractory, intermediate (3+) or high-risk MDS by the revised international scoring system (IPSS-R), or CMML, after failure of a standard HMA. The primary endpoint of Phase I was to determine a safe dose of guaD in combination with a fixed dose of atezo. A 3x3 dose escalation design for guaD was used, beginning with 30mg/m2 (Dose level -1) SC days 1-5 with atezo 840mg IV days 8 and 22 of a 28-day cycle. Escalation to the recommended dose of guaD, 60 mg/m2 (Dose level 1), was allowed if no dose-limiting toxicities (DLTs) were observed at Dose level -1. If no DLTs were observed at Dose level 1, 3 additional patients were treated to confirm safety. Phase II was planned to include 30 patients treated at Dose level 1, with the primary endpoint of efficacy measured by overall response rate (ORR), based on the 2006 IWG Response Criteria for MDS. Overall survival (OS) was a secondary endpoint.
Results: Between June 2017 and October 2020, 33 patients from 4 centers enrolled in the study. Median age was 73 (54-85) years, 22 (67%) were male, 11 (33%) had IPSS-R intermediate-risk and 20 (64%) had high- or very high risk MDS, 2 had CMML, and two-thirds were refractory to their prior HMA. No DLTs occurred in 3 patients treated at Dose level -1. No DLTs were seen among 6 patients treated at Dose level 1, so 24 additional patients were treated. The most common grade 4 toxicities at Dose level 1, regardless of attribution, were thrombocytopenia in 11 (36.7%), neutropenia in 10 (33.3%), and anemia in 5 (16.7%) patients. There were 4 grade 3 events considered autoimmune and attributed to atezolizumab – 2 encephalitis and 2 pneumonitis. Four deaths occurred while on therapy, including 1 patient with sepsis and brainstem herniation after lumbar puncture; 11 patients came off treatment due to disease progression, 3 due to clinical deterioration, 2 at their own request, 4 at physician's discretion, and 5 patients due to unacceptable toxicity. A median of 5 cycles (1-21) were administered and median follow-up is 25.3 (3.9-41.7) months with 4 patients still on treatment. ORR is 30% (CI 16-41%), with 2 CR (6%), 4 marrow CR (12%), 1 PR and 3 (9%) Hematologic Improvement. Median overall survival is 15.1 (8.5, 21.6) months among the 30 patients treated at Dose level 1, 17.3 (8.5, 27.3) months among those refractory to prior HMA and 10.5 (4.4, 21.6) months in patients who responded and then relapsed after prior HMA (p=0.58). There was a trend for better survival among females, 21.6 (10.5, 41.7+) vs 12.1 (2.5, 20.3) months (p=0.068).



Summary/Conclusion: In this phase I/II trial of patients with higher risk, predominantly HMA-refractory MDS, guadecitabine with atezolizumab yielded modest IWG responses, but overall survival appears better than predicted for this patient population, particularly among women. Ongoing correlative work will investigate immunologic characteristics of long-term survivors.

EP914 ASXL1 MUTATIONS PREDICT A POOR RESPONSE TO DARBEPOETIN ALFA IN ANEMIC PATIENTS WITH LOW-RISK MDS: A MULTICENTER, PHASE II STUDY

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Background: Myelodysplastic syndromes (MDS) develop and progress as a result of accumulation of genetic mutations.
Aims: This multicenter, open-label, phase II study examined impact of gene mutations on the effect of darbepoetin alfa (DA) for anemia. Death within 1 year and progression to acute myeloid leukemia (AML) were also examined.
Methods: DA ≤240 μg was administered once weekly for 16 weeks to DA-naive, low-risk MDS (low or Intermediate-1 [Int-1] risk defined by the International Prognostic Scoring System [IPSS] risk classification) patients with anemia. DNA was extracted from the peripheral blood of patients, and presence of previously reported high-frequency gene mutations in MDS (*SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, etc.) was analyzed by next-generation sequencing. Primary endpoint was association between frequently observed mutated genes and therapeutic effect of DA (IWG criteria 2006 (HIE)) at 16 weeks. A secondary endpoint was survival analysis results for death and progression to AML within

one year after 16 weeks of treatment. For AML, progression to AML and subsequent death were stated as events, and the patients without confirmed progression to AML were censored at the date of last known survival. For overall survival, death from any cause was considered an event, and for the survival cases, the study was terminated at the date of last known survival.
For the primary endpoint, relative risk and 95% confidence intervals (CI) were calculated using Wilson's score method; statistical significance was assessed using Pearson's chi-square test. Multivariate analysis was performed by adding baseline erythropoietin (EPO) levels (low: <91.8, high: 91.8+ [mIU/mL]) to the explanatory variables, and odds ratio was calculated using logistic regression model. Survival curve was estimated using Kaplan-Meier method and median survival time (MST) was calculated using Brookmeyer and Crowley method.
Results: Of the 85 patients enrolled between August 2016 and May 2019, 6 patients (4 were judged ineligible and 2 discontinued the study prior to the start of treatment) were excluded, and 79 subjects were included in the analysis. Of 79 subjects, 52 (65.8%) were male (median age 77.0 [29-90] years). IPSS risk was low in 27 (36.7%) and Int-1 in 50 (63.3%) subjects. The frequently mutated genes (≥10%) were *SF3B1* (24, 30.4%), *TET2* (20, 25.3%), *SRSF2* (10 cases, 12.7%), *ASXL1* (9, 11.4%), and *DNMT3A* (8, 10.1%). Overall response rate was 70.9%. Univariate logistic regression analaysis did not show any significant association between these mutations and therapeutic efficacy of DA. The same results were obtained when the analysis was limited to red blood cell transfusion-dependent subjects (n=15). After adjusting against baseline EPO values, mutations of *ASXL1* gene were associated with significantly worse response (odds ratio 0.180 [0.035-0.928], p = 0.040). Twenty-three deaths (29.1%) were observed, and the median survival time (95% CI) from the start of treatment to confirmed AML or death was 41.3 months (30.6 months - Not reached). Fifty-eight patients completed the 16 weeks of treatment without progression to AML. For these 58 patients, median survival time (95% CI) from the completion of 16 weeks of treatment was not reached (30.9 months – not reached) and the rate of survival without progression to AML within one year was 83.5% (70.7 – 91.1 %).
Summary/Conclusion: The results of this exploratory study suggest that the presence of *ASXL1* gene mutations may result in poor response to the anemic treatment with DA in low-risk MDS.

EP915 BENEFIT OF CONTINUING LUSPATERCEPT THERAPY IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES WHO DID NOT ACHIEVE RED BLOOD CELL TRANSFUSION INDEPENDENCE BY WEEK 25 IN THE MEDALIST STUDY

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Background: MEDALIST (NCT02631070) is an ongoing, randomized, placebo-controlled phase 3 trial evaluating the efficacy and safety of luspatercept, the first and only erythroid maturation agent, in patients with anemia due to lower-risk myelodysplastic syndromes (LR-MDS) with ring sideroblasts. A greater proportion of patients receiving luspatercept than placebo achieved the primary endpoint of red blood cell transfusion independence (RBC-TI) for ≥8 weeks during Weeks 1–24 (Fenaux P, et al. *N Engl J Med* 2020;382:140-151). However, for patients not achieving the primary endpoint during the first 24 weeks, the value of continuing luspatercept treatment is not yet well understood.
Aims: To evaluate the clinical benefit of continuing luspatercept treatment beyond 24 weeks in patients not achieving the RBC-TI primary endpoint during the first 24 weeks of the MEDALIST study.
Methods: Eligible patients were aged ≥18 years; were refractory, intolerant, or unlikely to respond to erythropoiesis-stimulating agents; and required regular RBC transfusions (≥2 units/8 weeks) in the 16 weeks prior to randomization. Overall, 229 patients were randomized 2:1 to receive either luspatercept (n=153) or placebo (n=76) every 3 weeks through the clinical assessment visit at Week 25, defined as 24 calendar weeks after the first dose, regardless of dose delays. Patients who did not achieve RBC-TI for ≥8 weeks on luspatercept by Week 25 but continued treatment were included in this analysis; the data cutoff was July 1, 2019. For this analysis, transfusion burden, serum ferritin (SF) levels, and hematologic improvement-erythroid (HI-E) response were assessed every 24 weeks. HI-E response was defined as a reduction in RBC transfusions of ≥4 units/8 weeks (for patients with baseline RBC transfusion burden of ≥4 units/8 weeks) or as an increase in hemoglobin level of ≥1.5 g/dL over 8 weeks (for patients with baseline RBC transfusion burden of <4 units/8 weeks).
Results: Of the patients receiving luspatercept, 68 did not meet the primary endpoint during the first 24 weeks and continued treatment. During Weeks 25–48, 16.2% (n=11/68) of these patients achieved RBC-TI for ≥8 weeks for the first time, and a mean change from baseline of –1.3 RBC units transfused was achieved in 36 pts. 44.1% (n=30/68) of patients who did not meet the primary endpoint achieved any degree of reduction in SF levels from baseline during Weeks 25–48, while 17.9% (n=7/39) shifted from a SF level ≥1,000 µg/L at baseline to <1,000 µg/L. During Weeks 1–48, 60.3% (n=41/68) of patients who did not meet the primary endpoint achieved ≥50% reduction in RBC transfusion burden for ≥8 weeks from baseline and 47.1% (n=32/68) achieved HI-E response. Over the entire treatment period up to the data cutoff, 60.3% (n=41/68) achieved ≥50% reduction in transfusion burden for ≥8 weeks from baseline, 22.1% (n=15/68) achieved RBC-TI for ≥8 weeks, and 48.5% (n=33/68) achieved HI-E response.
Summary/Conclusion: A considerable proportion of patients with LR-MDS in the MEDALIST study who did not achieve the primary endpoint, but continued to receive luspatercept beyond 24 weeks of treatment, experienced a broad range of clinical improvements, including reduced transfusion burden, reduced SF levels, and even TI.

EP916 PREDICTORS OF HYPOMETHYLATING AGENT DISCONTINUATION AMONG PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES

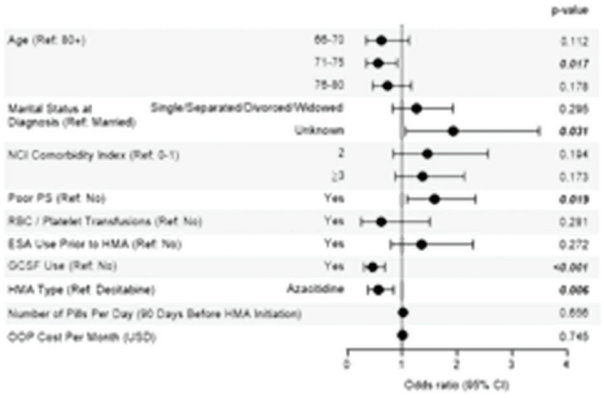
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Background: Real-world studies have shown that persistence with intravenous (IV) and subcutaneous (SC) hypomethylating agents (HMAs) among patients with higher-risk myelodysplastic syndromes (MDS) is poor, with over one-third of treated patients receiving <4 cycles or having a ≥90-day gap in therapy, despite recommendations for at least 4-6 cycles to elicit response in the absence of progression/unacceptable toxicity. Survival outcomes have also been shown to be worse, and direct medical costs higher, among HMA non-persistent versus persistent patients.
Aims: To explore factors associated with early discontinuation of HMA therapy among patients with higher-risk MDS in the real-world setting.
Methods: This was a retrospective cohort study among patients from the 2010-2016 SEER-Medicare linked database with a diagnosis of refractory anaemia with excess blasts (RAEB; a surrogate for higher-risk MDS) from 2011-2015. Included patients had to have received HMA therapy and have ≥12 months' continuous follow-up after diagnosis. Discontinuation was defined as stopping HMA therapy before 4 cycles. Multivariable logistic regression was used to assess predictors of HMA discontinuation.
Results: In total, 664 patients with RAEB and treated with HMAs were included. Overall, 193 patients (29%) discontinued before receiving 4

cycles of therapy; of these, 91 (47%) discontinued after 1 cycle, 57 (30%) after 2 cycles, and 45 (23%) after 3 cycles. Compared with patients continuing for ≥4 cycles, patients discontinuing before 4 cycles were generally older (mean age 79.1 vs 77.3 years; p<0.001) and more likely to be single/separated/divorced/widowed (35% vs 30%; p=0.024), have more comorbidities (National Cancer Institute [NCI] Comorbidity Index ≥3, 36% vs 26%; p=0.004), and have poor performance status (PS) (55% vs 40%; p<0.001). These trends were most pronounced among patients discontinuing HMA therapy after only 1 cycle vs ≥4 cycles (mean age, 79.2 vs 77.3 years; single/separated/divorced/widowed, 39% vs 30%; NCI Comorbidity Index ≥3, 41% vs 26%; poor PS, 63% vs 40%; p<0.05 for all comparisons). In multivariable analysis, age 71-75 vs ≥80 years (odds ratio [OR] 0.556, p=0.017) and poor PS (OR 1.585, p=0.019) remained significant predictors of HMA discontinuation. Among treatment-related factors, the most statistically significant association with HMA discontinuation was observed for granulocyte colony-stimulating factor (GCSF) use (OR 0.453, p<0.001). Number of pills/day in the 90 days before HMA initiation was not a predictor of HMA discontinuation (OR 1.009, p=0.656) (Figure).

Figure: Multivariable logistic regression analysis of predictors of early HMA discontinuation



In addition to the variables shown, the model controlled for gender, race/ethnicity, census location, and urban location. CI, confidence interval; ESA, erythropoiesis-stimulating agent; GCSF, granulocyte colony stimulating factor; HMA, hypomethylating agent; NCI, National Cancer Institute; OOP, out-of-pocket; PS, performance status; RBC, red blood cell; USD, US dollars.

Summary/Conclusion: In this real-world study, almost one-third of RAEB patients treated with IV/SC HMAs discontinued before 4 cycles, with almost half of these patients discontinuing after only 1 cycle. Predictors of HMA discontinuation included older age and poor PS. Novel therapeutic approaches and interventions are needed to improve persistence with HMA therapy, particularly among these higher-risk groups. Further research is also warranted to fully elucidate the reasons for early discontinuation in this population.

EP917 UPDATED SAFETY AND EFFICACY OF VENETOCLAX IN COMBINATION WITH AZACITIDINE FOR THE TREATMENT OF PATIENTS WITH TREATMENT-NAÏVE HIGHER-RISK MYELODYSPLASTIC SYNDROMES: PHASE 1B RESULTS

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Background: Hypomethylating agents (HMA) are the current standard of care for patients (pts) with higher-risk myelodysplastic syndromes (HR-MDS) who are ineligible for allogeneic hematopoietic stem cell transplantation (HSCT). However, overall response rates (ORRs) remain suboptimal in pts receiving azacitidine (Aza), and their expected median overall survival (OS) is less than 2 years. Venetoclax (Ven) is a selective, potent, oral BCL-2 inhibitor, which has demonstrated synergy with HMAs in preclinical and clinical studies of myeloid malignancies.
Aims: We report updated safety and efficacy in pts treated in an ongoing phase 1b study (NCT02942290) evaluating Ven+Aza for treatment-naïve HR-MDS.
Methods: Pts (≥18 years) with International Prognostic Scoring System (IPSS) intermediate-2 or high-risk MDS, bone marrow (BM) blasts <20% at baseline and ECOG ≤2 performance status were enrolled. Aza 75 mg/m^2 was administered on Days (d) 1–7 of each 28-d cycle. Ven was initially given at a dose of 400 mg or 800 mg daily in 28-d cycles. Due to poor tolerance among pts with MDS, the study was amended to examine feasibility of several dose cohorts (100, 200 and 400 mg x 14 d each 28d cycle). Primary objectives were to assess the Ven+Aza safety profile and to establish the RP2D. Key secondary objectives included assessment of ORR and OS. Safety and efficacy analyses were carried out on all pts who received ≥1 dose of study drug and efficacy endpoints evaluated per IWG 2006 response criteria. Neutropenia included neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis/infection, agranulocytosis. Thrombocytopenia included thrombocytopenia and platelet count decreased. Baseline mutational status was evaluated on BM aspirate samples using the Archer VariantPlex Myeloid panel.
Results: At data cutoff Dec 15, 2020, 78 pts had received Ven+Aza (51 pts received Ven at the RP2D of 400 mg x 14 d), with a median follow-up time of 23 mos (range 0.1–44.2). Median age was 70 years (range 26–87); 72% male; and 90% had excess BM blasts (>5 to ≤10%, n=21; >10 to ≤20%, n=49). Grade 3/4 neutropenia (59%) or thrombocytopenia (33%) were present at baseline. All pts experienced ≥1 treatment-emergent adverse event (TEAE), the most common being neutropenia (83%), nausea (55%), and constipation (54%). Grade 3/4 TEAEs were experienced by 96% of pts, with neutropenia (82%), febrile neutropenia (49%), and thrombocytopenia (42%) being the most common. Neutropenia (49%), including febrile neutropenia (45%), was the most common serious TEAE. The 30-day mortality rate after first dose was 1%. The intention-to-treat ORR was 80%, including complete remission (CR) in 40% and marrow CR (mCR) in 40% (42% of pts with mCR also had hematologic improvement; no partial remissions were recorded. For 31 pts with CR, median time to CR was 2.6 mos (range 1.2–19.6) and median duration of response was 13.8 mos (95% CI 8.9,–). Post-baseline transfusion independence rate (defined as no transfusion ≥8 weeks), for pts who were transfusion-dependent for RBC and/or platelets at baseline, was 46.5%. Median OS of the study population was 28.2 mos (95% CI 17.7, –). Median OS for 31 pts achieving CR was 28.6 mos (95% CI 27.5, –). 23% of the study population moved on to post-study allogeneic HSCT (incl. BM and peripheral blood stem cell).

Summary of efficacy	**n (% of N=78)**
Overall Response Rate (CR + mCR + PR)	62 (80)
CR	31 (40)
mCR	31 (40)
mCR + hematologic improvement[a] n/N (%)	13/31 (42)
Transfusion Independence Rate[b] n/N (%) [95% confidence interval]	20/43 (46.5) [31.2, 62.3]
	Months [95% confidence interval]
Median Overall Survival	28.2 [17.7, not estimable]
Median Overall Survival for CR	28.6 [27.5, not estimable]
Median Duration of Response for CR	13.8 [8.9, not estimable]

[a]Hematologic improvement (HI) includes pts who are eligible for HI evaluations and achieved neutrophil, erythroid, or platelet responses.
[b]For patients who were transfusion-dependent on RBC or platelet at baseline.
CR, complete remission; mCR, marrow complete remission; PR, partial remission

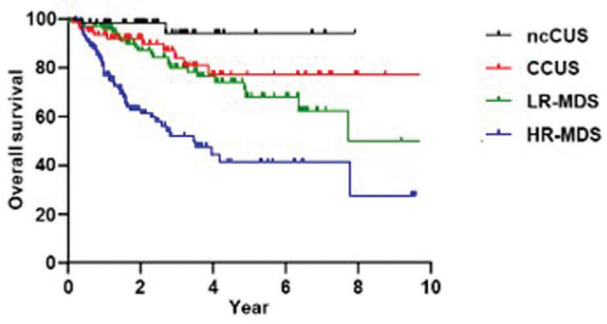
Summary/Conclusion: The combination of Ven+Aza was associated with a rapid and durable response, promising efficacy including remission rates and OS, and an acceptable safety profile for pts with HR-MDS. Additional correlation with disease risk features, including TP53 mutations, will be presented.

EP918 SIMILAR SURVIVAL AND GENETIC FEATURES BETWEEN CLONAL CYTOPENIA OF UNDETERMINED SIGNIFICANCE AND LOWER-RISK MYELODYSPLASTIC SYNDROME

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Background: Idiopathic cytopenia of undetermined significance (ICUS) is characterized by a persistent and clinically significant cytopenias which does not meet the diagnostic criteria for myelodysplastic syndrome (MDS). In some patients with ICUS, disease evolution to MDS or acute myeloid leukemia after variable periods of time was observed in several studies. However, the incidence and predictive factors of progression as well as management guidelines for ICUS patients are not well established.
Aims: We aimed to identify the clinical and genetic characteristics of ICUS in comparison with lower-risk MDS for understanding the pathophysiologic features and providing guidance for treating physicians.
Methods: We performed targeted deep sequencing including 61 myeloid neoplasm-related genes with a MiSeqDx sequencer (Illumina) using bone marrow (BM) samples obtained from the patients with ICUS (n=139) and MDS (n=226) between May 2009 and December 2019. The cut-off level of variant allele frequency (VAF) was set to 2.0% of mutant allele reads. Cloncal cytopenia of undetermined significance (CCUS) was defined as ICUS with ≥ 2% VAF of mutations and lower-risk MDS was defined as MDS with revised international prognostic scoring system ≤3.5.
Results: When we compared the overall survival (OS) of the patients according to the disease subtypes, OS of CCUS (77.0% at 5-year) was significantly better than that of higher-risk MDS (41.0%, *P*<.001) and worse than non-clonal ICUS (94.1%, *P*=.050), but it was similar to the OS of lower-risk MDS (67.9%, *P*=.363). Next, we compared the clinical and mutational features between CCUS (n=78) and lower-risk MDS (n=99). As shown in Table, there was no significant difference of patient characteristics between two groups except for higher hemoglobin level (10.5 vs. 9.0 g/dL, *P*=.008) in CCUS than lower-risk MDS, and the rate of red blood cell transfusion dependency was not different (*P*=.738). The median number of mutated genes of CCUS and lower-risk MDS were 1 (range, 0-4) and 1 (range, 0-6) (*P*=.651), and the median mutation numbers were 1 (range, 0-5) in CCUS and 2 (range, 0-7) in lower-risk MDS, respectively (*P*=.711). The mutational profiles of 61 genes were also similar between CCUS and lower-risk MDS except for *SF3B1* (2.6% in CCUS and 18.2% in lower-risk MDS; *P*=.001) and *STAT3* (5.1% in CCUS and 0% in lower-risk MDS; *P*=.023). Overall, 11 of 78 CCUS and 24 of 99 MDS died, and the causes of death were not different between two groups (*P*=.861).



Summary/Conclusion: In our study, CCUS and lower-risk MDS showed similar OS which was significantly better than higher-risk MDS and worse than non-clonal ICUS. The clinical and mutational characteristics were also similar except for the degree of anemia and the *SF3B1* and *STAT3* mutation. Our findings suggest that the patients with CCUS may be regarded and treated as the lower-risk MDS despite a lack of significant dysplasia or MDS-associated definitive chromosomal abnormality.

EP919 CHARACTERISTICS AND OUTCOMES OF MYELODYSPLASTIC SYNDROMES (MDS) WITH ISOLATED THROMBOCYTOPENIA: A RETROSPECTIVE, NATIONAL, COHORT STUDY

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Background: Ordinarily, patients with MDS present with anemia and other cytopenias. Rarely, MDS may present with thrombocytopenia as an isolated abnormality (MDS-IT). There have been few systematic studies on MDS-IT and data regarding its prognosis are conflicting. Previous studies have defined MDS-IT based on the IPSS i.e. hemoglobin ≥10 g/dL, neutrophil count (ANC) ≥1.8×10⁹/L, and platelet count (PLT) <100×10⁹/L. However, these thresholds were developed for prognostic—not diagnostic—purposes which means that mild anemia and/or neutropenia might be present concomitantly with "isolated" thrombocytopenia.
Aims: We investigated the characteristics, overall survival (OS), and leukemia-free survival (LFS) of patients with MDS-IT. In this study, thrombocytopenia was defined as PLT<150×10⁹/L.
Methods: We identified patients who had PLT<150×10⁹/L, Hb>13 g/dL (men) or >12 g/dL (women), ANC≥1.8×10⁹/L, and monocytes <1.0×10⁹/L, registered in the Hellenic National Registry of Myelodysplastic and Hypoplastic Syndromes which includes 2792 patients diagnosed with MDS (analysis cut-off date; July 7, 2016). Patients were stratified into 4 subgroups: subgroup 1 had PLT 149-100×10⁹/L; subgroup 2, 99-50×10⁹/L; subgroup 3, <50×10⁹/L; and subgroup 4, <25×10⁹/L.
Results: A total of 77 patients (45 men; 32 women) with MDS-IT were identified (2.9% of total MDS cohort). Median PLT was 87×10⁹/L (range, 12-145×10⁹/L). Twenty-two patients (28.6%) were classified in subgroup 1; 38 (49.4%) in subgroup 2; 11 (14.3%) in subgroup 3; and 6 (7.8%) in subgroup 4. Median hemoglobin was 13.6 g/dL, and white-cell count 4.6×10⁹/L. The proportion of bone-marrow blasts ranged from 0-9% (median, 2%). Median follow-up was 51.0 months (range, 41.6-60.4), during which 15 (19.5%) patients died. AML developed in 9 patients with MDS-IT (11.7%). IPSS-R score was ≤3.5 in 73.5% and 83.1% had favorable cytogenetics. Morphological classification was consistent with refractory cytopenia with multilineage dysplasia in 70.7%. Unilineage dysplasia was seen in only 10.7%. On subgroup comparisons, we noted no significant differences in age, sex, IPSS-R,

blast percentage, cytogenetic pattern, and histological features (WHO type; cellularity; myelofibrosis). Median OS was 109 months (95% CI 103-115) and LFS 108 months (101-115). On subgroup comparisons, we noted no significant between-group difference in OS (P=0.891) and LFS (P=0.871). As compared with the total MDS cohort, patients with MDS-IT presented at younger age (64.7 vs. 72.4 years, P<0.001). Importantly, MDS-IT was characterized by superior survival rates as compared with the total MDS cohort, even after adjusting for age, cytogenetics, IPSS-R, and platelets (P=0.013 for OS and P=0.017 for LFS). There were, however, no differences in the top causes of death: infection was the commonest cause followed by disease progression and cardiovascular disease. Major bleeding comprised 10.3% of deaths in MDS-IT vs. 12.7% in total MDS registry (P=0.217).

Summary/Conclusion: In this large cohort study, one of the world's largest cohorts of MDS-IT, we show that MDS-IT is associated with multilineage dysplasia and lower-risk IPSS-R score. Interestingly, the degree of thrombocytopenia did not seem to correlate with mortality in MDS-IT. The finding that MDS-IT is associated with better survival outcomes as compared with other MDS is important and has major implications for the management of this disorder.

EP920 LUSPATERCEPT REDUCES RED BLOOD CELL TRANSFUSIONS IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES REGARDLESS OF BASELINE TRANSFUSION BURDEN IN THE MEDALIST STUDY

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Background: MEDALIST (NCT02631070) is an ongoing, randomized, phase 3 trial evaluating the efficacy and safety of luspatercept, the first and only erythroid maturation agent, which reduced red blood cell (RBC) transfusion burden (TB) and led to significant rates of transfusion independence (TI) in patients (pts) with anemia due to lower-risk myelodysplastic syndromes (LR-MDS) with ring sideroblasts (Fenaux P, et al. *N Engl J Med* 2020;382:140–151). TI is associated with improved prognosis in pts with MDS. The effect of luspatercept treatment on red blood cell transfusion (RBCT) units and visits in pts with different baseline TB warrants further investigation.

Aims: To evaluate the effect of luspatercept on the cumulative number of RBCT units and visits in pts with LR-MDS according to their baseline TB levels in the MEDALIST study.

Methods: Eligible pts were ≥18 years old; were refractory, intolerant, or unlikely to respond to erythropoiesis-stimulating agents; and required regular RBC transfusions (≥2 units/8 weeks [wks]) in the 16 wks prior to randomization. Overall, 229 pts were randomized 2:1 to receive either luspatercept (n=153) or placebo (n=76) every 3 wks through the clinical assessment visit at Wk 25, defined as 24 calendar wks after the first dose, regardless of dose delays. Pts experiencing clinical benefit continued treatment beyond 24 wks. The data cutoff for this analysis was July 1, 2019. Cumulative mean number of RBCT units and visits were estimated using the Nelson-Aalen nonparametric estimator with robust variance estimate for each treatment group. Luspatercept responders were defined as pts achieving RBC-TI for ≥8 wks during wks 1–24. At baseline, pts with <6 RBCT units/8 wks were defined as low TB (LTB) and pts with ≥6 RBCT units/8 wks were defined as high TB (HTB).

Results: Similar proportions of pts in the luspatercept and placebo groups were LTB and HTB at baseline; 56.9% (n=87/153) in luspatercept vs 56.6% (n=43/76) in placebo were LTB, whereas 43.1% (n=66/153) vs 43.4% (n=33/76) were HTB, respectively. Regardless of baseline TB, pts receiving luspatercept had lower mean cumulative RBCT units and visits at 24 wks relative to placebo. Mean cumulative RBCT units (95% confidence interval [CI]) in LTB pts was 6.8 (5.6–8.4) in the luspatercept group (n=81/87) vs 13.2 (11.5–15.2) in the placebo group (n=38/43); and for HTB pts, was 17.2 (15.1–19.6) in the luspatercept group (n=47/66) vs 24.2 (21.3–27.4) in the placebo group (n=30/33). Mean cumulative RBCT visits (95% CI) in LTB pts was 4.0 (3.3–4.8) in the luspatercept group (n=81/87) vs 7.2 (6.3–8.3) in the placebo group (n=38/43); and for HTB pts, was 9.4 (8.3–10.7) in the luspatercept group (n=47/66) vs 12.5 (11.0–14.2) in the placebo group (n=30/33). Luspatercept responders continued to show additional reductions in RBCT units and visits beyond 24 wks through 144 wks, relative to non-responders in both LTB and HTB groups (Table).

Table. Mean cumulative RBCT units and visits in luspatercept responders and non-responders

	RBCT units (95% CI)		RBCT visits (95% CI)	
Patients with LTB	Responders[a] (N=52)	Non-responders (N=35)	Responders[a] (N=52)	Non-responders (N=35)
At 24 wks	2.7 (2.0–3.7) n=49	13.0 (11.4–14.9) n=32	1.7 (1.2–2.2) n=49	7.5 (6.5–8.6) n=32
At 48 wks	4.7 (3.5–6.3) n=43	22.8 (20.1–25.8) n=15	2.8 (2.1–3.7) n=43	13.1 (11.8–14.6) n=15
At 144 wks	15.2 (11.5–20.0) n=5	57.1 (50.5–64.6) n=1	9.3 (7.2–12.2) n=5	33.4 (28.8–38.9) n=1
	RBCT units (95% CI)		RBCT visits (95% CI)	
Patients with HTB	Responders[a] (N=6)	Non-responders (N=60)	Responders[a] (N=6)	Non-responders (N=60)
At 24 wks	3.7 (1.8–7.4) n=6	18.9 (16.9–21.1) n=41	2.0 (1.0–4.0) n=6	10.3 (9.2–11.5) n=41
At 48 wks	9.3 (3.5–25.0) n=6	34.7 (29.6–40.7) n=21	5.0 (1.8–13.5) n=6	18.5 (16.1–21.2) n=21
At 144 wks	26.1 (8.3–81.9) n=1	85.6 (70.1–104.5) n=1	15.5 (5.2–46.3) n=1	47.0 (39.1–56.5) n=1

[a]Luspatercept responders were defined as patients achieving RBC-TI for ≥8 wks during wks 1–24.
CI, confidence interval; HTB, high transfusion burden; LTB, low transfusion burden; RBCT, red blood cell transfusion; RBC-TI, RBC transfusion independence; wks, weeks.

Summary/Conclusion: In the MEDALIST trial, luspatercept reduced cumulative RBCT units and visits relative to placebo over the first 24-wk period in pts with LR-MDS regardless of their baseline TB level. Luspatercept responders showed additional benefits in RBCT unit and visit reduction relative to non-responders beyond 24 wks.

EP921 FLOW-CYTOMETRIC ASSESSMENT OF BONE MARROW MICROENVIRONMENT IN LOW-RISK MYELODYSPLASTIC SYNDROMES

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Background: Low-risk myelodysplastic syndromes (LR-MDS) are a very heterogeneous group of diseases, ranging from mild forms, deserving follow-up only, to life-threatening cytopenias with frequent complications. There is growing interest on the immunologic proinflammatory bone marrow (BM) microenvironment of LR-MDS that may be of pathogenic but even of therapeutic relevance, since novel drugs targeting several cytokine patterns are under study.

Aims: To evaluate BM microenvironment of LR-MDS and its relationship with disease features, somatic mutations, and response to recombinant EPO (rEPO).

Methods: BM multiparameter flow cytometry (MFC) of patients with LR-MDS according to the revised international prognostic scoring system (IPSS-R) followed at a tertiary hematologic center have been retrospectively evaluated by 2 MFC experts. The proportions of the various lymphocyte populations (T, B, and NK cells), monocytes, and mastocytes have been evaluated using monoclonal antibodies directed against CD3, CD10, CD14, CD16, CD19, CD34, CD45, CD56, CD117, and HLA-DR.

Results: 136 LR-MDS patients (48 multiple- and 38 single lineage dysplasia M-/SLD, 37 ring sideroblasts RS, 5 with 5q deletion, 5 MDS/myeloproliferative neoplasm overlap, and 2 excess of blasts type 1), 60% males and with a median age of 73.6 years (36-90.6), have been studied. Table 1 shows mean percentages of total lymphocytes, T-, B-, and NK-cells divided according to WHO type: MDS-RS showed significantly lower

B cells and monocytes compared to patients with MDS-SLD (p=0.008 and p=0.03, respectively) and MDS-MLD (p=0.01 for B-cells). Elderly patients showed higher mastocyte levels (1.88±1.3% in >65 years vs 1.2±0.7% in younger patients, p=0.05). Concerning cytopenias, patients with Hb<10g/dL showed lower monocytes (3.4±2.2 vs 4.45±3%, p=0.02) compared to not anemic patients; those with PLT<100x10^9/L showed lower T-cells (67.2±15.4 vs 72.4±10.3%, p=0.02) and higher B-cells (14.2±11.5 vs 10.5±6.5%, p=0.02) compared to those with higher PLT; and subjects with neutrophils <1x10^9/L displayed higher mastocytes (2.5±2 vs 1.6±1%, p=0.004) and monocytes (5.5±4.08 vs 3.7±2.3%, p=0.004), as compared to those with higher values. Hypocellular patients showed increased total lymphocytes (20±9.3 vs 13±7.5%, p<0.0001) and NK-cells (21±17 vs 16.6±8%), and decreased mastocytes (1.2±1 vs 1.8±1.2%, p=0.03) compared to normo/hypercellular cases. Concerning somatic mutations, present in 27 out of 35 patients tested, the presence of ≥3 mutations was associated with increased total lymphocytes (22.4±14 vs 10.8±3.7%, p<0.001). Mutations of DNA methylation genes were related to lower T cells (69±11 vs 76±9%, p=0.04) and higher NK (18±8 vs 14±7%); mutated chromatin and transcription factor genes were associated with higher total lymphocytes (25±14 vs 11±6%, p=0.001 and 22.5±16.5 vs 12.3±6.8%, p=0.02, respectively). Mutations in *TP53* or *PHF6* were associated with increased T cells (83±0.7 vs 73±10%, p<0.001), mastocytes (2.4±1.4 vs 1.7±0.7, p<0.01), and monocytes (7.5±5 vs 3.8±2.3%, p=0.05), and decreased NK (7±1.4 vs 16±8, p<0.001). Regarding therapy, patients responding to rEPO showed reduced T cells (69±14 vs 76±10, p=0.05) and increased B cells (13±11 vs 7.5±5%, p=0.01).

Table 1: bone marrow microenvironment cells in low risk myelodysplastic syndromes (LR-MDS) according to WHO classification.
Values are given as mean ± standard deviation.

WHO category	Lymphocytes	T-cells	B-cells	NK-cells	Mastocytes	Monocytes
All patients	14.7±8	71±12	11.5±8	17.2±10	1.8±1.3	4±2.7
MDS-SLD	13.9±6	69.9±10	12.8±6	16.9±10	1.7±1	4.4±2.5
MDS-MLD	15.3±9	70.4±13	12.7±8	16.7±9	1.8±1.4	3.8±3
MDS-RS	12.4±8	71.9±13	8.8±7	19.1±13	1.7±1.7	3.7±7
5q-	17±6	78.6±5	7.7±2	13.8±7	1.5±1	3.8±1.4
MDS/MPN	14.3±12	78.2±6	6.2±2	15.6±6	2.3±0.7	9.5±6
MDS-EB1	21±14	52±28	34.5±30	13.5±11	4.2±5	2.4±1.3

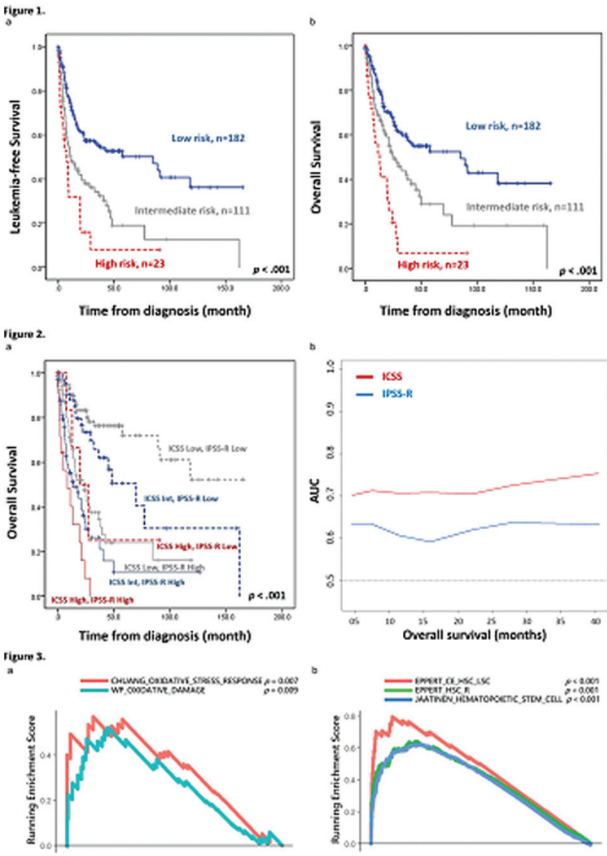
Summary/Conclusion: Different types of LR-MDS show variable levels of BM lymphocyte, mastocyte and monocyte percentages. BM microenvironment characteristics correlate with cellularity and peculiar molecular alterations. Patients with greater T-cell infiltrate display higher frequency of disrupting mutations (i.e. *TP53*) and lower response to rEPO.

EP922 A CIBERSORTX-BASED IMMUNE-CELL SCORING SYSTEM COULD INDEPENDENTLY PREDICT PROGNOSIS OF MYELODYSPLASTIC SYNDROME PATIENTS

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Background: Myelodysplastic syndromes (MDSs) are hematopoietic stem cell disorders with features of dysplasia in hematopoietic cells, ineffective hematopoiesis, and an increased risk of leukemia transformation. The revised international prognostic scoring system (IPSS-R) has been widely used to risk-stratify MDS patients and guide treatment strategies. Nevertheless, the prognosis of patients may vary greatly, even in the same risk group. Recent evidences dictate the central role of the bone marrow (BM) microenvironment, infiltrating immune cells, and relevant inflammatory pathways in the pathogenesis of MDS. However, the prognostic significance of immune cells in the BM of MDS patients remains unclear.
Aims: This study was aimed to investigate the clinical significance of BM-infiltrating immune cells in MDS patients and to construct an immune cell scoring system for better risk-stratification of these patients.
Methods: We recruited 316 primary MDS patients diagnosed at the National Taiwan University Hospital (1997-2019) who had adequate cryopreserved BM samples for RNA sequencing. We adopted TruSight myeloid sequencing panel and HiSeq platform to analyze the gene alterations of 54 myeloid-neoplasm relevant genes. The purified RNA was used to construct gene expression libraries with the Illumina Stranded mRNA Library Prep Kit and then sequenced on the Illumina NextSeq 500 platform. CIBERSORTx, a Next-generation of CIBERSORT (*C*ell type *I*dentification *B*y Estimating *R*elative *S*ubsets *O*f known *R*NA *T*ranscripts), which can quantify the relative expression of cell type-specific signatures in bulk tumors without doing cell sorting, was employed to estimate the relative cell fractions of 22 subtypes of immune cells that are intensely involved in innate and adaptive immunity.
Results: We applied univariate Cox regression analysis to examine the prognostic impact of 22 immune cell subtypes on the overall survival (OS) of MDS patients. A higher percentage of macrophages M0 was significantly correlated with better survival, whereas higher fractions of macrophages M2 and eosinophils, two cell types whose infiltration in tumors were correlated with prognosis, were associated with inferior survival. An immune-cell scoring system (ICSS) was constructed based on the fractions of M0, M2, and eosinophils, which could well divide MDS patients into three risk groups with distinct clinical outcomes. ICSS high-risk group, defined as having lower M0, higher M2, and higher eosinophils, had the worst leukemia-free survival (LFS) and OS among the three risk groups in the total cohort as well as in subgroups of patients with higher- or lower-risk IPSS-R (Figure 1, 2a). The prognostic significance was then confirmed in an independent validation cohort. Furthermore, ICSS high-risk group more frequently harbored mutations in *NPM1*, *TP53*, and *WT1*, but less commonly, *SF3B1* mutation. Time-dependent ROC curves revealed that ICSS could be complementary to IPSS-R in prognostication (Figure 2b). More importantly, multivariable analysis proved that the immune-cell score was an independent predictor of clinical outcomes in MDS patients. Bioinformatic analysis revealed that high-risk ICSS was significantly correlated with the oxidative stress and leukemic stem cell signatures (Figure 3).



Summary/Conclusion: In conclusion, we show that besides clinical features and genetic alterations, immune cells in the BM microenvironment also significantly impact LFS and OS in MDS patients. The ICSS is a

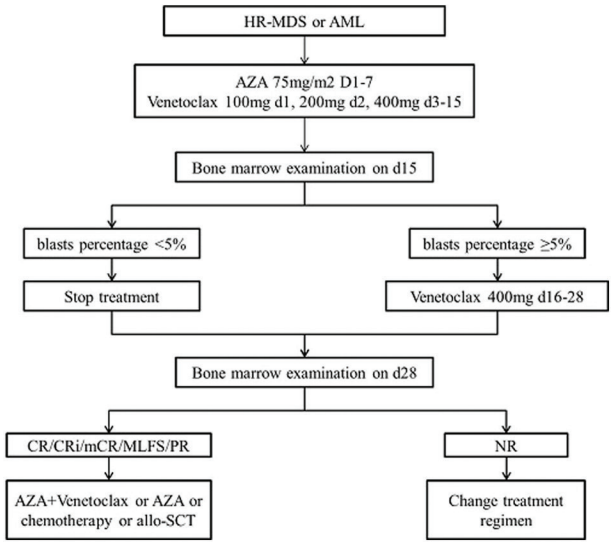
concise yet powerful risk-stratification system that can be incorporated into IPSS-R to refine the risk-stratification of MDS patients.

EP923 VENETOCLAX COMBINED WITH AZACITIDINE IN THE TREATMENT OF RELAPSED/REFRACTORY HIGH-RISK MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKEMIA: A RETROSPECTIVE SINGLE-CENTER STUDY

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Background: The treatment of patients with refractory and/or relapsed (R/R) high-risk myelodysplastic syndrome (HR-MDS) or acute myeloid leukemia (AML) remains a daunting clinical challenge. Venetoclax is a selective BCL-2 inhibitor, which combined with hypomethylating agents (HMA), has shown high response rates in unfit and previously untreated AML.
Aims: We performed a retrospective study of patients with R/R HR-MDS and AML receiving combination azacytidine (AZA) plus venetoclax (VEN) in order to determine their efficacy and toxicity in this context.
Methods: Venetoclax was recommended at a daily dose of 100 mg with a 3-day ramp to target dose of 400 mg for 28 days (VEN-28d) but was stopped on day 15 if bone marrow examination on day 15 showed residual blasts percentage was below 5% (VEN-15d). Azacitidine was administered 75 mg/m^2 subcutaneously daily on days 1 to 7 of each 28-day cycle. The treatment decision tree was depicted in Figure 1.
Results: We have included a total of 35 patients with R/R MDS, R/R AML, or denovo AML. Among them 17 patients were R/R MDS, 10 patients were R/R AML, and 8 patients were denovo AML. The overall response rate (ORR) and was 58.8 % in R/R MDS and 50% in R/R AML respectively, the complete remission (CR) rate was 29.4% in R/R MDS and 10% in R/R AML respectively. And the ORR was 71.4% in 14 R/R MDS and 10 R/R AML who stopped VEN on day 15, among them the CR rate was 35.7% in R/R MDS and 14.3% in R/R AML. The median OS was significantly different among the three groups (not reached in R/R MDS and denove AML vs. 5 months with 95% CI of 3.4-6.5 months in the R/R AML, p = 0.002). The most common treatment-emergent adverse events were peripheral blood cytopenias and infectious complications.



Summary/Conclusion: Our study showed that the real-world experience of treating patients with R/R MDS and AML with AZA plus VEN, which have high response rates but with a high frequency of myelosuppression. Of note, the dose reductions of venetoclax did not affect response and survival in our analysis. These data of combination AZA plus VEN in R/R AML and MDS warrant further prospective evaluation in clinical trials.

EP924 UPDATED OVERALL SURVIVAL OF ELTANEXOR FOR THE TREATMENT OF PATIENTS WITH HYPOMETHYLATING AGENT REFRACTORY MYELODYSPLASTIC SYNDROME

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Background: Patients (pts) with myelodysplastic syndrome (MDS) refractory to hypomethylating agents (HMAs) have limited therapeutic options and a dismal prognosis with a median overall survival (mOS) of 4-6 months. Eltanexor (ELTA) is a second-generation, oral, selective inhibitor of nuclear export (SINE) compound that showed anti-tumor activity and lower brain penetration compared to selinexor (SEL) in nonclinical models. It was hypothesized that ELTA could be dosed more frequently than SEL with a lower incidence of centrally mediated nausea. Early results from a phase 1/2 study of ELTA in pts with HMA refractory MDS demonstrated marrow complete responses (mCRs) and stable disease (SD); side effects were primarily low-grade, dose-dependent, and reversible (Lee ASH 2019).
Aims: In this abstract, we provide a subgroup analysis of and update on mOS in the efficacy evaluable population.
Methods: This phase 1/2 study (NCT02649790) evaluated single-agent oral ELTA in pts with higher-risk MDS, ie, high-risk or intermediate-2 MDS by International Prognostic Scoring System (IPSS) and 5%>19% myeloblasts. Of 20 pts enrolled, 15 pts were evaluable for efficacy and constitute the population studied in this analysis. Two doses of ELTA were evaluated: 10 mg (n=5) or 20 mg (n=15) every day for 5 days per week of a 28-day cycle.
Results: As of 1 Feb 2021, the 15 pts evaluable for efficacy (median age 76 years; range 62-89) had a median of 2 prior treatment regimens (range 1-4); 14 pts (93%) had higher-risk MDS including 9 pts (60%) high risk and 5 pts (33%) int-2. Similarly, using the global MD Anderson Cancer Center (MDACC) risk prognosis model (Kantarjian 2008), 14 pts (93%) had higher-risk MDS with 2 pts (13%) high risk and 12 pts (80%) int-2. Of the 20 enrolled patients, 7 (35%) had mCR and 5 (25%) had SD for a total disease control (mCR+SD) rate of 60%. Of the 15 pts evaluable for efficacy, 7 (47%) had mCR and 5 (33%) had SD. In the 10-mg cohort (n=5), all pts derived clinical benefit with 3 pts (60%) reaching mCR and 2 pts (40%) SD. In the 20-mg cohort (n=10), 4 pts (40%) had mCR and 3 (30%) had SD. Four pts had hematologic improvement (HI) and became transfusion independent for at least 8 weeks including 2 pts with tri-lineage HI. OS for pts who reached mCR (n=7) was significantly longer than for pts who did not reach mCR (n=8): median 11.86 vs 8.67 months (mo) (hazard ratio [HR]=0.27, p=0.05), and significantly longer than OS for pts with PD (n=3, mOS=3.15 mo, HR=0.23, p=0.04). Pts with disease control (n=12) had numerically longer mOS than pts with PD (9.86 vs 3.15 mo, HR=0.38, p=0.09). Pts with HI had a mOS of 10.58 months.
Summary/Conclusion: Single-agent oral ELTA was active in pts with high-risk, HMA-refractory MDS. Pts with mCR had significantly longer mOS than pts without mCR or with PD. Given the limited prognostic power of IPSS in HMA refractory pts, the MDACC model was also applied here for improved risk assessment. Further evaluation of ELTA in MDS as a single agent and in combination with other agents is ongoing.

EP925 EARLY DECREASE IN VARIANT ALLELE FREQUENCY IN PERIPHERAL BLOOD WITH DROPLET DIGITAL PCR IN MYELODYSPLASTIC SYNDROME (MDS) PATIENTS RESPONDING TO AZACITIDINE

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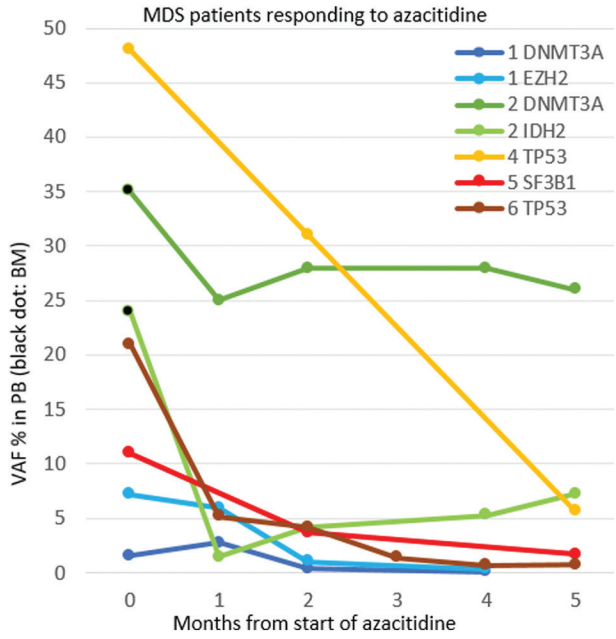
Background: Treatment response evaluation in MDS relies on serial assessment of peripheral blood (PB) counts, bone marrow (BM) morphology, and cytogenetics (IWG2006; Cheson et al, Blood 2006). BM

sampling is invasive, whereas biomarkers of response measured in PB could provide a less invasive alternative for monitoring treatment responses. Most MDS and CMML patients carry somatic driver mutations, that can be detected in PB. Consistent reductions in PB variant allele frequencies (VAFs) have been detected during decitabine therapy for MDS (Duncavage et al, Blood 2017), suggesting that detection of clonal dynamics in PB may be used as an early predictor of therapy response.

Aims: We evaluated whether changes in mutational load, using high sensitivity mutation-specific droplet digital PCR (ddPCR) of PB samples, could be used as an early sign of treatment response in MDS/CMML.

Methods: Patients were recruited between 1/2016-5/2018 at Helsinki University Hospital. All patients signed an informed consent. Serial PB samples were collected before treatment and during routine visits. Pre-treatment samples were analyzed with an in-house NGS myeloid panel of 45 genes. Mutation-specific ddPCR were designed, and on-treatment samples were analyzed with the QX200 Droplet Digital PCR system.

Results: The results of the first ten patients are reported here. Seven MDS patients were treated with azacitidine (AZA), one with lenalidomide (LEN), one CMML patient was treated with hydroxyurea (HU) and one with both HU and AZA. Median age at treatment initiation was 68 years (range 48-81). The median follow-up was 11 months (range 4-33). Altogether 17 myeloid driver mutations were found in the NGS and 15 of these (4 *SF3B1*, 2 *DNMT3A*, 2 *TP53*, 2 *IDH2*, 2 *EZH2*, 2 *NRAS, U2AF1*) were analyzed with ddPCR at 4-13 timepoints (median 7,5/patient). For one mutation in *SRFS2* there was not an available probe. For a mutation in *NF1* the analyses are pending. Using IWG2006 response criteria, seven patients responded to treatment (two CR, three mCR, two HI) and three patients had stable disease (SD). All responding (CR, mCR, HI) MDS-patients (n=6) had a decrease in VAF with a mean relative decrease of 71 % (range 20-94) from pretreatment to samples collected after the second AZA (n=5, figure) or LEN cycle (n=1). The decrease in VAF was detected 28-251 (median 43) days before the IWG2006-response was verified. Patient 2 in the figure had a *DNMT3A*-mutation that decreased only slightly (35% (BM) to 25 %), whilst the *IDH2* seemed to decrease rapidly after the first AZA-cycle, from 24% (BM) to 1,5 %, suggesting that the *DNMT3A*-mutation may reflect a pre-malignant clone. Two MDS cases with SD had mutations in *SF3B1*, one with stable VAF and the other with VAF-decrease (24 % to 11 %). One CMML-patient had a mCR-response at 10 months after HU and AZA; *NRAS* VAF decreased only from 46 % to 35 % and *IDH2* from 46 % to 36 %. The second CMML case had SD and reduction in *NRAS* from 45 % to 33% and *U2AF1* from 46 % to 32 %. Five patients lost their response during treatment. One patient in HI, had an increase from 5,7% to 20 % in *TP53* 55 days before progression. One patient in CR had an increase from 0,12 % to 25 % in *SF3B1* 49 days before progression. Another CR patient had an increase in *TP53* from 1,4 % to 4,9 % at progression. Two SD patients had moderate VAF-increases at progression; one in *SF3B1* from 18 % to 34 %, another in *NRAS* from 33 % to 43 % and *U2AF1* from 32 % to 42 %.



Summary/Conclusion: Detection of peripheral blood clonal dynamics using ddPCR may serve as a non-invasive tool for early response evaluation during azacitidine treatment in MDS.

EP926 COMPARISON OF DOSE MODIFICATION STRATEGIES TO ADDRESS EXPECTED HEMATOLOGIC TOXICITIES IN TREATMENT-NAÏVE HIGHER-RISK (HR) MDS PATIENTS TREATED WITH VENETOCLAX + AZACITIDINE

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Background: Venetoclax (Ven) is a selective, potent BCL-2 inhibitor. Ven + azacitidine (Aza) were associated with a combined complete remission (CR)/marrow CR (mCR) rate of 79% in a phase 1b study of patients (pts) with HR-MDS (NCT02942290).

Aims: We compared two different dose modification strategies to manage expected hematologic toxicities in two safety expansion cohorts with similar follow-up periods.

Methods: Pts (≥18 yrs) diagnosed with treatment-naïve IPSS intermediate-2 or high-risk MDS with ECOG ≤2 were enrolled. Aza 75 mg/m^2 (i.v. or sub-Q, daily) was administered for 7 days (d) and Ven was administered at 400 mg for 14d in each 28d cycle. In both cohorts, dose modification during Cycle 1 was not recommended; dose modifications in subsequent cycles were prescribed for adverse events. In Safety Expansion Cohort 1 (SE1), either Aza or Ven were initially reduced according to investigator's choice for significant neutrophil or platelet toxicity. Dose reductions per protocol were 33% for Aza and 50% for Ven (for 14d each cycle). In subsequent cycles, Ven duration could be shortened to 9d of each cycle. In Safety Expansion Cohort 2 (SE2), dose modification guidelines recommended stepwise reductions, first in Aza dose (first to 50 mg/m^2, then 36 mg/m^2) and subsequently in Ven duration to 7d of each cycle (Ven 400 mg). The impact of each dose modification strategy on safety and efficacy in SE1 *vs* SE2 was compared. Worsening of treatment-emergent adverse events (TEAE) grades from baseline (BL) was analyzed by cycle. Responses were evaluated using IWG 2006 criteria. Analyses included all pts who received ≥1 dose of study drug.

Results: We compared 22 pts in SE1 and 21 pts in SE2 with median (range) follow-up of 7.5 (1.0–8.9) and 7.9 (1.8–10.1) mos, respectively. A similar frequency of ≥G3 hematologic TEAEs (approximate %) were reported in SE1 and SE2, respectively, including anemia (14% and 33%), febrile neutropenia (46% and 48%), leukopenia (36% and 19%), neutropenia (55% and 48%) and thrombocytopenia (32% and 38%). Infections (59% and 38%) were more frequent in SE1 than SE2. In a longitudinal analysis, there were more TEAE grade increases from BL to Cycle 1 in SE2 vs SE1. This could be as accounted by pts in SE1 and SE2 having unbalanced susceptibility to AEs at BL, as SE1 and SE2 pts received identical Aza + Ven doses in Cycle 1. Response rates were identical: 86% of pts in both SE1 and SE2 had CR or mCR. For pts with mCR, hematologic improvement occurred in 50% of SE1 and 46% of SE2 pts.

Table. Any Grade Hematologic TEAEs and Infections (>20%)

%	SE1 n=22	SE2 n=21
Infections	59	38
Neutropenia	55	48
Febrile neutropenia	46	48
Thrombocytopenia	36	48
Leukopenia	36	19
Anemia	14	48

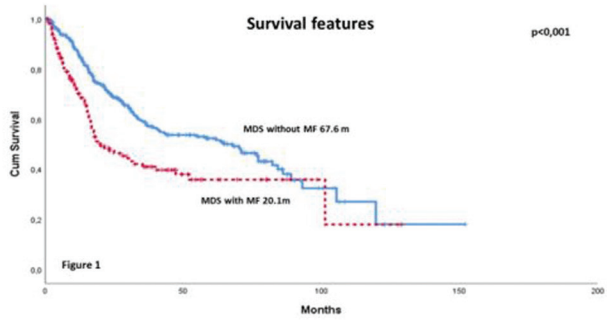
Summary/Conclusion: No obvious hematologic differences were observed when reducing Aza before Ven (SE2) in MDS compared to investigator's choice (SE1). Both approaches had a similar acceptable safety profile without compromising efficacy for pts with HR-MDS.

EP927 PROGNOSTIC IMPACT OF BONE MARROW FIBROSIS IN PRIMARY MYELODYSPLASTIC SYNDROMES

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Background: Myelofibrosis (MF) is observed in 10-20% of patients with myelodysplastic syndrome (MDS). The presence of MF≥2 according to the European Myelofibrosis Network (EUMNET 2005) has been recognized as an adverse histological finding associated with an aggressive course including early bone marrow failure, shortened survival and leukemic evolution. According to a previous survey performed by our group, the bone marrow biopsy is the most available complemental study in our media. Therefore improving the knowledge of variables related with MF and their prognostic role in patients with MDS is highly desirable.
Aims: To examine the influence of the presence of any degree of myelofibrosis (MF≥1) in overall survival (0S) in an Argentine MDS cohort and its association with clinical and histopathologic variables such as percentage of blasts, bone marrow cellularity, atypical erythroid localization and dysplastic megakaryocytes.
Methods: We identified 468 MDS patients from a multicentric retrospective database of 706 patients who were included in the Argentinian Registry of MDS from 2007 to 2017, with recorded evaluation of MF in the bone marrow biopsy. Statistical analysis included Kaplan-Meier and log rank test, Cox proportional hazard and Logistic regression.
Results: From the selected cohort, 32.7% had MF≥1, 25.8% (n=121) with MF-1, 5.7% (n=27) with MF-2 and 1% (n=5) had MF-3. When analyzing the characteristics of the population, we observe that the median age of these patients was 70 years old (Interquartile range 60-78) being 66.1% >65 years old and 55.8% were males. At the time of diagnosis we observe: median hemoglobin 9.0g/dL, platelet counts 121.500/mL and neutrophils 1.800/µL; 25.7% poor karyotypes and 26.7% IPSS-R>3.5.
The median overall survival (OS) of the MF≥1 subgroup was 20.1 months (95% CI 10.1-30.0, p<0.001) versus MF-0 subgroup with 67.6 months (95%CI 45.1-90.3, p<0.001, *Figure 1*). Cox regression analysis revealed that MF≥1 (HR 1.46, 95% CI 1.06-2.03, p=0.020), *performance status* >2 (HR 2.07, 95% CI 1.44-2.96, p<0.001), hemoglobin level <10gr/dL (HR 1.64, 95% CI 1.16-2.32, p=0.005), platelet count <100.000/µL (HR 1.94, 95% CI 1.42-2.65, p<0.001), poor karyotypes (HR 1.86, 95% CI 1.32-2.63, p<0.001), bone marrow blasts ˃5% (HR 2.94, 95% CI 2.06-4.20, p<0.001) and Charlson Comorbidity Index >3 (HR 2.17, 95% CI 1.48-3.19, p<0.001) were independently associated with a reduced OS.
Regarding the association between MF≥1 and clinical and histopathologic features; this subgroup presented hemoglobin level <10gr/dL (p=0.003), ferritin level >1000mg/dL (p=0.004), increased bone marrow cellularity (p<0.001), atypical erythroid localization (p=0.002) and dysplastic megakaryocytes (p=0.006). Among these parameters, ferritin level (OR 3.41; p=0.006) and the atypical erythroid localization (0R 2.65; p=0.004) were significantly associated with the presence of MF≥1.



Summary/Conclusion: Our results highlight the presence of any grade of myelofibrosis in MDS as an independent adverse prognostic factor for survival in MDS. MF≥1 was also significantly associated with higher ferritin level and erythroid abnormalities in bone marrow.

EP928 DOSE SELECTION OF PEVONEDISTAT + AZACITIDINE IN PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES/CHRONIC MYELOMONOCYTIC LEUKEMIA AND ACUTE MYELOID LEUKEMIA: A MODEL-BASED ANALYSIS

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Background: Pevonedistat (PEV) combined with azacitidine (AZA) has demonstrated promising efficacy and a similar safety profile to that of AZA alone with no added myelosuppression, following evaluation in patients with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML).
Aims: The objective of this pooled analysis was to assess the impact of PEV exposure on efficacy and safety.
Methods: The PEV exposure–efficacy analyses were conducted with data from NCT02610777, including overall survival (OS), complete response (CR), CR+partial response (PR) and event-free survival (EFS), in patients with higher-risk MDS/CMML who received PEV+AZA. The PEV exposure–safety analyses used pooled data from three studies (NCT01814826, NCT02782468 and NCT02610777), including ≥ grade 3 treatment-emergent adverse event (TEAE3), ≥ grade 3 neutropenia (NEU3), febrile neutropenia (FN), ≥ grade 3 aspartate aminotransferase elevation, ≥ grade 3 thrombocytopenia and ≥ grade 3 alanine aminotransferase elevation, in patients with higher-risk MDS/CMML and AML who received PEV+AZA. The exposure metrics for each patient were sourced from a previously developed population pharmacokinetic model using pooled data from eight phase 1/2 studies. Logistic regression was conducted to estimate PEV exposure–safety relationships for the toxicity endpoints, exposure–CR and exposure–CR+PR. The following covariates were assessed: age, sex, race, disease type and baseline Eastern Cooperate Oncology Group Performance Status (ECOG PS) score. The PEV exposure–survival for higher-risk MDS/CMML was assessed using Cox proportional-hazards models, with the

following potential covariates: age, sex, disease type, baseline ECOG PS score and Revised International Prognostic Scoring System score (IPSS-R).
Results: In total, the exposure–efficacy analyses included 41 patients (median age, 74 years; male, 76%; Caucasian, 90%; median IPSS-R, 5.5), and the exposure–safety analyses included 135 patients (median age, 74 years; male, 64%; Caucasian, 82%). Following a starting dose of 20 mg/m^2, there was a consistent clinical benefit in terms of OS, EFS, CR or CR+PR across the range of PEV exposures. Furthermore, PEV exposure was significantly related to the incidence of FN (p = 0.02), NEU3 (p = 0.003) and TEAE3 (p = 0.02), supporting PEV dose reductions for patients experiencing treatment-related adverse events.
Summary/Conclusion: These exposure–efficacy and exposure–safety results support a favorable benefit–risk profile of PEV 20 mg/m^2 on days 1, 3 and 5 in combination with AZA 75 mg/m^2 for 7 days in 28-day cycles. The study demonstrates consistent clinical benefit across ranges of PEV exposure following a starting dose of 20 mg/m^2 and supports PEV dose reductions for patients with treatment-related adverse events.

EP929 CLINICAL FEATURES OF MYELOID NEOPLASMS WITH DDX41 MUTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The World Health Organization has included myeloid neoplasms with germline predisposition into its classification since 2016. Especially, *DDX41* mutation is clinically unique due to its late onset compared with other germline lesions, such as *CEBPA* and *GATA2*.
Aims: This study was aimed to report the clinical features of *DDX41*-mutated myeloid neoplasms and describe phenotypes of different diagnosed entities utilizing both study- and individual- level data.
Methods: "*DDX41*" was searched in PubMed and Web of science between 2015/01/01 and 2020/12/31, with additional manual searching and individual-patient data seeking. Both study- and individual- level data were utilized to present the clinical features of the whole population and patients in different subgroups.
Results: 7 articles with 177 patients were finally included. Patients harboring mutated *DDX41* contributed to 3.1% [95%CI 2.7-3.6%] of myeloid neoplasms, with 81.3% [95%CI 69.6-90.7%] males and mean diagnosed age of 65.6 years [95%CI 62.9-68.3]. *DDX41*-mutattions were most common in patients with myelodysplastic syndromes (MDS) with excess blast-1/2 (38.7%) and acute myelocytic leukemia (AML, 36.8%). 76.9% [95%CI 59.9-90.2%] of patients carrying *DDX41*-mutattions had normal karyotype. 75.1% [95%CI 53.1-91.7%] patients had germline and 76.3% [95%CI 59.6-89.6%] patients had somatic *DDX41* variants. *ASXL1* and *TP53* were the top frequent concomitant somatic mutations. The pooled overall response rate for hypomethylating agents was 71.0% [95%CI 54.1-85.4] and all the patients with AML achieved complete remission at the first course. The median overall survival was between 32 months to not reached. Familial cases had younger age (p=0.0001), more germline p.D140fs variant (OR=2.88 [95%CI 1.09-7.76], p=0.021) and better response to treatment compared with sporadic cases.
Summary/Conclusion: Myeloid neoplasms carrying *DDX41*-mutations were mainly older, male, MDS EB-1/2 and AML patients. They had better response to the treatment and possible longer survival. Familial cases were diagnosed earlier and had more favorable response to treatment than sporadic cases.

EP930 QUANTIFYING THE HEALTHCARE RESOURCE USE AND CLINICAL OUTCOMES OF PATIENTS WITH MYELODYSPLASTIC SYNDROME WITH RINGED SIDEROBLASTS IN ENGLAND

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Background: Myelodysplastic syndromes (MDS) are characterized by cytopenias, ineffective haematopoiesis, and a risk of progression to acute myeloid leukaemia (AML). MDS with ring sideroblasts (MDS-RS) is a subtype of MDS, constituting ¬ 3-10% of all cases of MDS, in which excess iron accumulates in the mitochondria of the erythroid precursors.. The main clinical issues are severe anaemia, chronic blood transfusion requirement, and the subsequent risk of iron overload.
The Hospital Episodes Statistics (HES) database in England contains universal coverage of secondary care data from NHS hospitals, covering three main patient groups: 1) inpatient patient care; 2) Outpatient appointments and attendances (OP); and 3) Emergency Room (ER) visits with approximately 17 million episodes recorded each year.
Aims: To describe patients diagnosed with MDS-RS in England. In terms of demographics and clinical characteristics and to quantify the associated healthcare resource use (HCRU) and tariffs for this patient cohort including inpatient, day case, outpatient, and A&E care.
Methods: All data within an observation period between 01 January 2015- 31 December 2019, to include baseline characteristics for patients with ICD10 diagnosis code of D461 (MDS) were extracted from HES and presented as crude counts. Descriptive statistics including frequency and percentage were calculated as categorical variables; whereas, mean, median and interquartile range (IQR) were calculated for continuous variables. Length of follow-up was calculated as the total number of days between diagnosis date (index date) and end of study period. Tariffs were derived based on case mix; a method of classifying patient care based on expected clinical resource use for the provision of that care.
Results: Overall 914 patients (mean age at inclusion 76 years [youngest; 20, oldest; 96]; 40.26% female) were identified. During a mean observation period of 24.62 months (IQR 28.65) 103 (11.27%) patients experienced a disorder of iron metabolism, 278 (30.42%) suffered from sepsis and 235 (25.71%) from heart failure.
52 (2.62%) patients had no inpatient admissions. For those who had ≥1 event, the mean number of inpatient blood transfusion events per-patient-per-year was 15.93 (IQR 12.68), the mean number of outpatient blood transfusion events per-patient-per-year was 3.55 (IQR 1.55), 443 patients (51.39%) had ≥12 visits per year.
Overall HCRU is split by inpatient and outpatient care and ER attendance. In the inpatient setting there were a mean of 19.2 admissions per-patient-per-year, of which 99.11% were elective (resulting in a mean of 15.79 bed days per-patient-per-year). In the outpatient setting there were a mean of 4.08 appointments per-patient-per-year. There were a mean of 2.54 ER visits per-patient-per-year.
Overall tariff costs to the health service per-patient-per-year were £19,047 (inpatient tariff £10,389, outpatient tariff £579, transfusion £7,686, ER visits £393).
Summary/Conclusion: The results of this database analysis offer insights into the real-world management of patients with MDS-RS in England and the HCRU with its management. A burden on patients and the healthcare system has been identified due to the frequent hospitalisations and secondary care visits. This highlights the need for novel treatment options in the management of MDS-RS.

EP931 HIGH TRANSFERRIN SATURATION PREDICTS INFERIOR CLINICAL OUTCOMES IN PATIENTS WITH MDS

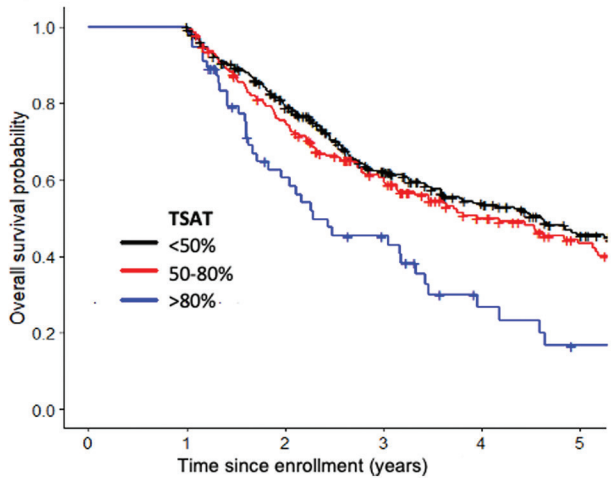
J. Teichman [1,*], M. Geddes [2], N. Zhu [3], M.-M. Keating [4], M. Sabloff [5], G. Christou [5], B. Leber [6], D. Khalaf [7], E. St-Hilaire [8], N. Finn [8], A. Shamy [9], K. Yee [1], J. Storring [10], T. Nevill [11], M. Elemary [12], V. Banerji [13], L. Mozessohn [14], L. Chodirker [1], L. Zhang [15], M. Siddiqui [16], A. Parmentier [16], H. Leitch [17], R. Buckstein [1]

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Background: Iron overload (IO) reflected by increased ferritin level is associated with increased mortality in patients with myelodysplastic syndromes (MDS). However, ferritin is an imperfect metric of true IO. Elevated levels of oxidatively damaging non-transferrin bound iron and labile plasma iron correlate with transferrin saturation (TSAT) >70% and >80% respectively, but are not readily measurable.

Aims: We aimed to describe trends in TSAT in transfusion dependent MDS and to determine its relation to ferritin level and clinical outcomes.
Methods: Patients enrolled in the Canadian MDS registry from January 2008 to June 2019 were evaluated. Mean values of ferritin and TSAT were calculated at six-month intervals, and general linear mixed model analysis was used. Transfusion density was calculated at landmark year 1 and defined as the median number of units transfused per month since the onset of transfusion dependence (TD), with TD-low and TD-high defined as above or below the median. Survival was evaluated by TSAT category (<50%, 50-80%, >80%), and ferritin (≤500ug/L, 501-800ug/L, >800ug/L) using the mean values from enrolment onwards.
Results: 718 patients were included. Median age was 74 years. 12%, 31%, 29%, 15% and 13% were IPSS-R very low, low, intermediate, high and very high, respectively. With a median follow up of 2.1 years, actuarial overall survival (OS) was 2.4 years. 17% developed AML and 61% have died. AML, MDS progression, infection, cardiac events, and bleeding accounted for 26%, 20%, 19%, 9.6% and 6.34% of known causes of death, respectively. Mean TSAT increased with incremental ferritin categories, however TSAT and ferritin were only moderately correlated over time (r=0.63, p < 0.0001). Among all patients, ferritin increased from enrolment up to 42 months (p<0.0001), while TSAT remained stable over time (p=0.094). In TD patients, there was a significant increase in TSAT over time (p=0.0063). Median transfusion density was 2.7 units/month by landmark year 1. Higher TSAT and ferritin were both associated with inferior 5-year OS, PFS and LFS (Figure 1). In patients with ferritin >1000ng/mL, stratifying by TSAT category showed a trend toward OS. Higher transfusion density was also associated with inferior 5-year OS. In TD patients, TSAT category predicted cardiac death-free survival (DFS) (p= 0.0011), while ferritin category predicted infectious death. In univariate analysis, age, IPSS-R, blast percentage, ECOG, frailty score, Charlson Comorbidity Index, iron chelation (Y/N), transfusion density, TSAT category and ferritin category were significantly associated with inferior OS. In multivariate analysis, TSAT >80% (HR 1.58 95%CI 1.13-2.21) and high-TD (HR 1.90 vs. low-TD 95%CI 1.39-2.60) remained significant for OS (R^2 30.35%).

Figure 1.



Summary/Conclusion: Among a cohort of predominantly low-intermediate risk MDS patients, TSAT correlated moderately with serum ferritin. TSAT >80%, ferritin >800 ug/mL and high transfusion density were each associated with inferior survival. TSAT may be an indicator of the degree of oxidative stress present, and is readily measurable in a clinical setting. The relationship between elevated TSAT and reduced cardiac DFS warrants further study.

EP932 CIRCULATING MICRORNA MIR-99B AND MIR-125A IN MYELODYSPLASTIC SYNDROME-NONINVASIVE DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

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Background: Myelodysplastic syndrome (MDS) is a group of heterogeneous clonal hematologic disorders of hematopoietic stem cells, followed by ineffective hematopoiesis of one or more cell lines with the onset of consequent cytopenia with an increased risk of progression to acute myeloid leukemia. According to the World Health Organization classification, the diagnosis of MDS is based on morphological, clinical, cytogenetic, immunophenotypic and biological criteria.
In everyday clinical practice, the diagnosis of MDS is based on invasive cytomorphological analysis of peripheral blood and bone marrow cells, determination of blast percent, type and degree of dysplasia, presence of ring sideroblasts, and cytogenetic analysis of bone marrow cells.
Micro Messenger Ribonucleic Acids (miRNAs) are short, non-coding molecules of 18 to 25 nucleotides in length that play an important role in regulating cell development and metabolism, their differentiation and proliferation, regulation of the cell cycle and cell death. Tumor cells release miRNAs into the circulation (plasma, serum) where they remain relatively stable. Although their discovery allowed linking of disease and miRNA gene expression, a precondition for their clinical application was the determination of gene expression by real-time quantitative polymerase chain reaction with satisfactory efficacy and specificity. In the literature, gene expression of miRNAs has been linked to the diagnosis, classification and progression of various diseases.
Many studies have been conducted so far about the molecular mechanisms and epigenetic pathways in MDS and their prognostic and therapeutic significance, but few studies have analyzed the importance of miRNAs in MDS.
Aims: The aim of this study was to examine the level of change of gene expression of specific mRNAs (miR-125a, miR-99b, miR-126, miR-125b, miR-let-7a) in plasma of healthy volunteers and subjects diagnosed with MDS.
Methods: Gene expressions of miRNAs were determined at the Clinical Institute of Medical Biochemistry and Laboratory Medicine, Merkur University Hospital, accredited according to EN ISO 15189:2012, in plasma samples of 20 healthy volunteers and 41 MDS patients diagnosed at the Institute of Hematology of the Clinic for Internal Diseases of Merkur University Hospital, Reference Center of the Ministry of Health of the Republic of Croatia for Diagnosis and Treatment of MDS.
Results: A significant difference was found between the study group and healthy control in miR-99b level, where at normalized values relative to miR-126, an increased level in subjects compared to control was observed 4,521 times (P = 0.004).
There was negative correlation between miR-125a(rho=-0,326; P=0,038), RBC count and hemoglobin level (rho=-0,381; P=0,014).
miR-99b showed statistically significant positive correlation with WBC count (rho=0,310; P=0,048).
Summary/Conclusion: MiR-99b and 125a could serve as diagnostic and prognostic noninvasive biomarkers in MDS.
The results of the study suggest that gene expression of miRs (125a, 125b, 99b, let7a) could be regulated by the same mechanism and may be clinically relevant in subjects with MDS.

EP933 THE R-IPSS DOES NOT SEEM TO ACCURATELY PREDICT FATAL EVENTS IN MYELODYSPLASTIC SYNDROME PATIENTS WITH AUTOIMMUNE DISEASES

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Background: Myelodysplastic syndromes (MDS) are clonal hemopathies with a heterogeneous spectrum of presentation and a variable risk of transformation into acute myeloblastic leukemia (AML). Autoimmune diseases (AID) are present in 10 to 30% of cases, with unclear prognostic significance in this context. To date, the role of the R-IPSS in the context of an AID after an SMD has not yet been established.
Aims: To test the R-IPSS as a predictor as a predictor score of death/AML progression in MDS patients with AID. Secondary objectives were to study the association between the R-IPSS and the occurrence of an AID and the impact of AIDs on overall survival and leukemia-free survival (LFS).

Methods: We retrospectively collected data from primary MDS adult patients followed-up in the University Hospital of Poitiers between January 2010 and December 2019. Immunosuppressive therapy secondary-MDS were excluded. The date of onset and type of AID, as established by the standard criteria were collected. Simultaneous diagnoses of MDS and AID were considered if established in a 3-month interval from the MDS one. Left-censored patients (AID diagnosis before SMD) were dropped for the final survival analysis. A multistate cox model was performed with AID as an intermediate state. Baseline hazards proportionality for transitions to fatal events was tested by graph methods and checking the Schoenfeld residuals.
Results: AIDs were identified in 22 of 212 MDS patients (10.4%). MDS-AID patients were equally sex-distributed (p=0.45). Associated AIDs were as specified in table 1. At the time of SMD diagnosis, 54.2% of patients had general signs and 13% had cutaneous and/or joint signs. No association between AID and WHO MDS-subtypes was observed. We found a trend-significant benefic effect of low-risk R-IPSS (<3.5 points) on the development of an AID (HR 0.44; 95%CI 0.2-1.2; p=0.1). In this setting, skin symptoms were the only associated factor in our cohort (HR 6.7; 95%CI 2.7-16.4; p<0.001). Fifteen of 22 MDS-AID patients suffered from death/AML progression. As expected, R-IPSS was a good predictor for the combined endpoint of death and AML progression in the whole MDS cohort. However, once patients develop an AID, R-IPSS did not associate with fatal events (HR 3.5; 95%CI 0.5-24.1; p=0.2). In this setting, only the presence of cutaneous and general symptoms were associated with death/AML.

Autoimmune disease	n(%)
Rhizomelic Pseudopolyarthritis	1
Lupus	1
Hashimoto Tyroidite	1
Pyoderma gangrenosum	1
Dermatomiositis	1
Sweet's syndrome	5
Dysimmunity with anti-Ro52 positive anticorps	1
Lymphocytic colitis	1
Autoimmune hemolytic anemia	2
Horton's disease	1
Vascularitis NOS	2
Leukocytoclastic vasculitis	1
Sarcoidosis	1
Necrotizing cutaneous vasculitis	1
Sclerodermia	1
Chronic inflammatory demyelinating polyradiculoneuritis	1

Summary/Conclusion: The association of MDS to AIDs is of clinical heterogeneous expression. It tends to occur in low-risk MDS and does not seem to impact overall survival in our cohort.
The R-IPSS score (trend significantly) predicts the development of an AID (with an excess of risk for low-risk patients in our cohort) but once the autoimmune disease developed, it does not predicts accurately fatal events (AML and death). This finding lets us hypothesize the bigger role of AIDs severity than MDS factors in the mortality of MDS-AID.

EP934 IMPACT OF TRANSFORMATION TO ACUTE MYELOID LEUKEMIA (AML) ON OVERALL SURVIVAL (OS) AMONG PATIENTS (PTS) WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (HR-MDS) IN THE UNITED STATES OF AMERICA (USA)

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Background: MDS is a clonal blood stem cell disorder characterized by dysplasia and ineffective hematopoiesis leading to cytopenias and risk of transformation to AML. *Post hoc* analyses of a randomized phase 2 trial (NCT02610777) that compared pevonedistat + azacitidine (AZA) versus AZA alone, demonstrated that transformation to AML was associated with deterioration of quality of life (6/12 pts and 7/12 pts reported worsening of physical functioning and fatigue, respectively).[1] Furthermore, OS was longer (median, 27.7 months [mths]) in pts who did not transform to AML [n=53] vs 13.6 mths in pts who did [n=14]; hazard ratio (HR), 0.289; p=0.0002).[2]
Aims: This retrospective study assessed the impact of AML transformation on OS in pts with HR-MDS receiving first-line therapy (1LT).
Methods: Pts with HR-MDS (≥18 years old) who initiated 1LT between Jan 1, 2008, and Jun 30, 2019, were identified from a large USA electronic medical record (EMR) database. Owing to lack of complete cytogenetics in the EMR, HR-MDS was defined based on International Classification of Diseases (ICD) coding for HR-MDS (≥1 ICD-9/-10 codes: 238.73, D46.2[0-2]) or an adapted HR-MDS algorithm based on the Revised International Prognostic Scoring System classification (intermediate or higher risk). Pts were followed from the start of HR-MDS 1LT until death, loss to follow-up or study end. Probability of transformation to AML following HR-MDS 1LT was assessed using Kaplan–Meier analysis. To account for differential follow-up time between pts who transformed to AML and pts who did not, a landmark analysis was conducted. The landmark time of 6 mths was chosen based on the guideline-recommended minimal duration of MDS treatment (6 cycles) and the median time to transformation (5.9 mths) among pts treated with AZA who transformed to AML (n=9/14) from the aforementioned study.[2] In the landmark analysis, AML status (transformed to AML or not) was defined in the 6 mths following 1LT initiation in pts with ≥6 mths of follow-up. Cox proportional-hazards model was used to assess the impact of AML on OS from the landmark. To further validate the association between transformation to AML and OS, a time-varying Cox proportional-hazards model was considered, such that AML status was included as a time-varying variable. Both Cox models involved adjustments for baseline differences between pts with HR-MDS who transformed to AML and those who did not.
Results: 874 pts with HR-MDS were identified. Mean age was 71.9 years, and 43% had a Charlson comorbidity index of ≥2. Hypomethylating agents were the most common 1LT, with 62% of pts receiving AZA and 20% receiving decitabine. Median follow-up was 11.2 mths. In pts treated with 1LT, the rate of transformation to AML was 26.9% at 1 year and 39.4% at 2 years. The unadjusted landmark analysis showed shorter OS in pts who transformed to AML than in pts who did not (**Table**). These results were also consistent in subgroup of pts treated with AZA. Multivariable Cox proportional-hazard analysis also showed that transformation to AML was associated with worse survival. Pts who transformed to AML had a higher risk of death than pts who did not after adjusting for baseline differences in the 6-mth landmark analysis (HR, 1.82; 95% confidence interval [CI]: 1.18–2.81) and in the adjusted time-varying analysis at 1 year (HR, 2.85; 95% CI: 2.19–3.72).

Table: 6-month landmark analysis results.

Parameter	Pts who transformed to AML	Pts who did not transform to AML
Overall population	**n=76**	**n=543**
Median OS, months	9.7	15.4
KM survival rate 6 months after landmark, %	62.5	74.2
	p=0.006	
Azacitidine subgroup	**n=42**	**n=343**
Median OS, months	9.1	15.4
KM survival rate 6 months after landmark, %	63.9	74.6
	p=0.029	

KM, Kaplan–Meier; OS, overall survival; pts, patients; AML, acute myeloid leukemia.

References

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2. Sekeres MA *et al.* Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777) [abstract 653]. Presented at 62nd American Society of Hematology Annual Meeting and Exposition, December 5–8, 2020, virtual.

Summary/Conclusion: Among treated pts with HR-MDS, transformation to AML was associated with inferior OS. These results highlight the importance of delaying transformation to AML as a treatment goal.

EP935 CHANGES IN THE CONCENTRATION OF TUMOR NECROSIS FACTOR TNF-□ IN BLOOD SERUM AND THE LEVEL OF CD33+ SUBSTRATE CELLS IN THE BONE MARROW OF PATIENTS WITH MYELODYSPLASTIC SYNDROME.

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Background: Myelodysplastic syndrome (MDS) belongs to a clinically, morphologically, genetically heterogeneous group of diseases characterized by clonality and arising from mutations in the hematopoietic progenitor cell, moreover, the disease has a progressively unfavorable course and a high probability of transformation into acute leukemia.
CD33+ expression is known to occur mainly on myeloid progenitor and hematopoietic stem cells and maturing granulocytes. At the same time, CD33+ has been shown to constitutionally inhibit the production of proinflammatory cytokines such as IL-1 and TNF-a. There are isolated pieces of evidence of increased cytokine secretion and cytokine-induced hematopoietic cell proliferation with decreased CD33+ expression.
Aims: The study aimed to establish the relationship between TNF-a and CD33+ cells in the bone marrow of patients with MDS RAEB I depending on the level of response to Lenalidomide therapy.
Methods: The object of the study was 25 patients with MDS RAEB I aged 36 to 81 years (mean age 58 years). The diagnosis was made based on clinical data and mandatory laboratory tests. Verification of the diagnosis of MDS RAEB I was carried out in accordance with the WHO criteria for myeloid neoplasms and acute leukemias, 2008. The duration of the disease at the time of inclusion of patients in the examination varied from 4 to 9 months. All patients included in the study corresponded to the functional state of ECOG-1 ECOG-2.
The immunophenotypic profile of tumor cells was established by flow laser cytometry. Determination of TNF-a concentration was performed by enzyme-linked immunosorbent assay using standard kits using an enzyme-linked immunosorbent assay "MultiScan EX" at a wavelength of 430 nm. The control was the plasma of healthy individuals. Student's test was used for statistical processing of the received data.
Results: Analysis of the obtained data shows an increase in the number of CD33+ cells in the bone marrow of patients with MDS RAEB I 1.4 times before treatment 13.9±1.7%, with an improvement of 19.8±1.3% (p<0, 05). The level of TNF-a with improvement decreased to 8.9±0.3 pg /ml at the pre-treatment rate of 11.3±0.5 pg/ml (7.9±0.5 pg/ml healthy individuals). In the group of 11 people (40.7%) with stabilization of the disease, the indicators of CD33+ and TNF-a remained at the pre-therapeutic level. Progression of the pathological process occurred in 33.3% (9 people) with reduced CD33+ cells in the bone marrow to 9.5±0.5%, which is 1.5 times lower than in patients before treatment and 2.08 times less, than in the period of improvement (19.8±1.3%). At the same time, there was an increase in the concentration of TNF-a in 1.4 times, compared with the improvement group (12.9±0.2 pg / ml and 8.9±0.3 pg / ml), respectively (p <0.05). The level of TNF-a in the groups before treatment and in the period of stabilization of the process did not differ significantly.
Summary/Conclusion: Thus there is an inverse relationship between TNF-a and CD33+ in different responses to treatment with Lenalidomide in patients with MDS RAEB I.

Myeloma and other monoclonal gammopathies - Biology & Translational Research

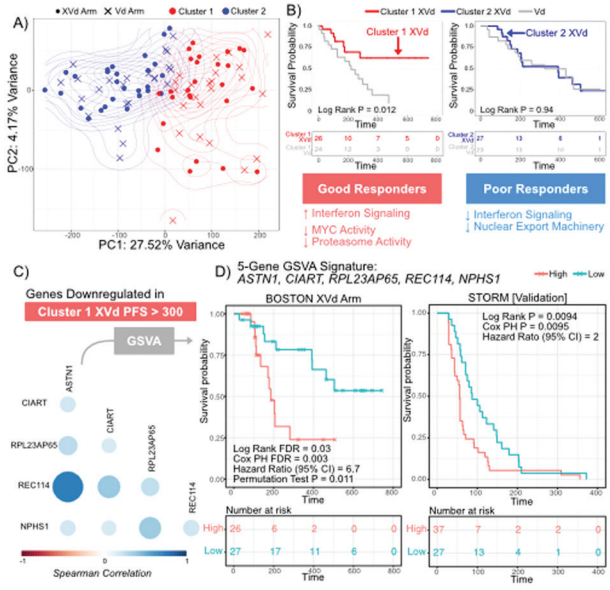
EP936 GENOMIC CORRELATES OF RESPONSE TO SELINEXOR IN MULTIPLE MYELOMA FROM THE BOSTON STUDY REVEAL A PREDICTIVE SIGNATURE

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Background: The BOSTON study, a phase 3, randomized, open label clinical trial, has shown a clinical benefit of selinexor combined with bortezomib and dexamethasone (XVd) in patients with multiple myeloma. Selinexor acts by inhibiting the nuclear export protein XPO1, however, XPO1 expression does not correlate with response and the biological mechanisms underlying treatment response remain unclear. Additionally, while the overall response rate for XVd in the BOSTON study was 76.4%, there are currently no known genomic biomarkers to help guide treatment recommendations.
Aims: In this study, we characterized genomic and transcriptomic correlates of response to selinexor and identified potential biomarkers for clinical use.
Methods: We performed RNA sequencing on CD138+ cells from 100 patients who participated in the BOSTON study. We performed differential expression, followed by pathway analysis, to compare patients with long and short progression-free survival (PFS) in the XVd arm of the BOSTON dataset. Using the differentially expressed genes, we calculated GSVA (Gene Set Variation Analysis) scores and performed time-to-event univariate Cox proportional hazard models and log-rank testing to identify a novel gene expression signature that predicts PFS in the BOSTON dataset. We validated our signature using transcriptomic data from 64 patients from STORM, a clinical trial of selinexor combined with dexamethasone in patients with penta-refractory multiple myeloma.
Results: Through gene expression analysis, we identified a cluster of patients who are more likely to experience longer PFS with XVd as opposed to Vd (log rank p = 0.012, Fig 1A-B). We found that patients within the XVd arm in this cluster tend to be younger (wilcoxon p = 0.0029). Within this cluster of responders, we identified a total of 198 unique genes associated with longer PFS in the XVd arm (FDR < 0.05) that were not significantly associated with PFS in the Vd group. Furthermore, pathway analysis revealed increased interferon signaling, Myc deactivation, and proteasome downregulation in patients with longer PFS in this cluster (FDR < 0.05, Fig 1B). We identified a GSVA-based expression signature consisting of five genes, *ASTN1*, *REC114*, *CIART*, *RPL23AP65*, and *NPHS1*, that were downregulated in XVd patients with PFS > 300 days (Fig 1C). Using this signature, we accurately distinguished patients with long term PFS in the XVd arm of the BOSTON study (Cox proportional hazard model, FDR=0.003, hazard ratio=6.7, Fig 1D). Three of these five genes, *ASTN1*, *NPHS1*, and *RPL23AP65*, were also downregulated in patients that had better depth of response, defined as very good partial response (VGPR) or better. This signature validated successfully in the STORM study (Cox proportional hazard model, p=0.0095, hazard ratio=2, Fig 1D).

Figure 1. *Expression-based clusters identify patients likely to see longer PFS from XVd as opposed to Vd*



Summary/Conclusion: We report a novel, prognostic biomarker signature for selinexor, bortezomib and dexamethasone response in patients with multiple myeloma. We have validated our findings in the STORM cohort and are currently validating our findings in additional, independent cohorts of multiple myeloma patients treated with selinexor. This signature has important clinical relevance as it could identify patients most likely to benefit from treatment with selinexor-based therapy.

EP937 DEVELOPMENT OF NEXT-GENERATION ANTITUMOR ANTIBODIES ARMED WITH BRIDGING-BITE TO ADVANCE ANTI-MYELOMA IMMUNOTHERAPY

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Background: Immunotherapy using monoclonal antibodies (mAbs) has improved clinical outcomes of patients with multiple myeloma (MM). Nevertheless, the prognosis of relapsed/refractory MM (RRMM) patients still remains poor probably due to the heterogeneity of myeloma cells, highlighting the need for the development of novel therapeutic approaches. Recently, new antibody-based modalities have been developed, and tested in clinical trials for RRMM. Bispecific T-cell engager (BiTE) which can induce antitumor T-cell responses has a potential to treat RRMM. In contrast, some issues would be raised to improve advantages of this modality. First, BiTE lacks an Fc domain which needs to induce NK-cell responses. Second, BiTE is continuously administered to induce sufficient antitumor effects because of its low molecular weight. Third, BiTE can target an antigen expressed by tumor cells, suggesting the weakness against heterogenous tumors. To overcome these obstacles, we have developed a novel BiTE-based modality, Bridging-BiTE (B-BiTE), which endows a series of clinically available mAbs with both NK-cell and T-cell activation capacity.
Aims: In this study, we have investigated the efficacy, universality, and safety of a mAb armed with B-BiTE for the treatment of MM.
Methods: B-BiTE, which encodes a single chain fragment variable (scFv) specific for an Fc domain and an scFv specific for the CD3ε, was designed. B-BiTE was mixed with a mAb at the molar ratio of 1:1 to generate B-BiTE/mAb complex. Proliferation and cytokine production by human peripheral blood T cells/NK cells for target cells in the presence of B-BiTE/mAb was measured by flow cytometry. Their cytotoxicity against target cells was assessed by ^{51}Cr-release assays. Five-week-old NOG mice were inoculated with MM1S myeloma cells. Then, antitumor effects and overall survivals of mice treated with a mAb alone or B-BiTE/mAb were compared.
Results: Using the CD20-specific mAb, Rituximab as a model, we have demonstrated that B-BiTE/Rituximab successfully bound to both CD20$^+$ tumor cells and human T cells, and activated human peripheral blood T cells as well as NK cells against tumor cells *in vitro*. Therefore, we applied B-BiTE to the CD38-specific mAb, Daratumumab (Dar) and the SLAMF7-specific mAb, Elotuzumab (Elo) to target myeloma cells. Human peripheral blood CD8$^+$ and CD4$^+$ T cells proliferated, and produced multiple cytokines against both CD38$^+$SLAMF7$^-$ and CD38$^-$SLAMF7$^+$ myeloma cells in the presence of B-BiTE/Dar and B-BiTE/Elo without increasing the frequency of regulatory T cells. Moreover, their antitumor cytotoxicity induced by B-BiTE/Dar and B-BiTE/Elo was enhanced when compared with that mediated by Dar/Elo alone *in vitro* and *in vivo*. Importantly, human peripheral blood T cells and NK cells obtained from patients with myeloma cooperatively responded to their own myeloma cells in the presence of B-BiTE/mAb. Furthermore, in the presence of polyclonal immunoglobulin, B-BiTE/mAb activated T cells/NK cells for myeloma cells, but did not induce any reactivity to normal cells.
Summary/Conclusion: B-BiTE can be a new modality to easily generate stable, safe, and effective bispecific antibodies from clinically available mAbs. This modality can allow us to prepare a panel of next-generation antibodies which induce both T-cell and NK-cell responses, resulting in further advancement of immunotherapy for RRMM.

EP938 ISB 1342: A FIRST-IN-CLASS CD38 T CELL ENGAGER FOR THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA

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Background: ISB 1342 is a bispecific antibody heterodimer based on the Ichnos proprietary Bispecific Engagement by Antibodies based on T cell receptor (BEAT®) platform. ISB 1342 is a first-in-class CD38 T cell engager under investigation in subjects with relapsed multiple myeloma refractory to proteasome inhibitors (PIs), immunomodulators (IMiDs) and daratumumab (study ISB 1342-101).
Aims: The aim of this study is to assess on target specificity and potency of ISB 1342 in vitro and in vivo.
Methods: ISB 1342 was engineered with a single chain variable fragment (scFv) arm that specifically recognizes a cluster of differentiation (CD)3-epsilon (CD3ε) and a fragment antigen binding (Fab) arm which specifically recognizes CD38 and does not compete with daratumumab. By co-engaging CD3ε on T cells and CD38 on tumor cells, ISB 1342 redirects T cells to kill CD38-expressing tumor cells. This mechanism of action is differentiated from existing monospecific CD38 targeting therapies and was designed to overcome resistance to daratumumab in multiple myeloma
Results: *In vitro*, ISB 1342 killed a large range of CD38-expressing tumor cell lines (EC50:12 to 90 pM) with 8 to 239-fold superior efficacy than daratumumab. ISB 1342 was also able to efficiently kill CD38 low-intermediate-expressing tumor cells that were poorly killed by daratumumab. ISB 1342 retained the potency to kill CD38 low-intermediate-expressing tumor cells when used in sequential or concomitant combination with daratumumab. In addition, the presence of soluble CD38 or glucocorticoid did not impact ISB 1342 killing potency. ISB 1342 was constructed with a double LALA mutation that dampens the binding to Fcγ receptors and C1q. Consistently, ISB 1342 showed only residual Fc-mediated effector functions and its mechanism of tumor cell killing critically relies on the engagement and the activation of T lymphocytes. ISB 1342 showed a favorable on target specificity profile *in vitro* and was unable to activate T cells in the absence of CD38 positive target cells. Further, ISB 1342-induced tumor cell killing was not associated with a detectable T cell fratricide *in vitro*. Finally, the potency of ISB 1342 was assessed *in vivo* in a therapeutic model of a subcutaneously established Daudi tumor co-xenografted with human PBMCs. In marked contrast to daratumumab, which induced only a partial tumor control, ISB 1342 induced complete tumor eradication when injected intravenously weekly at 0.5 mg/kg. As anticipated, the ISB 1342 control molecule (ISB 1342_13DU) made of an irrelevant CD38 binder failed to control tumor growth. The release of the Granzyme A and B, TNF-alpha and CXCL-10 in the tumor micro-environment one week post-treatment was strongly and significantly increased by ISB 1342 but not by daratumumab and ISB 1342_13DU; this represents a correlate of anti-tumor immunity associated with ISB 1342 efficacy *in vivo*.
Summary/Conclusion: Hence the higher potency of ISB 1342 relative to daratumumab supports the ongoing clinical development in multiple myeloma patients.

EP939 A NOVEL ONCOLYTIC LENTIVIRAL VECTOR FOR THE TARGETED AND THERAPEUTIC IFNB- EXPRESSION IN MULTIPLE MYELOMA

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Background: Multiple myeloma (MM) is a plasma cell malignancy that remains incurable for most patients and, thus, new therapies are urgently needed. Oncolytic viruses are a promising new class of therapeutics that provide tumor-targeted therapy. In the context of developing a novel therapeutic approach for MM, we generated an IFNβ-expressing lentiviral vector (LV), pseudotyped with the measles virus HF glycoproteins that target myeloma cells through the binding to CD46 and SLAM receptors.
Aims: The purpose of this study was to assess the therapeutic efficacy of IFNβ/HF *in vitro* in H929 and JJN3 myeloma cell lines, as well as in primary cells from MM patients on first-diagnosis.
Methods: Production of IFNβ/HF and control GFP/HF LVs was carried out by transient co-transfection of HEK-293T cells. Vector titration and vector copy number per cell (VCN/cell) were determined by flow cytometry and qPCR, respectively. Cell survival and cytotoxicity were evaluated using Trypan blue exclusion and CCK-8 colorimetry assays, respectively. Apoptosis was estimated by Annexin V/7-AAD staining. The expression of apoptotic gene expression was determined by qPCR and Human Apoptosis Antibody Array, at mRNA and protein level, respectively. IFNβ secreted by IFNβ/HF-transduced cells was determined by ELISA, while its paracrine mechanism of action was evaluated by the Transwell® co-culture assay. Cell cycle analysis was performed with flow cytometry and propidium iodide. Lastly, serum neutralizing antibody activity was evaluated by flow cytometry on JJN3 cells transduced with GFP/HF LV, previously incubated with MM and normal donors' serum.
Results: IFNβ/HF LV exhibited a mean transduction efficiency of 29.5% (H929) and 23.1% (JJN3) and a mean VCN/cell of 1.6 and 1.2, respectively. Moreover, IFNβ/HF-transduction at MOI of 1, led to a dramatic 90.6% and 95.2% reduction of cell survival in H929 ($p=0.01$) and JJN3 ($p=0.04$) cells, respectively. Regarding apoptotic cells in H929 and JJN3 cells, a marked 90.3% ($p\leq0.001$) and 74.1% ($p\leq0.001$) increase was observed. Notably, the increase of Caspases 3 and 9 as well as of HtrA/Omi and Endo G proteins, both at the RNA and protein level, highlights the crucial role of the intrinsic apoptotic pathway as well as the caspase-independent pathway in the IFNβ-induced apoptosis. Moreover, a great reduction in the expression of the anti-apoptotic genes Bcl-2 and Bcl-xl was observed in IFNβ-transduced H929 and JJN3 cells. After Transwell® co-culture, IFNβ secreted by the transduced cells, was capable of significantly decreasing the viability of *untransduced* cells while the percentage of untransduced apoptotic cells surpassed 30% for both H929 ($p=0.004$) and JJN3 ($p=0.01$) cells. Furthermore, IFNβ/HF efficiently transduced primary cells (MOI=10) from patients with MM, decreasing cell survival up to 49.8% ($p=0.0089$), with a 51.8% increase of apoptosis ($p=0.01$) and induction of cell cycle arrest at a mean VCN/cell of 3.6. Finally, it was showed that the barrier of pre-existing immunity can be overcome using a higher MOI of 20, a positive outcome for its *in vivo* administration in patients vaccinated against measles virus.
Summary/Conclusion: Overall, the results of our study demonstrate that the IFNβ/HF LV can efficiently target and kill myeloma cells, providing evidence about the molecular mechanisms involved in cell death. Thus, our findings suggest that IFNβ/HF is a promising therapeutic candidate as a selective antitumor agent for the treatment of MM.

EP940 LONG-ACTING STARCH NANOPARTICLE DRUG DELIVERY SYSTEM TO TREAT MULTIPLE MYELOMA

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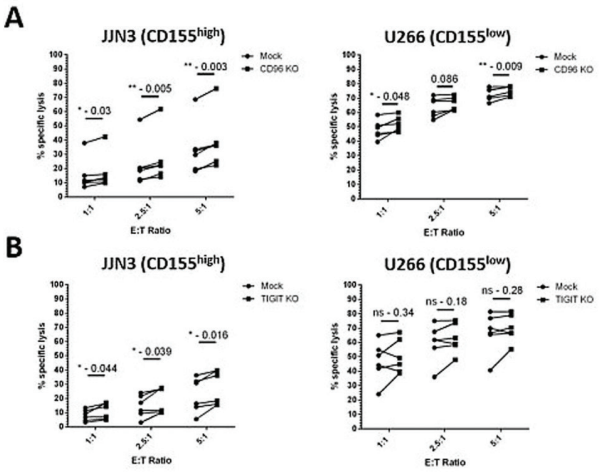
Background: Nanoparticle delivery systems offer a new approach to increase the effectiveness of treatment and decrease side effects in normal tissues by delivering drugs to the target tissue. Nanoparticle delivery systems have the potential to improve multiple myeloma treatment by increasing specificity and efficacy for example by improving localized concentration in the bone marrow and reducing adverse systemic effects. Furthermore, since orally administered drugs require strict patient compliance, some patient populations can benefit from intermittent dosing and sustained drug release properties. Bone is an advantageous microenvironment for tumor growth in multiple myeloma. Targeting tumor cells within the bone marrow remains a complex challenge due to issues with bone penetration and resistance in the tumor microenvironment.
Aims: Starch is one of the most abundant biomass materials in nature, and is non-toxic, biodegradable, edible, and relatively inexpensive material. The aim of the study was to develop a starch nanoparticle matrix for bone-targeted drug delivery and controlled release of the encapsulated drug for long-acting drug formulations.
Methods: We have previously patented a method for preparing starch nanoparticles (WO2015144983A1) using mechanical high-pressure homogenization at decreased temperatures. The chosen drug pomalidomide was encapsulated inside the starch nanoparticle matrix in situ during the fluidization process. Bone-targeting was achieved by modifying the matrix with alendronic acid. The efficacy of the starch nanoparticle formulations were studied in vitro and in vivo using mouse xenograft models.
Results: In vivo biodistribution of pomalidomide encapsulated with the modified starch nanoparticles showed increased retention and accumulation in the bone microenvironment. A significantly longer survival and decrease in tumor burden was shown when comparing the nanoparticle-delivered pomalidomide with standard oral dosing. Bone strength and volume was additionally improved. Even up to Q3W dosing was achievable using the starch nanoparticle encapsulated pomalidomide.
Summary/Conclusion: The starch nanoparticles offer a simple setup of a bio-based, non-toxic matrix for preparing drug nanoparticles without the use of any toxic chemicals. The present study demonstrates that the modified starch nanoparticles maintained a long-acting therapeutic concentration of pomalidomide and decreased tumor burden in the mouse models. Bone microenvironment targeting was achieved by modifying the nanoparticles in situ. The maximum drug loading capacity of the starch nanoparticle formulations was in the range required for a potential human dosing scheme. The presented method is clinically relevant and holds potential to decrease tumor growth in multiple myeloma.

EP941 KNOCKOUT OF CD96 OR TIGIT USING CRISPR/CAS9 ENHANCES NK INDUCED CYTOTOXICITY AND CYTOKINE PRO DUCTION IN THE PRESENCE OF CD155 EXPRESSING MYELOMA CELLS

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Background: Natural Killer (NK) cells are cytotoxic lymphocytes with an innate ability to recognize and destroy malignantly transformed cells. Using an array of activating and inhibitory receptors, cells are screened by NK cells and a net stimulus determines whether the target cell is released or destroyed. CD96 (TACTILE) is an inhibitory receptor expressed by NK cells, and ligand binding studies have shown that CD96 competes with the co-activating receptor DNAM-1 (CD226) for the shared ligand CD155. Blocking CD96 using a monoclonal antibody can reduce metastasis of solid tumours in mouse models. However in human NK cells conflicting data has shown CD96 to be both an activating and inhibitory receptor. Here, we identify CD96 as a human NK cell inhibitory receptor in Multiple Myeloma (MM), with CRISPR/Cas9-mediated KO of CD96 enhancing NK cell cytotoxicity and cytokine release. We conducted these experiments in parallel with CRISPR/Cas9-mediated KO of TIGIT in NK cells, as TIGIT has been documented as an inhibitory receptor, also binding CD155.
Aims: Using CRISPR/Cas9, target and knockout CD96 and TIGIT in expanded primary NK cells (epNK) and study the effect of KO on NK cell cytotoxicity and cytokine release when co-cultured with $CD155^{positive}$ MM cell lines JJN3 and U266
Methods: NK cells were isolated from fresh blood supplied by consenting healthy donors and expanded using NK Macs Medium. NK cells were incubated with either a multi-guide sgRNA-Cas9 complex (KO) or electroporation buffer (Mock) and electroporated using the MaxCyte GT. NK cells were cultured to allow for complete KO. Mock and KO NK cells were co-cultured with JJN3 or U266 MM cell lines at several E:T ratios. MM cell death was measured using the ZOMBIE fixable viability dye. $4x10^5$ Mock and KO NK cells were cultured at a 1:1 E:T ratio with JJN3 and U266 MM cell lines. The supernatant was used to test for the presence of TNF-α and IFN-γ using specific ELISA kits.
Results: Expression of CD155 was observed on a panel of MM cell lines. CD96 and TIGIT expression was observed on epNK cells (CD96:95%±1.45, TIGIT:27.55%±2.8). JJN3 were classed as $CD155^{high}$ and U266 as $CD155^{low}$. Using CRISPR/Cas9, over 90% and 75% KO was observed for CD96 and TIGIT ($p<0.0001$). Enhancements in cytotoxicity were observed by CD96 and TIGIT KO NK cells, compared to Mock controls. Particularly, the strongest enhancements were against the $CD155^{high}$ JJN3 MM cells (Fig.1). While TIGIT KO did not enhance secretion of TNF-α, CD96 KO resulted in a strong increase in TNF-α secretion when CD96 KO NK cells were co-cultured with U266 ($p=0.0011$), no observable change was observed with JJN3. TIGIT KO NK cells secreted significantly more IFN-γ when co-cultured with JJN3 (ns) and U266 ($p=0.0094$), while CD96 KO NK cells secreted more IFN-γ than when co-cultured with both JJN3 (ns) and U266 ($p=0.0012$). NK cells isolated from MM patient bone marrow aspirates were observed to have higher proportion of CD96 positive cells (45.8%±2.75) than NK cells from healthy peripheral blood (24%.16±3.1, $p=0.0043$).



Summary/Conclusion: This study identifies CD96 conclusively as an inhibitory receptor on human NK cells, regulating cytotoxicity and cytokine release which are enhanced upon KO using CRISPR/Cas9. Elevated CD96 expression on NK cells from MM patient bone marrow aspirates suggests that the tumour microenvironment may exaggerate the CD96/CD155 axis to promote immune-evasion of NK cells. In carrying out this research, we also present efficient genetic manipulation of NK cells to eliminate inhibitory receptor expression as a promising approach for personalised cancer treatments.

EP942 INDUCTION OF ELOTUZUMAB'S ADCC ACTIVITY BY TH1-LIKE GAMMA DELTA T CELLS TOWARDS OSTEOCLASTS AS WELL AS MYELOMA CELLS

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Background: Antibody-dependent cellular toxicity (ADCC) is among predominant MOAs of anti-CD38 and anti-SLAMF7 therapeutic monoclonal antibodies (mAbs), which is augmented with IMiDs, lenalidomide (LEN) and pomalidomide (POM). However, effector function of immune cells is attenuated and exhausted in patients with MM, especially after repeated relapses or elderly frail patients, which hampers clinical efficacy of these therapeutic mAbs. To overcome this issue, we have been studying the utilization of γδ T cells for MM treatment. Human γδ T cells are important effectors in the first-line defense against infection and tumors, and we reported that such expanded γδ T cells effectively target and impair not only MM cells but also osteoclasts (OCs) (Cui, et al. IJH 2011) and that LEN and POM are able to activate and expand Th1-like γδ T cells and enhance their cytotoxic activity against MM cells in combination with recombinant phosphoantigens as well as zoledronic acid (Harada et al. Leukemia 2017).
Aims: The present study was undertaken to explore the effects of anti-CD38 and anti-SLAMF7 therapeutic mAbs on cytotoxic activity of the expanded human Th1-like γδ T cells against OCs and MM cells.
Methods: Th1-like γδ T cells were expanded from peripheral blood mononuclear cells (PBMCs) *ex vivo* by aminobisphosphonates in combination with IL-2. OCs were induced from PBMCs or isolated monocytes using M-CSF plus RANK ligand. The suface markes and protein expression were detected by flow cytometry and Western blotting.
Results: The expanded Th1-like γδ T cells highly expressed CD16, FcγRIIIa, together with perforin and granzymeB as well as the cytotoxicity-associated costimulatory molecules NKG2D and DNAX accessory molecule-1 (DNAM-1; CD226), similar to NK cells. The expanded Th1-like γδ T cells exerted direct cytotoxic activity towards OCs as well as MM cells. Addition of the anti-SLAMF7 mAb elotuzumab (ELO) further increased the cytotoxic activity of Th1-like γδ T cells against SLAMF7-expressing MM.1S and OPM-2 cells but not RPMI 8226 cells with marginal SLAMF7 expression, indicating induction of ADCC activity by Th1-like γδ T cells in combination with ELO. Induction of ADCC activity by Th1-like γδ T cells was much more potent with ELO compared to anti-CD38 therapeutic mAbs, daratumumab and isatuximab, suggesting suitability of Th1-like γδ T cells for ADCC induction with ELO. Interestingly, cytotoxic activity of Th1-like γδ T cells against OCs was also augmented in combination with ELO, although ELO alone did not show any cytotoxic activity against OCs, indicating the emergence of ELO's ADCC with Th1-like γδ T cells towards OCs. SLAMF7 expression was induced and robustly upregulated during osteoclastic differentiation from monocytes with M-CSF and RANK ligand, and ELO could target preOCs as well as OCs. MM cells interact with OCs to form vicious cycle between MM cell growth and osteoclastogenesis (Abe, et al. Blood 2004); however, ELO markedly potentiated

the γδ T cell-induced cell death against both MM cells and OCs in their cocultures.
Summary/Conclusion: These results collectively demonstrate that SLAMF7 is highly expressed in both MM cells and OCs, and that OCs as well as MM cells are susceptible to ELO's ADCC with Th1-like γδ T cells. Further study is warranted on ELO's ADCC activity for ambient cells in MM bone marrow and effective revitalization and expansion of Th1-like γδ T cells to make the better use of ELO's ADCC activity.

EP943 PROGRESSION AND DISSEMINATION OF EXPERIMENTAL MULTIPLE MYELOMA IS ASSOCIATED WITH LOSS OF INNATE AND ADAPTIVE IMMUNE-MEDIATED TUMOR CONTROL

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Background: Multiple myeloma is an incurable plasma cell malignancy and identifying mechanisms driving disease progression is crucial for future development of novel therapies. Immune-mediated control of tumor progression is an important factor in many malignancies, yet the cells and signals that constitute an effective anti-myeloma immune response are incompletely defined.
Aims: To identify immune-related mechanisms of disease progression in experimental multiple myeloma.
Methods: Intravenous transfer of 10^6 5TGM1-GFP murine myeloma cells into KaLwRij mice leads to myeloma development in 3 weeks. In contrast, C57BL/6 mice are reported to be resistant to myeloma development. We used both mouse strains and monitored tumor development through serum M-protein levels. Bone marrow and spleen were harvested to analyze the immune microenvironment and determine tumor dissemination with flow cytometry and histology.
Results: Myeloma was defined by >5% tumor cells in BM, presence of tumor cells in the spleen and detection of M-protein >2 mg/ml. In KaLwRij mice, myeloma developed in 100% (14/14) of mice while C57BL/6 mice did not develop myeloma based on these criteria. Interestingly, 65% (9/14) of C57BL/6 mice presented with myeloma cells in the bone marrow, but with significantly lower tumor load (M-protein 1.1 mg/ml vs. 5.8 mg/ml) compared to KaLwRij mice. This low tumor burden remained stable and was confined to the bone marrow, without any splenic involvement, suggestive of active tumor restraint. To identify the mechanism of successful immunological containment of myeloma cells, we compared the cytotoxic immune response in C57BL/6 and KaLwRij mice. In both murine strains, NK cell activation was apparent, with upregulation of early activation markers such as CD69 in response to tumor presence. In contrast, while activation was accompanied by an increase in NK cell numbers in the C57BL/6 mice, this expansion was absent from KaLwRij mice. Similarly, $CD8^+$ T cell activation and an increase in number of $CD11b^+$ recently activated $CD8^+$ T cells was present in C57BL/6 mice, yet absent from KaLwRij mice.
These data suggest a combined innate and adaptive immune-mediated control of multiple myeloma in C57BL/6 mice. To determine the stability of this immune-mediated control of multiple myeloma we followed C57BL/6 mice injected with 5TGM1 myeloma cells over time while monitoring tumor load through serum M protein. At 6 weeks post injection, 71% (5/7) of the C57BL/6 mice with low tumor load at 3 weeks had developed progressive disease, with serum M protein levels > 2 mg/ml and >5% myeloma cells in the bone marrow. Reassessing cytotoxic immune responses in myeloma-bearing C57BL/6 mice revealed a stark decline in absolute numbers of activated NK cells, very similar to the phenotype in KaLwRij mice. Interestingly, loss of $CD8^+$ T cells was seen in about half (2/5) of the C57BL/6 mice and was associated with loss of bone marrow-containment and the appearance of myeloma cells in the spleen.
Summary/Conclusion: Failure to mount adequate anti-myeloma immune responses is one of the drivers of disease development in KaLwRij mice. Transfer of 5TGM1 myeloma cells in C57BL/6 mice leads to tumor control via expansion of innate and adaptive immune cells. With time, immune-mediated restraint of multiple myeloma fails, exemplified by loss of NK cell and $CD8^+$T cell expansion, culminating in tumor outgrowth and systemic dissemination. This model will allow generation of novel insights into the mechanisms of immune escape by multiple myeloma cells.

EP944 SEA-BCMA, AN ENHANCED ANTIBODY FOR MULTIPLE MYELOMA, COMBINES EFFECTIVELY WITH MULTIPLE THERAPEUTIC MODALITIES

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Background: Despite newly emerging therapies, significant unmet need remains in Multiple Myeloma (MM). Patients require multiple lines of therapy and ultimately succumb to disease. Therapies that are active, but well tolerated are crucial for these patients. Therapeutic antibodies have transformed the MM treatment paradigm, allowing patients to achieve deeper responses with minimal added toxicity, particularly in the therapeutic combination setting. SEA-BCMA is an investigational humanized nonfucosylated IgG1 antibody targeting BCMA, which shows preclinical evidence of encouraging activity and tolerability[1]. Preclinical studies show SEA-BCMA elicits anti-tumor activity through three mechanisms of action: (1) increased binding to FcγRIII through SEA technology leading to enhanced antibody dependent cellular cytotoxicity; (2) engagement of antibody dependent cellular phagocytosis; (3) blockade of the proliferative signals from BCMA ligand binding.
Aims: Here we show the preclinical combination of SEA-BCMA with therapeutics relevant to MM and BCMA targeting
Methods: We tested in vitro and in vivo combinations of SEA-BCMA with daratumumab, IMiDs, ADCs, and gammasecretase inhibitors.
Results: SEA-BCMA combines effectively with daratumumab in preclinical MM tumor xenograft models, creating an opportunity for a well-tolerated, antibody-based combination regimen. We also show increased anti-MM activity when SEA-BCMA is combined with standard of care IMiDs. In addition, SEA-BCMA combines effectively with antibody-drug conjugates in preclinical MM tumor xenografts leading to improved anti-tumor activity and prolonged survival in mice. Lastly, we evaluated SEA-BCMA in combination with gamma secretase inhibitors (GSIs), which block membrane cleavage of BCMA leading to increased membrane BCMA and decreased soluble BCMA[2]. We show here that GSI treatment enhances the SEA-BCMA activity by increasing Fcγ receptor activation and subsequent effector function.
Summary/Conclusion: In summary, SEA-BCMA shows preclinical evidence of combinability with multiple agents. SEA-BCMA is currently enrolling in a Phase 1 clinical trial for relapsed / refractory multiple myeloma (NCT03582033), and ongoing preclinical work supports potential combination strategies for future clinical investigation.
1) Van Epps et al., Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14-18; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 3833
2) Laurent et al. *Nat Commun* **6**, 7333 (2015). https://doi.org/10.1038/ncomms8333

EP945 MELFLUFEN RAPIDLY ACCUMULATES WITHIN TUMOR CELLS AND DISTRIBUTES AN ALKYLATING PAYLOAD TO THE NUCLEUS AND MITOCHONDRIA

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Background: Melphalan flufenamide (melflufen) is a novel peptide–drug conjugate that rapidly delivers a cytotoxic alkylating agent into tumor cells. High lipophilicity of melflufen allows for increased cellular uptake, and once inside the cell, aminopeptidases hydrolyze melflufen leading to entrapment and increased concentration of cytotoxic alkylating agents. Previous studies demonstrated that treatment of myeloma cells with melflufen results in significantly higher intracellular concentrations and cytotoxicity than melphalan. In addition to increased intracellular concentration, the increased lipophilicity of melflufen has the potential to contribute to altered intracellular distribution and distinct mechanisms of action.
Aims: The subcellular localization of melflufen and melphalan could have consequences regarding unique mechanisms of action and overcoming resistance mechanisms. Therefore, understanding the subcellular localization patterns of melflufen and melphalan, and the specific effects within organelles, will provide insight into the activity of these agents in myeloma and other tumor cells.

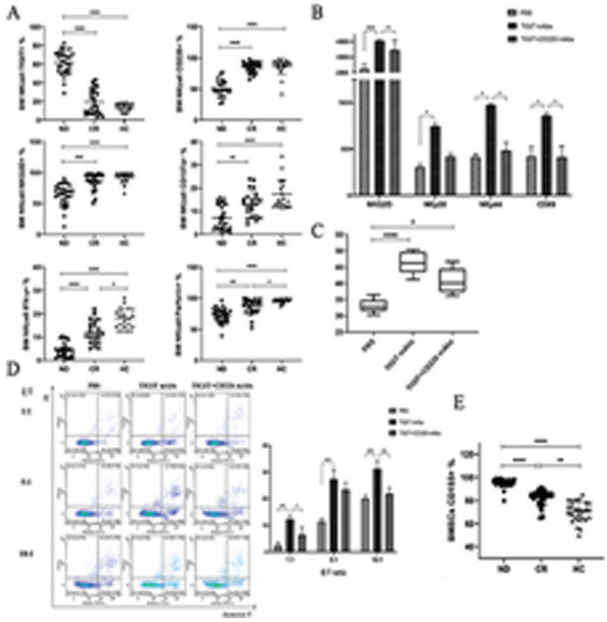
Methods: Using radiolabeled melflufen and melphalan, we directly examined the uptake of melflufen compared to melphalan within the cytosol of the cell, as well as within the nucleus, mitochondria, lysosomes and endoplasmic reticulum (ER). Furthermore, we assessed the effects of melflufen with regard to inducing mitochondrial DNA damage as well as effects on mitochondrial reactive oxygen species, mitochondrial specific gene expression and membrane potential to assess mitochondrial function in response to melflufen and melphalan treatment.
Results: We confirmed the increased cellular uptake of melflufen into the cytosol of myeloma cells, and further established that unlike melphalan, melflufen rapidly accumulated within the nucleus, where DNA alkylators are expected to function. Additionally, we determined that melflufen, but not melphalan, localized significantly within lysosomes, ER, and importantly, mitochondria where resulting effects on mitochondrial stress were analyzed. We also examined mitochondrial expression of specific aminopeptidases with potential to hydrolyze melflufen to deliver the alkylating payload within the mitochondria. Finally, expression of mitochondrial specific gene transcripts was analyzed for effects unique to melflufen treatment resulting from melflufen accumulation.
Summary/Conclusion: The increased lipophilicity of melflufen functions not only to increase tumor cell intracellular exposure, but also redistributes the alkylating payload within the cell which may have implications for additional mechanisms of action, and contribute to overcoming resistance mechanisms.

EP946 STUDY OF BONE MARROW MESENCHYMAL STEM CELLS REGULATING NK CELLS FUNCTION THROUGH TIGIT/CD226 IN PATIENTS WITH MULTIPLE MYELOMA

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Background: Bone marrow microenvironment plays a significant supporting role in the proliferation, differentiation, migration, survival and drug resistance of myeloma cells.
Aims: To detect the expression of the co-inhibitory receptor TIGIT and the co-stimulatory receptor CD226 on the surface of natural killer cells (NK cells) in multiple myeloma (MM) patients, and changes in the immune phenotypes and killing function of NK cells. Furthermore, to explore the underlying mechanism of bone marrow mesenchymal stem cells (BMSCs) regulating NK cells function through TIGIT/CD226 in patients with MM.
Methods: 1. The expressions of TIGIT, CD226, activated molecules NKG2D and CD107a and functional molecules IFN-γ and Perforin on the NK cells in bone marrow or peripheral blood were detedted by FCM. 2. BMSCs and NK cells were co-cultured at a ratio of 1:4 in vitro, which was grouped according to different monoclonal antibodies (mAbs) added. After co-cultured, the changes in the expression of NKG2D, NKp30, NKp44 and CD69 of NK cells and IFN-γ concentration were examined by FCM. 3. NK cells and U266 were co-cultured with different E:T ratio and the apoptosis of U266 was detected to evaluate the killing function of NK cells by FCM. 4. The expressions of CD155 on BMSCs and CD138+CD38+cells in the bone marrow were detected by FCM. The correlations between CD155 expression on BMSCs and the production of IFN-γ and Perforin in bone marrow NK cells, as well as clinical characteristics were analyzed.
Results: 1. In bone marrow, expression of TIGIT was significantly higher in patients with NDMM than those in patients with CR and HC (both P values <0.01). CD226 was significantly lower in NDMM patients than those in patients with CR and HC (both P values <0.01). NK cell surface activated molecules NKG2D and CD107a, and functional molecules IFN-γ and Perforin were significantly decreased in NDMM (Fig. A). In peripheral blood, TIGIT, CD226 and above immune phenotype expression levels were basically consistent with the trend in bone marrow. 2. In co-culture experiments of BMSCs and NK cells, only added anti-TIGIT mAbs, compared to both added anti-TIGIT and CD226 mAbs, the immune phenotypes of NK cells significantly increased (Fig. B). And the concentration of IFN-γ in the co-culture supernatants also increased (Fig. C). 3. After co-cultured with BMSCs, NK cells were co-cultured again with U266 in vitro, the apoptosis level of U266 in TIGIT mAbs group increased than those in TIGIT+ CD226 mAbs group at different E: T ratio (Fig. D). 4. The expression of CD155, the ligand of TIGIT and CD226, increased notably on the surface of BMSCs in MM patients(P<0.01) (Fig. E). 5. The expression of CD155 on BMSCs was negatively correlated with the production of IFN-γ and perforin in bone marrow NK cells with NDMM patients. And it has correlation with clinical characteristics including β2-MG, LDH, ALB, Hb, ISS stage and R-ISS stage in patients with MM.



Summary/Conclusion: 1. BMSCs may regulate NK cells through TIGIT/CD226. High expression of TIGIT on NK cells may mediate the inhibitory effect of BMSCs in MM patients. Blocking TIGIT could restore NK cells activation and killing function. 2. CD155, a common ligand of TIGIT and CD226, was overexpressed on BMSCs in NDMM patients. And it has correlation with NK cells function and clinical characteristics, indicating that CD155 maybe involved in the regulation of NK cells function by BMSCs.

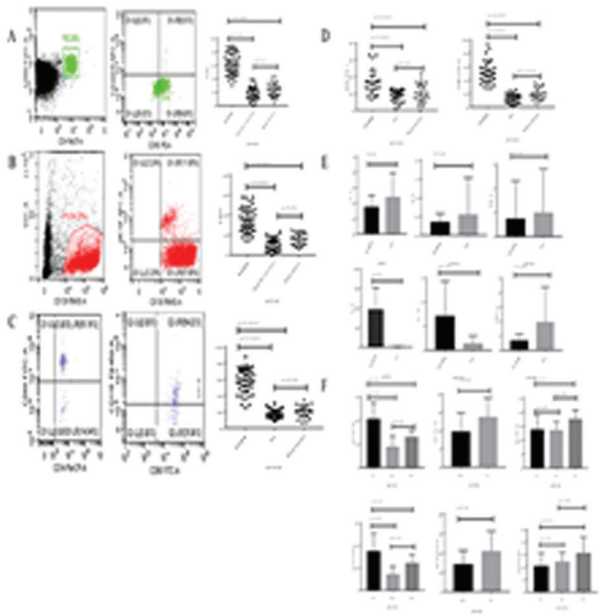
EP947 TUMOR ASSOCIATED MACROPHAGES INHIBIT CD8+T CELLS IMMUNE RESPONSES VIA PD-1/PD-L1 PATHWAY IN MULTIPLE MYELOMA

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Background: Tumor-associated macrophages (TAMs) arise from in situ maturation of recruited circulating monocytes and constitue a significant part of myeloma tumor microenvironment. TAMs maybe contribute to the immune escape of multiple myeloma (MM).
Aims: Our study detected the expression of TAMs, CSF1R on macrophages and CSF1 on myeloma cells in bone marrow, and PD-1 on CD8 + T cells and PD-L1 on TAMs.
Methods: March 2020 to January 2021, 53 newly diagnosed MM patients, 33 remission MM (VGPR and above) patients and 28 healthy controls were selected as observation objects. The expression of TAMs, CSF1R on macrophages and CSF1 on myeloma cells, PD-1 on CD8 + T cells and PD-L1 on TAMswere detected by flow cytometry. Bone marrow mononuclear cells from newly diagnosed MM patients were extracted and cultured into TAMs, and then cocultured with CD8 + T cells to detect the expression of perforin and granzyme B.
Results: 1. The expression of TAMs in NDMM group was significantly higher than remission group (P<0.001) and healthy control group (P<0.05)(Figure A). 2. The expression of CSF1 on CD138+ cells in the NDMM group was higher than the remission group (P<0.0001) and the healthy control group (P<0.05), the difference was statistically significant (Figure B). 3. The expression of CSF1R on macrophages in NDMM group was higher than the remission group (P<0.0001)and healthy control group, and there was no statistical significance between remission group and healthy control group(Figure C). 4. The expression of PD-1 on CD8+ T cells in the NDMM group was significantly higher than that in the remission group (P<0.05) and the healthy control group, but there was no significant difference between the remission group and the healthy control group (P>0.05).The expression of PDL-1 on TAMs in the NDMM group was higher than that in remission group(P<0.01)

and healthy control group (P<0.05) (Figure D). 5. The expression of cytokines in the supernatants of TAMs cultured with mononuclear cells extracted from bone marrow. IL-6 and IL-10 in the NDMM group was significantly higher than that in the healthy control group (both P<0.05). TNF-α in the NDMM group was significantly lower than that in the healthy control group (P<0.05)(Figure E). 6. The expression of functional molecules was detected after coculture of TAMs and CD8+ T cells. CD8+ T cells cultured alone were defined as group A (perforin: 17.82 ±1.887%, granzyme B: 29.82±3.882%). TAMs+CD8+ T cells cocultured alone as group B (perforin: 9.622±056%, granzyme B: 14.91±1.711%). TAMs+CD8+ T cells and PD-1 inhibitor cocultured as group C (perforin: 13.61±1.258%, granzyme B: 20.97±2.5%). TAMs, CSF1R inhibitor and CD8+ T cells were cocultured as group D (perforin: 13.37±0.789%, granzyme B: 25.37±2.297%). TAMs, CSF1R inhibitor, CD8+ T cells and PD-1 inhibitor were cocultured as group E (perforin: 17.42±0.806%, granzyme B: 34.47±3.486%). There were significant differences among three groups of A, B and D (P < 0.05), and between two groups of B and C (both P<0.05), and the difference among the three groups of C, D and E was statistically significant (P<0.05)(Figure F).



Summary/Conclusion: CSF1 combined with CSF1R on the surface of macrophages, recruits macrophages to tumor areas, and promotes the formation of TAMs. TAMs can express PDL-1, bind to PD-1 on the surface of CD8 + T cells, inhibit the function of CTL, and participate in MM immune escape.

EP948 COEXISTENCE OF MYELODYSPLASTIC SYNDROMES (MDS) AND MULTIPLE MYELOMA (MM)

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Background: Myelodysplastic syndromes (MDS) have been described as a complication of chemotherapy with alkylating agents in patients treated for multiple myeloma (MM). However, there are also reports on the extremely rare coincidence of MDS and MM in the absence of preceding chemotherapy or together at the time of diagnosis. The exact causes of the uncommon co-occurrence of *de novo* MM and MDS are not known and therefore further studies are needed. Recurrent chromosomal aberrations are well characterized in both diagnoses and cytogenomic examination is part of the prognostic stratification of patients with MM and MDS as well. In MM, the most common findings are translocations involving the *IgH* gene (14q32), monosomy 13/del(13q), gain of 1q21, and deletion of the *TP53* gene (17p13). In MDS, these are mainly del(5q), monosomy 7/del(7q), trisomy 8 and del(20q). It can be assumed that cases of two distinct clones underlying MDS and MM may often be underdiagnosed.
Aims: The aim of the study was to perform a retrospective analysis of cytogenomic findings in a sufficiently large group of patients with MM, to identify cases with the independent cell clones bearing MM and MDS specific chromosomal aberrations and to assess its frequency and effects on patient survival.
Methods: In the 2004-2020 we examined the karyotype of 1415 patients with MM using a combination of cytogenomic methods. Conventional cytogenetic analysis was performed on bone marrow cells cultivated for 24 hours without stimulation. The presence of the most common MM aberrations in immunofluorescently labeled plasma cells was studied using the cIg-FISH method with locus specific DNA probes for detection of: *IgH* translocations, deletion of *TP53* gene, deletion 13q/monosomy 13 and loss/gain of 1p32/1q21 (Abbott Vysis, Kreatech, MetaSystems). The clonality of aberrations characteristic for MDS was confirmed using I-FISH on the whole bone marrow. Complex karyotypes were analyzed with the mFISH/mBAND method (MetaSystems).
Results: We detected a total of 13 patients with the simultaneous occurrence of independent clones with MM and MDS aberrations (5 males, 8 females with median age 66 years). Using the cIg-FISH method, we proved MM aberrations in 11 of them, in 2 remaining patients no aberrations were detected by specific panel. In nine cases, a myeloid cell clone was detected at repeated cytogenetic examination after the MM therapy [1x del(20q), 2x del(5q), 1x trisomy 8, 1x del(11q), 4x complex karyotype]. The median time to occurrence of myeloid clone was 40.5 months (range 3.5 to 169 months). The malignant MM clone persisted with the onset of secondary MDS in 5/9 cases. In addition, we identified four previously untreated MM patients with clonal aberrations characteristic of MDS at the first cytogenetic examination [2x del(20q), 1x del(7q), 1x del(5q) and trisomy 8]. Eight of 13 patients died 0.3 to 19 months from the occurrence of MDS cell clone (median 7 months).
Summary/Conclusion: We report nine cases of secondary MDS after MM therapy and four untreated patients with rare coincidence of MM and primary MDS. In this study, the finding of MDS specific aberrations was associated with a worsened prognosis. Therefore, especially in longer-treated patients with MM, it is necessary to take into account the risk of the onset of secondary myeloid disease and to focus on these aberrations in cytogenomic analysis.
Supported by RVO-VFN64165 and ProgresQ28/LF1.

EP949 CLINICAL AND PHENOTYPIC FEATURES OF EXTRAMEDULLARY DISEASE IN MULTIPLE MYELOMA PATIENTS: THE POSSIBLE LACK OF CD38 EXPRESSION.

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Background: Extramedullary disease (EMD) is a clinical manifestation of multiple myeloma (MM), characterized by a plasma cell (PC) proliferation outside of the bone marrow (BM). The expression modulation of adhesion molecules, including CD44 and CD56, involved in BM homing, supports clonal PCs migration through the bloodstream. CD38 is a multifunctional transmembrane glycoprotein, expressed by PCs, which also plays a role as adhesion molecule. CD38 is considered a hallmark of MM cells and a therapeutic target for anti-CD38 antibody-based approach, however, CD38 expression profile by extramedullary PCs is still unknown.
Aims: To analyze the clinical and cytogenetic features of EMD patients (pts) with a comparative analysis of phenotypic differences, including CD56, CD44 and CD38 between BM PCs and EMD PCs in order to disclose antigenic changes related to the EMD onset.
Methods: We investigated 22 pts (median age 67 years, range 47 – 76), affected by MM (n°20) and primary PC leukemia (n°2) with a biopsy-proven soft tissue EMD. Clinical data included the type of disease, age at the time of diagnosis and at the time of EMD, myeloma type, ISS stage, cytogenetic abnormalities. The immunostaining from BM and EMD biopsies were scored using a semiquantitative evaluation of the percentage of CD56, CD44 and CD38, on MM cells on a 5-tiered scale (score 0, < 5% positive tumor cells; score 1, 5% to 24% positive tumor

cells; score 2, 25% to 49% positive tumor cells; score 3, 50% to 75% positive tumor cells; score 4, > 75% positive tumor cells).
Results: Three pts presented EMD at diagnosis while 19 pts presented EMD at relapse. The median time to EMD appearance during the relapse phase was 29 months (range 9-201 months). The most frequent MM subtype was light chain MM (41%) followed by IgG and IgA. 35% of the pts presented a high stage (ISS III) and a median LDH value above the normal limit. Overall 15 of 18 (88%) pts with available FISH, showed two or more cytogenetic alterations suggesting a high clonal heterogeneity. The most frequent cytogenetic aberration reported was amp(1q21) (72%), followed by del(13q) (65%), del(1p32) (47%), and hyperdiploidy (24%). Overall, 12 of 22 (55%) pts with EMD developed multiple plasmacytomas. The most common site was soft tissue (muscle, subcutaneous fat) and liver/spleen which represents 42%, of the total EMD followed by lymph nodes (15%). In 41% of the pts, the EMD relapse was dissociated from BM relapse that showed polyclonal plasmacytosis. CD56 showed a high score (3-4) in 5 of 22 (23%) EMD samples and was absent in 14 of 22 (64%) pts. 3 out 13 patients with discordant CD56 expression (18%) showed a strong down-regulation of CD56 in the EMD samples compared to BM. CD44 showed a high score (3-4) in 16 of 20 (80%) EMD samples and was absent in 2 of 20 (10%). Four pts with discordant CD44 expression (27%) showed an up-regulation of CD44 in the EMD samples compared to BM. CD38 had a high immunohistochemical score (3-4) in 16 of 19 BM samples (84%) and in two pts was negative. CD38 was absent (score 0) in 3 of 22 (14%) EMD samples and showed a low score (1-2) in 4 of 22 (16%) patients. Discordant CD38 expression was observed in 26% of samples with a down-regulation of CD38 in the EMD samples compared to BM.
Summary/Conclusion: Our data indicate that discordant expression of CD56, CD44 and CD38 may occur in EMD lesions compared to BM. The possible lack of CD38 expression in EMD was highlighted for the first time and it should be considered for its therapeutic impact.

EP950 INTEGRATIVE APPROACH TO FIND PREDICTIVE MARKERS OF RESPONSE TO DARATUMUMAB IN MULTIPLE MYELOMA

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Background: In newly diagnosed as well as in relapsed/refractory multiple myeloma, the anti CD38 monoclonal antibody daratumumab (Dara) has become essential in the therapeutic arsenal. Unfortunately, a subset of patients is not responding to Dara, or is progressing quickly after initiation of therapy. Different characteristics of the disease can be studied to predict and try to understand those response profiles. In addition to clinical markers, we looked at karyotypic and genomic parameters. We have also used plasma cell phenotyping with multiparametric flow cytometry (MFC) on CD200, CD117, CD56, CD38, CD45 and CD27. In particular, CD200 has been shown to be an independent pejorative prognostic factor for progression-free survival in myeloma patients and could play an important role in immunosuppression and regulation of anti-tumor activity.
Aims: Find clinical, karyotypic, genomic or phenotypic predictive markers of response to daratumumab in multiple myeloma.
Methods: We retrospectively included 97 multiple myeloma patients treated with Dara at Montpellier University Hospital. Standard clinical and therapeutic data were collected for all patients. Transcriptomic data were available in 68% of patients, and cytogenetic data in 47.5% of patients. All the patients had MFC data available before treatment with Dara. We collected the expression of CD200, CD117, CD27, CD45, CD56 and the mean fluorescence intensity of CD38 at diagnosis. Patients who obtained at least a partial response were considered as responders.
Results: The median age at Dara start was 68 years, and 59.8% of patients were responders versus 39.2% non-responders. The majority of patients were treated in monotherapy (48.5%). The Dara was given in combination with lenalidomide in 23.7% of patients, with bortezomib in 15.5%, with pomalidomide in 5.2% and with both lenalidomide and bortezomib in 3.1%. The median number of prior lines of therapy was 3 [0-7]. As expected, response to Dara was significantly associated with longer PFS (P<0.0001) and OS (P<0.0001). Within the various clinical and therapeutic data, the only significant parameter associate to the presence of response in multivariate analysis was the use of Dara in combination (P=0.03). Of note, complex karyotype was significantly associated with the absence of response to Dara, but only in univariate analysis (probably due to small number of events: 7 patients with complex karyotype). Comparing gene expression profiling (GEP) data of responder (n=24) versus non-responder patients (n=12) using GSEA revealed a significant enrichment in inflammatory response genes, genes encoding extracellular matrix and polycomb PRC2 as well as H3K27me3 target genes. Finally, Maxstat analysis of CD200 expression found that an expression of this protein in more than 95% of plasma cells was significantly associated with the absence of response to Dara (Figure). Similarly, expression of CD27 and CD45 were significantly associated with poor response to Dara. We did not find any significant correlation between Dara response and CD117 expression, CD56 expression nor CD38 mean fluorescence intensity (all patients were CD38 positive).

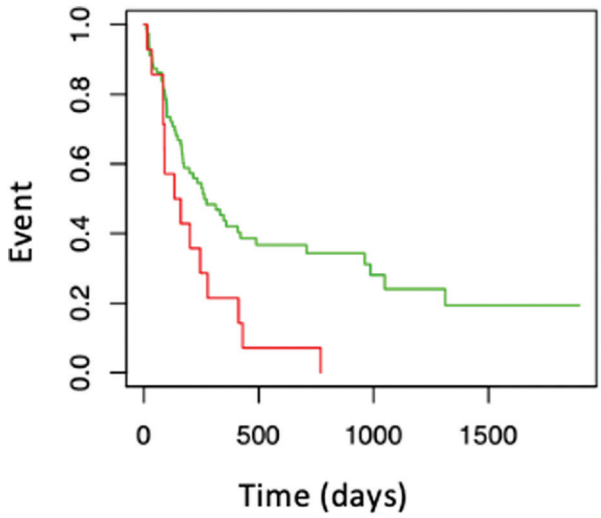


Figure 1: Expression of CD200 according to the response to daratumumab, in red: CD200 > 95%, and in green:CD200 ≤ 95%. P=0.008

Summary/Conclusion: Overall, our data seem to show that low expression of the checkpoint inhibitor CD200 and enrichment in inflammatory response genes expression is associated with good response to Dara. Further work is ongoing to understand the underlying mechanisms and to determine whether phenotypic or gene expression data could be used as predictive markers of response to Dara.

EP951 ALKBH5 PROMOTES THE PATHOGENESIS OF MULTIPLE MYELOMA THROUGH REGULATING LNCRNA SNHG15

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Background: Our previous results indicated that the demethylase of RNA N-6 methylation (m6A) modification, ALKBH5, played an oncogenic role in multiple myeloma via modulating HIPPO pathway(the results have not yet been published). While latest researches have also showed m6A modification on non-coding RNAs. Besides, the interaction between m6A RNA and histone modifications have arouse the researchers' interest. Here we find that ALKBH5 demethylases the long non-coding RNA (lncRNA)-small nucleolar RNA host gene 15 (SNHG15) and positively regulates its expression. Further experiments also disclose that ALKBH5 may alter the H3K36me3 level and promotes the pathogenesis

of multiple myeloma through regulating lncRNA SNHG15 m6A and RNA expression.
Aims: We aim to further display the potential epigenetic mechanisms between ALKBH5, ncRNA and histone modification involved in the progression of MM
Methods: The expression of SNHG15 and SETD2 were detected by RT-qPCR and western blot. ALKBH5-siRNA lentivirus and NC were transfected into MM cells to knockdown ALKBH5 gene. SNHG15-siRNA lentivirus, SNHG15-cNDA lentivirus and NC were transfected into MM cells to knockdown and knockin SNHG15 gene. MeRIP-seq was previously accomplished (the results have not yet been published). CCK8 assays were performed to determine the proliferation of myeloma cells. Flow cytometry assays were performed to determine the apoptosis of myeloma cells. Transwell assays were performed to determine the migration of myeloma cells.
Results: 1. MeRIP-qPCR reveals that the m6A level of lncRNA SNHG15 is increased after ALKBH5 knockdown. RT-qPCR finds that the expression of lncRNA SNHG15 is increased and decreased after ALKBH5 knockin and knockdown. 2. Through overexpressing lncRNA SNHG15 in MM PMI8226 ALKBH5$^-$ cells, we established the in vitro compensated model (marked control, ALKBH5$^-$ and ALKBH5$^-$SNHG15$^+$ group). CCK8 assays show that lncRNA SNHG15 rescues the inhibited cell proliferation caused by ALKBH5 knockdown. Transwell assays display that lncRNA SNHG15 compensates the suppressed cell migration caused by ALKBH5 knockdown. And flow cytometry assays show that the rate of cell apoptosis in ALKBH5$^-$SNHG15$^+$ group RPMI8226 cells is lower in ALKBH5$^-$ group RPMI8226 cells. 3. RT-qPCR shows that lncRNA SNHG15 is upregulated in primary MM cells (cells from the bone marrow of MM patients sorted by CD138 antibody beads) and MM cell lines (RPMI8226, NCL- H929,U266, MM1R, MM1S and ARH-77 cells). After downregulation of lncRNA SNHG15 by SNHG15-siRNA lentivirus in RPMI8226 cells, the proliferation of SNHG15$^-$ group PMI8226 cells is decreased. 4. Western blot analysis reveals the expression changes of histone H3K36me3 methyltransferase SETD2 among control, ALKBH5$^-$, ALKBH5$^-$SNHG15$^+$ group MM RPMI8226 cells.
Summary/Conclusion: The RNA m6A demethylase ALKBH5 acts on lncRNA SNHG15 in multiple myeloma and positively regulates its expression. The overexpression of SNHG15 in ALKBH5$^-$ cells rescued the inhibited cell proliferation, the suppressed cell migration, and the accelerated cell apoptosis caused by ALKBH5 knockdown. LncRNA SNHG15 was highly expressed in CD138 + plasma cells from MM Patients and MM cell lines. LncRNA SNHG15 positively regulates MM cells proliferation. ALKBH5 regulates histone modification through lncRNA SNHG15.

EP952 INTESTINAL MICROBIOTA AS A PROGNOSTIC BIOMARKER IN MULTIPLE MYELOMA

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Background: There is an increasing evidence that the gut microbiota exerts an influence on the immune system, inflammatory mechanisms, and the tumor microenvironment. The presence of these microorganisms and their activity could have an impact on immune cells and the bone marrow, playing an important role in the origin and development of multiple myeloma (MM).
Aims: In this work we explore which microorganisms of the intestinal microbiota could be imbalanced in monoclonal gammopathies and their possible role in the development of multiple myeloma.
Methods: 22 stool samples from patients with monoclonal gammopathy of undetermined significance (MGUS) (n = 8), and multiple myeloma at diagnosis (MM) (n = 9) and in complete remission (CR) (n = 5, 3 of them paired with their diagnostic samples). Furthermore, healthy patients (n = 5) whose median age and gender ratio were similar to that of the patients were included as controls. After the extraction of the microbial DNA with the Qiagen AllPrep® PowerFecal® DNA / RNA kit, the ribosomal subunit of the bacterial 16S gene was sequenced using the Quick-16S ™ NGS Library Prep Kit (Zymo Research) for library generation. After sequencing on the Illumina® MiSeq ™, bioinformatic analysis and quantification of absolute abundance were carried out.
Results: The absolute abundance of bacterial 16 rRNA was decreased in patients with gammopathies (1A). The abundance levels of Saccharibacteria and Betaproteobacteria classes was increased in patients with MGUS and MM. Moreover, there was a significant increase in MM compared to MGUS patients in the Betaproteobacteria class and the *Lachnoclostridium sp32445* specie. By contrast, the abundance of the specie *Intestinibacter barletti* was higher in MGUS compared to MM patients (Fig. 1B). When comparing the paired samples, it was observed that an increase in the microorganisms of Fibrobacteria class and Prevotellaceae family upon reaching complete remission, contrary to *Bacteroides doreii* specie, which was increased at the diagnosis moment (1C).

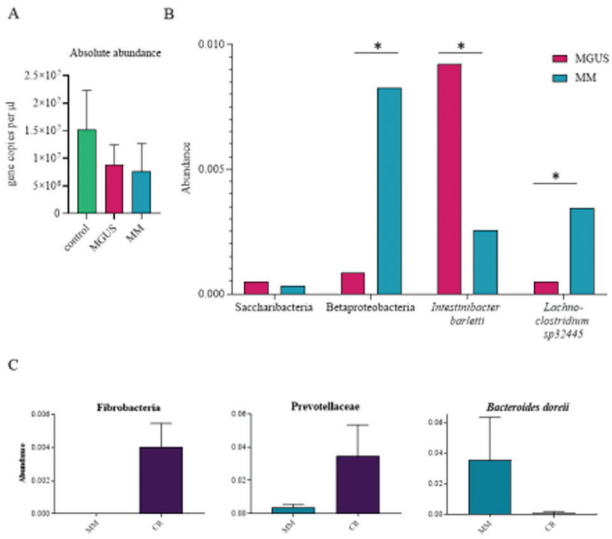


Figura 1. (A) Absolute abundance of bacterial 16S rRNA in control, monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) patients. **(B)** Abundance levels of Betaproteobacteria and Sacharibacteria classes and *Intestinibacter barletti* y *Lacnoclostridium sp32445* species in control, MGUS and MM patients. **(C)** Abundance levels of Fibrobacteria class, Prevotellacea family and *Bacteroides dorei* specie in paired in MM at diagnosis and at complete remission in paired patients.

Summary/Conclusion: The level of abundance of the microorganisms studied shows differences between the groups of MGUS and MM patients at diagnosis compared to controls, as well as in MM patients between at diagnosis and at RC moments. This study suggests that the analysis of the intestinal microbiota in patients with monoclonal gammopathies could be of prognostic utility.

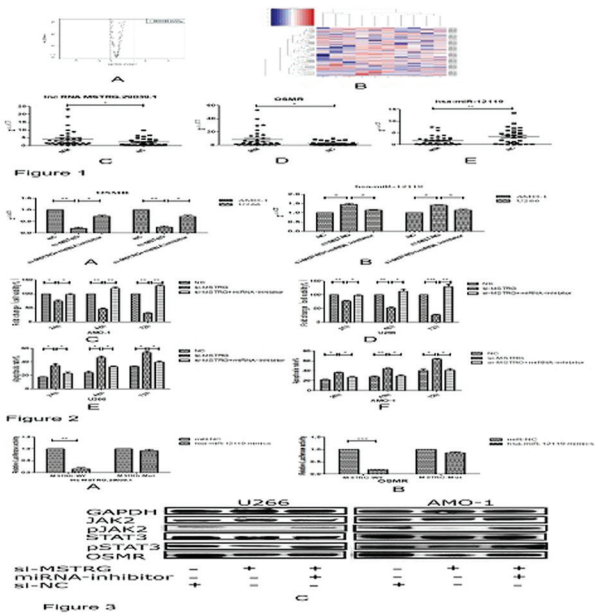
EP953 LNCRNA MSTRG.29039.1 PROMOTES PROLIFERATION BY SPONGING HSA-MIR-12119 VIA JAK2/STAT3 PATHWAY IN MULTIPLE MYELOMA

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Background: lncRNA is involved in the occurrence, development, metastasis and drug resistance of tumors, and involves a variety of biological functions. In addition, miRNA can regulate proliferation, migration, and even regulate epigenetics to promote the development of MM. However, the mechanism of ncRNA involved in MM is still unclear, and there are many unknown ncRNAs to be explored. Recently, there are more and more researches on the pathogenesis of various tumors with competitive endogenous RNA (ceRNA). ceRNA refers to transcripts that have a common miRNA binding site (MRE) and regulate each other at the post-transcriptional level,which could be used as a potential targeted drug to inhibit tumors. However, how ceRNA plays a role in multiple myeloma (MM) and the mechanism of action of specific ceRNA in the occurrence and development of MM is not fully clear.
Aims: This research aims to discover unknown ncRNAs in MM through high-throughput sequencing, and to study the mechanism and role of ceRNA involved in the pathogenesis of MM for the development of novel molecular markers and potential new targeted drugs.

Methods: In this study, the differentially expressed lncRNA and its target genes were analyzed to predict the lncRNA-miRNA-mRNA interaction pathway though high-throughput sequencing from 8 MM patients and 2 healthy controls. After verifying differential lncRNA and target genes by RT-PCR, lncRNA MSTRG.29039.1 was screened out. We knocked down the expression of MSTRG.29039.1 in MM cell lines by siRNA, detected proliferation by CCK8 as well as apoptosis level by FCM. Besides, we knocked down the miRNA for rescue experiment. The role of OSMR pathway JAK2/STAT3 was verified by Western blot.
Results: 262 new lncRNAs were screened by RNA sequencing with statistical differences, 203 were up-regulated and 59 were down-regulated, revealing the characteristics of 63 target genes that were highly expressed in 8 MM patients(Figure1.A B). According to the function and novelty of the target genes and the expression of lncRNA in MM, we screened out lncRNA MSTRG.29039.1, and verified that it and its target gene OSMR were highly expressed in MM(Figure1. C D), while the miRNA hsa-miR-12119 was low level in MM(Figure1.E). After knockdown of MSTRG.29039.1 in AMO-1 and U266 MM cell lines, the expression of OSMR was decreased, and the expression of hsa-miR-12119 was up-regulated, which can also promote cell apoptosis and inhibit proliferation. Then,we knocked down hsa-miR-12119 as well as knocked down MSTRG.29039.1 and found that apoptosis was reduced and cell proliferation increased(Figure2.A-F). We further found that MSTRG.29039.1 and OSMR have a common miRNA binding site, and the direct binding relationship was verified by dual-luciferase reporter assay system(Figure3.A-B). Thus, MSTRG.29039.1 can spangy miRNA to counteract the inhibitory effect of miRNA on OSMR. We found that OSMR regulates cell proliferation and apoptosis through the JAK2/STAT3 pathway by Western blot(Figure3.C).



Summary/Conclusion: Knockdown of MSTRG.29039.1 could reduce the expression of OSMR to promote apoptosis and inhibit cell proliferation though JAK2/STAT3 pathway, while knockdown of hsa-miR-12119 at the same time could counteract the above phenomenon. This can be a molecular marker and potential therapeutic target for MM.

EP954 DYSREGULATED EXOSOMAL MICRORNA EXPRESSION IN BONE MARROW MICROENVIRONMENT OF MULTIPLE MYELOMA, EXTRAMEDULLARY MULTIPLE MYELOMA AND PLASMA CELL LEUKEMIA

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Background: Multiple myeloma (MM) is a heterogeneous plasma cell (PC) malignancy. These malignant PC are dependent on the bone marrow (BM) microenvironment. However, a subclone of PCs can escape the BM microenvironment and infiltrate soft tissues and organs in the so-called extramedullary myeloma (EM). This subclone may also escape to peripheral blood; if there are more than 20% of circulating PC (cPC), the disease is reclassified as plasma cell leukemia (PCL).
All cells of the BM microenvironment release exosomes. Exosomes are small membranous vesicles that originate from internal multivesicular bodies; they are found in all body fluids, including peripheral blood, breast milk, etc. Exosomes are important in intercellular communication, and they have been implicated in disease relapse, resistance to chemotherapy and many other processes important for tumorigenesis. They contain proteins and nucleic acids, such as microRNAs (miRNAs) - short non-coding RNA molecules that are involved in many physiological and pathological processes.
Aims: The aim of this work was to analyze expression of exosomal miRNAs in BM plasma samples of MM, EM and PCL patients.
Methods: Exosomes were isolated using qEV columns. MiRNAs were isolated from exosomes using qEV original Size Exclusion Columns, following miRNA isolation using miRNeasy Micro Kit. For next generation sequencing (NGS), 8 MM, 7 EM and 8 PCL samples were used. Results from NGS were validated on 40 MM, 25 EM and 21 PCL samples by RT-qPCR using Taqman Advanced MiRNA Assays.
Results: NGS analysis showed 1128 different miRNAs that were present in analyzed samples. Out of these, 239 miRNAs were found in at least 8 samples and had more than 1 read per million; thus, they were included in subsequent analysis. Out of these miRNAs, there are 6 miRNAs (miR-140-3p, miR-584-5p, miR-744-5p, miR-223-3p, miR-191-5p and miR-151a-3p) ($p<0.05$) that are significantly dysregulated between MM, EM and PCL patients. Furthermore, 11 miRNAs ($p<0.05$) were significantly dysregulated between MM and EM patients, 4 miRNAs ($p<0.10$) between MM and PCL patients and 7 miRNAs ($p<0.05$) between PCL and MM patients. After validation, we performed ROC analysis for sensitivity and specificity of these miRNAs.
Summary/Conclusion: Using NGS, we showed that they are differentially expressed exosomal miRNAs between MM, EM and PCL patients suggesting their role in pathogenesis of individual diseases.

EP955 LACK OF CD56 AS A POOR PROGNOSTIC MARKER IN PATIENTS WITH MULTIPLE MYELOMA

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Background: CD56 or neural cell adhesion molecule (NCAM) is a membrane glycoprotein expressed on neural cells, muscle tissues and myeloma cells. Expression of CD56 has been studied in patients with multiple myeloma (MM), however with controversial results.
Aims: The scope of this study was to examine the expression of CD56 and investigate its association with clinicopathologic parameters.
Methods: We retrospectively collected and analyzed data from 109 patients with MM diagnosed over the last decade (January 2010 to June 2020). We assessed the expression of CD56 in bone marrow biopsies with immunohistochemistry and investigated its association with a variety of clinicopathological parameters. For the statistical analysis χ^2 test and Mann-Whitney U test were used to compare categorical and continues valuables in $CD56^+$ and $CD56^-$ patients, respectively. Statistical analysis was performed using SPSS 21.0 for Windows (SPSS, Chicago, IL).
Results: We assessed 109 patients with MM; Based on the expression of CD56 the patient population was divided to $CD56^+$patients and $CD56^-$ patients; Sixty-eight patients were CD56+ and 41 patients were CD56-. The median age at diagnosis of MM was 70 years in CD56+ patients and 72 years in CD56- patients (p=0.7). Lack of CD56 expression was associated with unfavorable prognostic parameters such as elevated lactate dehydrogenase (LDH) and β2-microglobulin levels, advanced stage in International Staging System (ISS) and clonal bone marrow plasma cell percentage ≥ 60%, while the expression of CD56 was associated with good differentiation of neoplastic plasma cells. The clinical and

biological parameters of the patients at the time of diagnosis of MM are presented in Table 1.

Characteristic	CD56 +	CD56 -	p-value (χ^2)
Age of diagnosis >65	47/68 (69,1%)	26/41 (63.4%)	0.69
Hemoglobin<10 g/dl	12/68 (17,6%)	12/41 (29.3%)	0.24
eGFR<40 mL/min/1.73m²	14/68 (20,6%)	10/41 (24.4%)	0.82
Increased LDH	16/68 (23.5%)	21/41 (51.2%)	0.006
Serum Ca^{2+} >11 mg/dL	10/67 (14,9%)	8/41 (19.5%)	0.72
β2-microglobulin (>5.5 mg/L)	9/63 (14,3%)	15/40 (37.5%)	0.013
Bone lytic lesions	37/65 (56.9%)	19/37 (51.4%)	0.74
Stage III (ISS)	10/63 (15.9%)	14/40 (35%)	0.046
SPEP M protein	48/66 (72.7%)	31/41 (75.6%)	0.92
Bence Jones Protein	26/48 (54.2%)	15/31 (48.4%)	0.79
Clonal bone marrow plasma cell infiltration >60%	26/68 (38.2%)	27/41 (65.9%)	0.009
Mature type neoplastic plasma cells	50/68 (73.5%)	21/40 (52.5%)	0.044

Table 1: Clinical and biological characteristics of patients with newly diagnosed multiple myeloma and their association with the expression of CD56. e-GFR: estimated Glomerular Filtration Rate, LDH: lactate dehydrogenase, SPEP: Serum protein electrophoresis

Summary/Conclusion: Our study confirmed that CD56 is a possible marker of poor prognosis in patients with MM. The measurement of expression of CD56 via either immunohistochemistry or flow cytometry is simple and cheap, and it could be incorporated in future prognostic or predictive scores. Prospective studies are needed in order to evaluate the role of expression of CD56 as a predictive biomarker in the era of novel regimens.

EP956 TRANSCRIPTOMIC ANALYSIS IDENTIFIED GENE CO-EXPRESSION AND CORRELATION WITH MULTIPLE MYELOMA PROGRESSION.

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Background: There is a gap in our understanding of the molecular mechanisms behind the chemoresistance seen in early multiple myeloma (MM) patients who receive standard treatment (i.e. Lenalidomide/revlimid, Bortezomib/velcade, and Dexamethasone (RVD)). The reason for the relatively high percentage of patients that progress after early RVD treatment is unknown. Therefore, the identification of clinically relevant clusters of co-expressed genes or biomarkers for MM progression in patients on RVD treatment would help identify novel mechanisms, drug targets, and prognostic markers.
Aims: Aim 1 will establish the clinical significance of BDKRB1, and associated genes co-expressed during MM progression.
Aim 2 will determine the molecular mechanisms by which bradykinin-BDKRB1 signaling affects MM cell growth and chemoresistance.
Methods: In this project, we employed a transcriptomic analysis approach to identify hub genes that correlate with MM progression and RVD chemoresistance. One of the most significantly expressed hub genes identified was the bradykinin receptor B1 (BDKRB1) gene, a G protein-coupled receptor. BDKRB1-signaling has been demonstrated in cell adhesion, signal transduction, and calcium flux, all of which can promote MM progression. The specific role of BDKRB1 in MM is undefined; therefore, an understanding of the molecular mechanisms mediated by BDKRB1 interactions in MM patients is urgently needed. To this end, we investigated the gene expression profiles and their correlation with MM clinical outcomes, using a novel weighted gene network co-expression analysis (WGCNA) method.
Results: WGCNA constructed 21 modules using the MMRF COMMpass dataset (n = 175) based on gene co-expression correlations between RVD treatment and age at diagnosis and/or death. The grey60 module contained BDKRB1 and 247 other upregulated co-expressed genes, which were significantly and positively correlated (p < 9.7E-07, R^2 =0.38) with MM progression following initial RVD treatment. The top biological processes associated with this module include the G protein-coupled receptor protein signaling pathway, calcium influx, inflammatory response, regulation of growth, and biological adhesion. Notably, gene expression driven by NF-Kβ is known to be activated by the bradykinin-BDKRB1 signaling axis, which significantly correlates with the lethal molecular subset of MM, MM proliferation and patient survival. The receiver operator characteristic (ROC) curve analysis predicted BDKRB1 as a statistically significant biomarker for MM progression (*p-values=0.00016*).
Summary/Conclusion: Our preliminary studies showed BDKRB1-signaling networks are significantly co-expressed and associated with MM progression. This is the first study to identify BDKRB1-associated gene networks and analyze their potential impact on MM progression. BDKRB1 is highly expressed in African Americans. AA is known to be 3 to 4-fold more likely to develop MM. Hence, the completion of my projects may shed new light on the impact of bradykinin-BDKRB1 signaling in MM progression, and RVD chemoresistance, and MM health disparities

EP957 THE ADIPONECTIN RECEPTOR AGONIST, ADIPORON, EXERTS ANTIPROLIFERATIVE AND PRO-APOPTOTIC EFFECTS THROUGH THE REGULATION OF ADIPORS/AMPK/ACC PATHWAY ON HUMAN MULTIPLE MYELOMA CELLS

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Background: Multiple myeloma (MM) represents approximately 10 % of all blood tumors, which is characterized by abnormally uncontrolled clonal expansion of malignant plasma cells within the bone marrow. Despite advances in multimodal treatment regiments, it remains an incurable and fatal malignancy. Obesity has been implicated as a risk factor in multiple myeloma, but the specific biologic mechanisms have not yet been fully elucidated. As is reported, obesity might in part mediate its effects on myeloma cells via interaction with adipokines. Adiponectin is one of the most abundant and well-understood adipokines, and has been implicated as a protective character in the development of MM, according to its potent role in insulin-sensitizing, anti-lipotoxic, anti-apoptotic and anti-inflammatory properties. Hypoadiponectin was correlated with an increased risk in MM and in vitro study has confirmed that adiponectin could induce anti-proliferation and pro-apoptosis in MM cells, suggesting a promising therapeutic target in MM. However, the complex quaternary structure and rapid turnover may add to the difficulty in converting adiponectin to an applicable drug form, which pose a limitation in the use of adiponectin. AdipoRon was capable of binding and activating both adiponectin receptor 1(AdipoR1) and adiponectin receptor 2(AdipoR2) at a low micromolar concentration. Nevertheless, there is little data focusing on the roles of AdipoRon in MM cells.
Aims: To investigate the effects of AdipoRon on MM cells and the potential functional and molecular mechanisms.
Methods: We use the small-molecule agonist, AdipoRon, to treat the two MM cell lines: U266 and RPMI8226. The cell proliferation was detected by CCK-8. The early apoptosis and cell cycle were analyzed by flow cytometry. A real-time quantitative(RT-PCR) and western blot were used to determine the transcript and protein levels of potential signaling pathways.
Results: The western blot assay showed that both AdipoR1 and AdipoR2 were available in the two cell lines. The CCK-8 test indicated that AdipoRon significantly reduced the proliferation of MM cells with an increase concentration at a certain range. Moreover, at the same concentration, AdipoRon gradually suppressed the proliferation of MM cells with prolongation of exposure time. Flow cytometry results showed both the U266 and RPMI8226 cells were arrested in the G0/G1 phase and with fewer cells present in the S phase. Additionally, AdipoRon promoted apoptosis in the U266 and RPMI8226 cells, with up-regulation of cleaved-PARP and cleaved-Caspase-3. Molecular analysis further demonstrated that the phosphorylation of AMPK was strengthened gradually in AdipoRon-treated MM cells over time, while the phosphorylation of ACC decreased. Moreover, we found that CPT1A and ACC2 were up-regulated in AdipoRon-treated U266 cells.

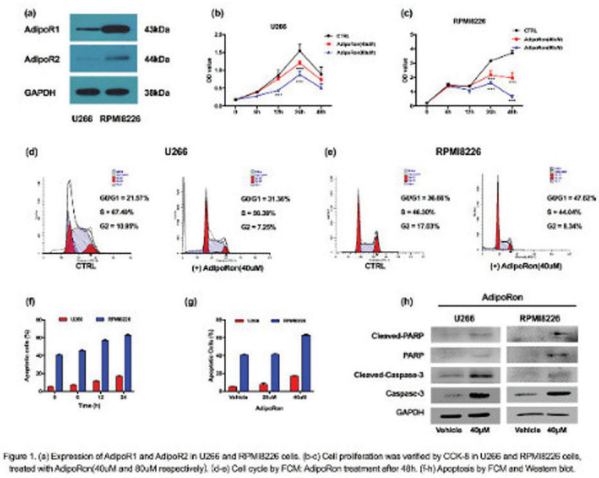


Figure 1. (a) Expression of AdipoR1 and AdipoR2 in U266 and RPMI8226 cells. (b-c) Cell proliferation was verified by CCK-8 in U266 and RPMI8226 cells, treated with AdipoRon(40uM and 80uM respectively). (d-e) Cell cycle by FCM: AdipoRon treatment after 48h. (f-h) Apoptosis by FCM and Western blot.

Summary/Conclusion: Our results demonstrated that the adiponectin receptor agonist, AdipoRon, suppressed the proliferation, induced apoptosis and cell arrest in U266 and RPMI8226 cells in a time- and dose-manner, possibly via regulation of AMPK/ACC pathway. Additionally, the abnormal up-regulation of metabolism-related gene ACC2 and CPT1A suggested that an imbalance of energy metabolism might participated in the regulation of AdipoRon on MM cells.

EP958 DECIPHERING CLINICAL IMPLICATION OF DYSREGULATED SERUM MICRORNAS IN NEWLY DIAGNOSED MULTIPLE MYELOMA: A RESULT OF COMPREHENSIVE MICRORNA PROFILING BY DEEP SEQUENCING

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Background: Multiple myeloma (MM) is an incurable plasma cell (PC) malignancy with genetic heterogeneity and variable therapeutic outcome. Despite the availability of several prognostic markers, treatment failure remains an unpredictable challenge in MM. Recent studies have identified serum/plasma-microRNA as a clinically relevant biomarker in many malignancies, including MM. The prognostic impact of serum miRNAs has been studied in MM. However, its role in the prediction of therapeutic response is still unknown. We studied serum-microRNA profiling by deep-sequencing in newly diagnosed-MM (NDMM) and evaluated its clinical utility.
Aims: To study the expression profile of plasma/serum microRNAs and identify clinically relevant dysregulated microRNAs.
Methods: The study cohort included **65-NDMM** (age range, 27-74; median-54 years) treated with Bortezomib-based therapy and could not be treated with autologous stem cell transplant due to various reasons as well as **10 age-matched controls**. Serum/plasma microRNAs profiling was performed by **deep sequencing** on BGISEQ-500 platform in diagnostic samples. The **initial therapeutic response** was monitored at the end of 4 and 8 cycles of Bortezomib-based therapy. The standard prognostication, including ISS staging, cytogenetics, and clonal-PCs assessment in bone marrow samples by flow cytometry, was performed.
Results: RNA-seq data analysis identified a total of 1098 microRNA. **Differential expression analysis** revealed 37 microRNA dysregulated in MM (fold change≥2, p-adjusted<0.05), greater majority being up-regulated (31/37). 14/37 have been previously reported in MM pathogenesis. Top dysregulated microRNAs (Log_2 fold change≥4, p-adjusted<0.05) included hsa-miR-92b-5p/hsa-miR-4775/hsa-miR-642a-5p/hsa-miR-103a-2-5p/hsa-miR-296-5p/hsa-miR-4665-5p/hsa-miR-4772-3p/hsa-miR-214-3p/hsa-miR-370-5p/hsa-miR-185-3p/hsa-miR-769-5p/hsa-miR-365a-3p/hsa-miR-365b-3p/hsa-miR-6843-3p. Among them, **hsa-miR-629-3p** was found significantly associated with **poor initial therapeutic response**. Additionally, hsa-miR-103a-2-5p, hsa-miR-296-5p, hsa-miR-4772-3p, hsa-let-7i-3p, hsa-miR-148a-3p and hsa-miR-328-3p are significantly associated with an increased (>95%) clonal PCs; hsa-miR-103a-2-5p, hsa-miR-625-3p, hsa-miR-342-3p, hsa-miR-532-3p and hsa-miR-625-3p demonstrated significant association with the ISS-stage-I and III. We also found a strong association of hsa-miR-103a-2-5p, hsa-miR-199a-3p and hsa-miR-204-5p with chromosome 17p deletion.
Summary/Conclusion: We have identified **37 dysregulated serum-microRNA** specific to and targeting functionally relevant pathways in MM, including p53-mediated signaling and proteasome-mediated processes. We, for the first-time report an association of hsa-miR-629-3p upregulation with poor initial response to Bortezomib-based therapy. We also report unique miRNAs associated with patients with high tumor burden MM (clonal-PC>95%). Thus, in addition to **prognostication and risk stratification,** our data demonstrated the value of serum microRNAs in **predicting initial response** to Bortezomib-based treatment in NDMM.

EP959 THE CLINICAL UTILITY OF A PLASMA MIRNA SIGNATURE IN MULTIPLE MYELOMA BONE DISEASE

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Background: Multiple myeloma bone disease (MMBD) affects approximately 80% of newly diagnosed multiple myeloma (MM) patients and is associated with poor quality of life and worse survival. The pathophysiology of MMBD is complex and results from deregulation of bone remodeling. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at post-transcriptional and/or translational level. miRNAs are implicated in the regulation of key physiological processes, including bone remodeling. However, little is known about their implication in MMBD.
Aims: The purpose of the current study was the evaluation of an established panel of 19 miRNAs associated with bone disease in osteoporosis of different etiology, in MMBD.
Methods: Small RNAs were isolated from blood plasma samples of 64 newly diagnosed MM cases, i.e. 37 patients with and 27 without osteolytic lesions, assessed via whole-body low-dose computed tomography. After RNA polyadenylation and first-strand cDNA synthesis, 19 miRNAs (let-7b-5p, miR-17-5p, miR-19b-3p, miR-29b-3p, miR-31-5p, miR-127-3p, miR-133b, miR-141-3p, miR-143-3p, miR-144-5p, miR-152-3p, miR-188-5p, miR-203a, miR-214-3p, miR-320a, miR-335-5p, miR-375, miR-550a-3p, miR-582-5p) were quantified by means of real-time qPCR, using LNA-enhanced forward and reverse primers as well as miGreen for detection. Spike-in control RNAs were used for normalization of miRNA levels. Last, biostatistical analysis was performed.
Results: Significantly lower levels of miR-143-3p (p=0.022), miR-17-5p (p=0.023), miR-214-3p (p=0.003), and miR-335-5p (p=0.018) were observed in MM patients with osteolytic lesions, compared to MM patients without osteolytic lesions. Receiver operating characteristic (ROC) curve analysis showed that each of the aforementioned miRNAs can accurately distinguish MM patients with MMBD from MM patients without MMBD: miR-17-5p (AUC=0.67; p=0.023), miR-143-3p (AUC=0.68; p=0.022), miR-214-3p (AUC=0.74; p=0.003), and miR-335-5p (AUC=0.69; p=0.018). In order to obtain a miRNA signature with higher discriminatory ability regarding MMBD, we built multivariate logistic regression models combining the levels of multiple miRNAs, selected among miR-17-5p, miR-143-3p, miR-214-3p, and miR-335-5p. The best predictive model resulted from the combination of these 4 miRNAs (function: $F=0.66 \times log(miR\text{-}335\text{-}5p) - 0.90 \times log(miR\text{-}17\text{-}5p) - 0.44 \times log(miR\text{-}143\text{-}3p)$

–1.67 x log(miR-143-3p) + 5.378. The evaluation of the proposed model using ROC analysis showed its significantly increased performance to successfully detect the presence of osteolytic bone disease in MM patients (AUC=0.80; p=0.001). Furthermore, a cutoff value of F_c=0.40, corresponds to increased diagnostic sensitivity of the described model (sensitivity: 96%, specificity: 53%), while a cutoff value of F_c=0.77 corresponds to increased diagnostic specificity (sensitivity: 48%, specificity: 94%).

Summary/Conclusion: Our study proposes a diagnostic model consisting of 4 miRNAs (miR-17-5p, miR-143-3p, miR-214-3p, and miR-335-5p) which and predict the occurrence of osteolytic lesions in MM patients. The suggested miRNA signature could be a useful tool able to guide therapeutic decision making, especially in ambiguous cases.

Acknowledgement: This research is co-financed by Greece and the European Union (European Social Fund - ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning 2014-2020» in the context of the project "*Study of the expression of small non-coding RNAs in multiple myeloma and their correlation with bone disease.*"(MIS 5047940).

EP960 METABOLIC ADAPTATIONS IN CARFILZOMIB-RESISTANT MULTIPLE MYELOMA CELLS - A PILOT STUDY

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Background: Multiple myeloma remains incurable mostly due to acquired resistance. Understanding the mechanisms of resistance would allow to create an algorithm for selecting optimal therapies and pave the road to new treatments.

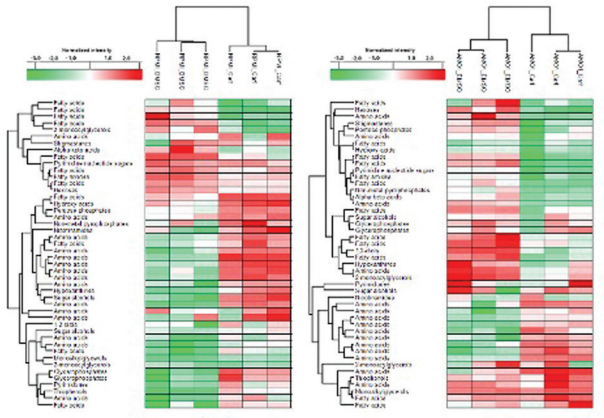
Aims: Since proteomic and genomic analysis of myeloma cells did not reveal therapeutically relevant findings, we applied metabolomics to analyze biological alterations that allow for acquisition of resistance to carfilzomib – widely used proteasome inhibitor.

Methods: GC-MS-based comparative metabolomics was applied to compare the primary carfilzomib sensitive myeloma cell lines AMO1 and RPMI (RPMI 8226) with their carfilzomib resistant progenies generated by prolonged carfilzomib exposure. Cells were lysed, fractionated metabolite extracts were derivatized and submitted to GC/MS analysis performed with Agilent 7890A GCxGC (Agilent Technologies) combined with Pegasus 4D TOF-MS (Leco). MS data were normalized to total ion current (TIC) and analyzed using Perseus and MetaboAnalyst. The significance was estimated by the two-sample T-test and one-way ANOVA with FDR correction. Multivariate analyses were carried out by untargeted principal component analysis (PCA) and hierarchical clustering. Differentially accumulated metabolites (DAMs) were subjected to the MetaboAnalyst and Ingenuity Pathway Analysis software to determine canonical pathways, biological functions and upstream regulators.

Results: PCA revealed significant differences between sensitive and resistant progenies. 24 and 34 DAMs were identified in AMO1- and RPMI-resistant (Fig. 1) cells respectively, as compared to primary cells, 16 DAMs were common for both comparisons. The top-ranked canonical pathways included: aminoacyl-tRNA biosynthesis, amino acid's metabolism and biosynthesis of unsaturated fatty acids.

The analysis of functions of DAMs revealed overrepresented categories associated with oxidation of glucose-6-phosphate (p 1.6E-08 for AMO1, 1.84E-08 for RPMI) and accumulation of lipids (p 1.39E-05 for AMO1, 5.97E-08 for RPMI) - the oxidation of glucose-6-phosphate was activated (z-score 2.86 for RPMI and 2.00 for AMO1), while accumulation of lipids was inhibited in resistant cells (z-scores -2.37 for AMOA1, -1.91 for RPMI).

Network analysis of DAMs in AMO1 revealed that PML transcription regulator was predicted to be the top positive regulator, while ARNT (Aryl hydrocarbon receptor nuclear translocator) and D-glucose were predicted to be the negative regulators in resistant cells (p 4.49E-05 and 9.46E-06, z-scores: 2 and 2.23). The DAMs negatively regulated by ARNT and D-glucose and positively regulated by PML belonged to processes related to lipids accumulation, acylglycerol and pyruvic acid, molecules down-regulated in AMO1 resistant cells. Downregulation of these compounds induces an oxidation of glucose-6-phosphate in resistant cells. In RPMI, UCP1 (Uncoupling protein 1) transporter was identified as the positive upstream regulator of observed differences in resistant cells and functionally connected to lipid accumulation and D-glucose level. It might suggest that increased level of this regulator can lead to observed inhibition of lipids accumulation.



Summary/Conclusion: We successfully applied metabolomics to assess biological alterations in myeloma resistant cells. Our results are in line with previous studies underlining the role of glucose and fatty acids metabolism in acquired resistance in myeloma. Confirmation of results in clinical setting is needed for potential development of new drugs targeting disrupted metabolic pathways to overcome resistance.

EP961 SINGLE CELL MULTI-OMIC ANALYSIS AND IMMUNE CELL TYPE PROFILING OF MULTIPLE MYELOMA WITH T(4;14).

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Background: Multiple Myeloma (MM) is an incurable plasma cell (PC) malignancy and high risk (HR) MM remains an unmet clinical need. Translocation 4;14 occurs in 15% of MM and is associated with an adverse prognosis. A deeper understanding of the biology and immune micro-environment of t(4;14) MM is necessary for the development of effective targeted therapies.

Aims: Here we utilized Proteona's ESCAPE™ single cell multi-omics platform to study a cohort of patients with t(4;14) MM with the goal of better understanding the biology underlying this high risk patient cohort.

Methods: Diagnostic bone marrow (BM) samples from 14 patients with t(4;14) MM were analysed using the ESCAPE™ platform from Proteona which simultaneously measures gene and cell surface protein expression in single cells. Cryopreserved BM samples were stained with 65 DNA barcoded antibodies and subsequently sorted on CD138 expression. The CD138 positive and negative fractions were recombined at a known ratio for analysis using the 10x Genomics 3' RNAseq kit. Resulting data were analyzed with Seurat and MapCell.

Results: The patients had a median age of 63 years. All received novel agent based induction. Median progression free and overall survival (PFS and OS) were 22 and 34 months respectively. MMSET was overexpressed in all PCs while FGFR3 expression could be categorized into zero cells expressing FGFR3, low expression (<10% of cells expressing FGFR3) or high expression (>80% of cells expressing FGFR3). We also found heterogeneity in the expression of cancer

testis antigens (CTA) such as FA133A and CTAG2 between PC clusters across samples.
Variation in the immune microenvironment of the BM was seen across all patient samples with no correlation between cell types and PFS or OS. However, an analysis of BM samples at diagnosis and relapse in one patient showed a shift in the ratio of T cells to CD14 monocytes with a ratio of 5.7 at diagnosis compared to 0.6 at relapse. Further analysis of PCs in this patient found 8 PC populations, each containing variable numbers of cells from both the diagnostic and relapse samples. This suggests that all populations present at relapse were also present at diagnosis, although at variable proportions. Increased expression of RCAN3 (associated with cereblon depletion) was detected at relapse.
Summary/Conclusion: We present the first application of single cell multi-omics immune profiling in high risk MM. The heterogeneity in expression of CTA has implications for the application of immunotherapies, while the upregulation of RCAN3 may explain failure of immunomodulatory therapy. Our small sample size may explain the lack of correlation between gene or protein expression with clinical outcomes. We propose that t(4;14) MM is a genomically and immunologically heterogeneous disease. Single cell analysis of larger cohorts is required to build on our findings.

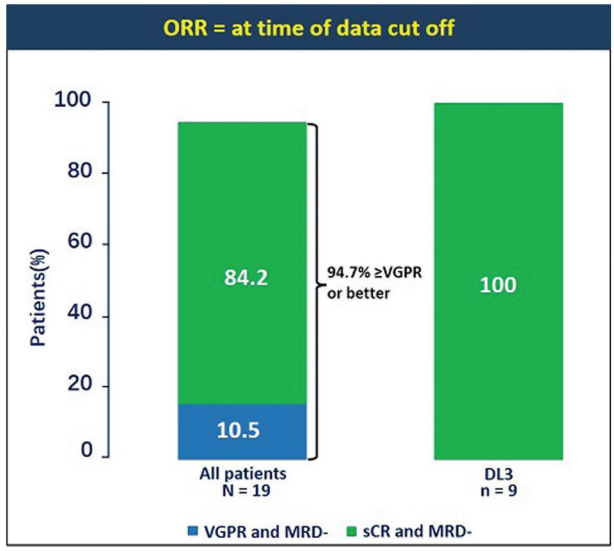
Myeloma and other monoclonal gammopathies - Clinical

EP962 LONG-TERM FOLLOW-UP RESULTS OF A MULTICENTER FIRST-IN-HUMAN STUDY OF THE DUAL BCMA/CD19 TARGETED FAST CAR-T GC012F FOR PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

J. Du [1,*], H. Jiang [1], B. Dong [2], L. Gao [3], L. Liu [4], J. Ge [5], A. He [6], L. Li [1], J. Lu [1], X. Chen [2], Y. Zhao [7], Y. Han [7], Y. Chen [7], C. Han [7], X. Ye [7], H. Zhang [7], L. Shen [7], J. Liu [7], M. Sersch [7], W. Fu [1]

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Background: The dual CAR-T GC012F - developed on the novel FasT CAR-T platform, targeting both B cell maturation antigen (BCMA) and CD19, was designed to improve depth of response and overall efficacy for CAR-T as therapy for Multiple Myeloma.
Aims: Here we present updated data for the single-arm multicenter phase 1 study (NCT04236011; NCT04182581) including additional pts treated.
Methods: From October 2019 to July 2020, 19 heavily pretreated Relapsed/Refractory Multiple Myeloma (RRMM) pts (age 27-71) with a median of 5 prior lines (range 2-9) received a single infusion of GC012F. 94.7% (18/19) were high risk (HR; defined by mSMART), 5 pts had extramedullary disease, 1 pt presented with plasma cell leukemia, and 15/19 were refractory to last therapy. 4/19 pts had received prior anti-CD38, 18/19 pts prior IMiD. 18/19 pts were refractory to PI, 17 pts to IMiD, 3 pts being primary refractory. After lymphodepletion over 2-3 days (30 mg/m2/d, 300mg/ m^2/d Flu/Cy) CAR-T cells were administered as single infusion at 3 dose levels:1x10^5/kg (DL1) n=1, 2x10^5/kg (DL2) n=9 and 3x10^5/kg (DL3) n=9.
Results: As of Jan 12th 2021 cut-off, 19 pts were evaluated for response. Overall response rate (ORR) was 94.7% - all responses were VGPR or better (94.7% - 16/18 sCR, 2/18 VGPR) with all pts (19/19) being Minimal Residual Disease negative (MRD$^-$) by flow cytometry (10^{-4};10^{-6}) - earliest response d28 post infusion. 100% of pts achieved a reduction of paraprotein, 18/19 a 100% reduction. Best response was MRD$^-$sCR in 16/19 pts (84.2%). In DL3 (n=9) 4 additional pts were response evaluable for 6 mth follow-up: 100% (9/9) of pts achieved MRD$^-$sCR as best response, 87.5% (7/8) of response evaluable pts maintained MRD$^-$sCR at a landmark analysis at 6 mths. At data cut off, the median time to follow up was 13.8 mths (6.1-16.4) – with the median duration of response not yet reached. Cytokine Release Syndrome (CRS) and ICANs were graded by ASBMT criteria: grade 1-2 n=16 (84.2%), grade 3 n=2 (10.5%). Median duration of CRS was 4d (1-8d). No grade 4/5 CRS or Immunce effector cell-associated Neurotoxicity syndrome (ICANS) were observed. 2 deaths occurred on study and were assessed as not related to therapy – one reported previously; one patient was diagnosed with pseudomonas pneumonia on Day 52, refused life-saving treatment and passed. CAR-T median T_{max} was 10d (range 8-14d), median peak copy number (C_{max}) was 127548 (16,011-374,346) copies /ug DNA with a long duration of persistence of up to 60 weeks at time of data cut-off. Patients continue to be monitored for safety and efficacy.



Summary/Conclusion: BCMA-CD19 dual FasT CAR-T GC012F showed early, deep and durable responses with a high ORR (94.7%; VGPR or better) including a high MRD negative sCR rate (DL3=100%, n=9) in high risk RRMM pts including those refractory to anti-CD38, PI and IMIDs with a favorable safety profile consistent with previous findings. BCMA-CD19 dual FasT CAR-T GC012F may present a new treatment approach for patients with RRMM including those with high-risk features refractory to standard of care.

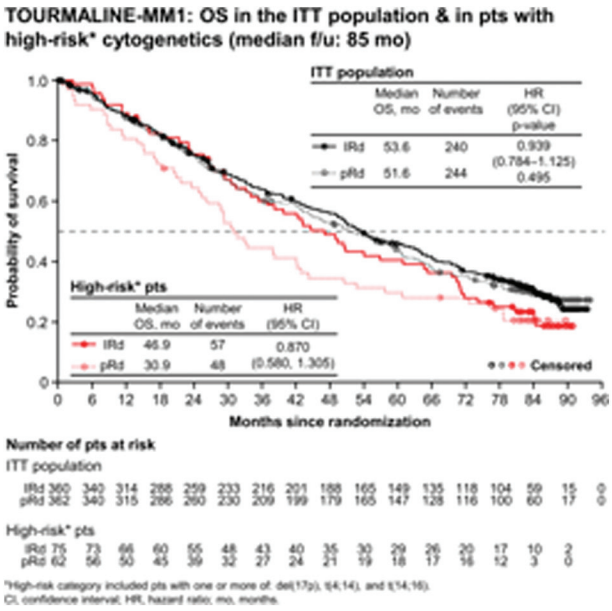
EP963 FINAL ANALYSIS OF THE PHASE 3 TOURMALINE-MM1 STUDY INVESTIGATING IXAZOMIB + LENALIDOMIDE-DEXAMETHASONE (IRD) VS PLACEBO-RD (PRD) IN RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (RRMM) PATIENTS (PTS)

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Background: Despite an increasing number of treatment options for RRMM, there remains a need for efficacious & tolerable therapies for pts who are refractory to treatment or continue to relapse. Proteasome inhibitors (PIs) are a backbone of therapy, but parenteral PIs may be limited by treatment burden & the need for clinic/hospital visits. The first oral PI, ixazomib, is approved in combination with Rd (IRd) for the treatment of MM pts who have received ≥1 prior lines of therapy. Approval was based on the double-blind, placebo-controlled, phase 3

TOURMALINE-MM1 study (Moreau NEJM 2016), which demonstrated a statistically significant improvement in progression-free survival (PFS) with IRd vs pRd (median PFS 20.6 vs 14.7 mo, HR 0.74, p=0.01). With limited additional toxicity vs pRd, all-oral IRd is an important option for RRMM pts.
Aims: To report final analyses for overall survival (OS) in the intent-to-treat (ITT) population (a key secondary endpoint) & subgroups of interest.
Methods: Randomization to IRd (n=360) or pRd (n=362) was stratified by number of prior therapies (1 vs 2/3), PI exposure, & International Staging System (ISS) disease stage (I/II vs III). Treatment continued until disease progression/unacceptable toxicity.
Results: At data cutoff (9/28/2020), median follow-up (f/u) was ~7 y (85 mo). Pts had received a median of 18 (range 1–99) & 16 (1–100) cycles of IRd & pRd, respectively. Overall, 32% of pts were alive at last OS f/u; 4% in each arm were still on treatment. Median OS with IRd vs pRd (ITT population) was 53.6 vs 51.6 mo (HR 0.939, p=0.495, Figure); this favorable trend was not statistically significant, but occurred in the context of the longest OS (both arms) reported to date in phase 3 Rd studies in RRMM. OS benefit with IRd vs pRd (lower HRs) was seen in predefined subgroups with adverse-risk characteristics including: refractory to any (HR 0.794) or last (HR 0.742) treatment line; age >65–75 y (HR 0.757); ISS stage III (HR 0.779); 2/3 prior therapies (HR 0.845); high-risk cytogenetics [≥1 of del(17p), t(4:14), t(14;16) (HR 0.870, Figure), & 1q21 amplification (HR 0.862)]. OS benefit was also seen in pts with standard-risk cytogenetics (HR 0.875). Imbalances in subsequent therapy in both arms may have led to inconsistencies in OS benefit for IRd pts. While 72% of IRd & 70% of pRd pts received ≥1 subsequent anticancer therapy, pRd pts began this therapy earlier than IRd pts. Of IRd vs pRd pts receiving ≥1 subsequent therapy, 25 vs 34% received daratumumab, 72 vs 77% received PIs (57 vs 62% bortezomib, 27 vs 33% carfilzomib), & 4 vs 10% had an autologous stem cell transplant. Most pts (IRd 92%, pRd 85%) remained blinded at time of next treatment, and while similar proportions of blinded pts received a PI or non-PI next-line therapy in both arms, unblinding strongly influenced next-line therapy decisions. OS benefit was reduced in pts who received a PI immediately after progression on IRd vs pts who received a PI after pRd. No new/additional safety concerns were evident during the 7-y f/u period, & the rate of new primary malignancies was similar in both arms (IRd 10%, pRd 12%).



Summary/Conclusion: At this final analysis of TOURMALINE-MM1, median OS with IRd & pRd were the longest reported to date in phase 3 Rd studies in RRMM. Although OS benefit with IRd vs pRd was not statistically significant in the ITT population, greater OS benefit was seen in subgroups with adverse prognostic factors, including high-risk cytogenetics. OS interpretation was confounded by imbalances in subsequent therapies, including extensive use of PIs & novel monoclonal antibodies.

EP964 UPDATED CARTITUDE-1 RESULTS OF CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

S. Usmani [1,*], J. Berdeja [2], D. Madduri [3], A. Jakubowiak [4], M. Agha [5], A. Cohen [6], P. Hari [7], T.-M. Yeh [8], Y. Olyslager [9], A. Banerjee [10], C. Jackson [8], A. Allred [10], E. Zudaire [10], W. Deraedt [9], X. Wu [11], M. Carrasco-Alfonso [11], M. Akram [11], Y. Lin [12], T. Martin [13], S. Jagannath [3]

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Background: Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T (CAR-T) cell therapy with two B-cell maturation antigen–targeting single-domain antibodies. CARTITUDE-1 (NCT03548207) is a phase 1b/2 study conducted to evaluate cilta-cel in patients with relapsed/refractory multiple myeloma (R/R MM).
Aims: We report updated CARTITUDE-1 results in patients with a longer duration (median 12.4 months) of follow-up.
Methods: All patients provided informed consent. Eligible patients had MM, had received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and had received a PI, IMiD, and anti-CD38 antibody. Bridging therapy was permitted after apheresis. Patients received a single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg; range $0.5–1.0\times10^6$) 5–7 days after lymphodepletion with 300 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine daily for 3 days. The primary objectives of the study were to characterize the safety of cilta-cel, confirm the recommended phase 2 dose (RP2D; phase 1b), and evaluate efficacy (phase 2). Cytokine release syndrome (CRS) was graded by Lee *et al* (Blood 2014) and neurotoxicity by Common Terminology Criteria for Adverse Events (CTCAE), v5.0 (in phase 1b). CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by American Society for Transplantation and Cellular Therapy (ASTCT) criteria (in phase 2). In this analysis, Lee *et al* and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively.
Results: As of Sept 1, 2020, a total of 97 patients with a median of 6 prior lines of therapy received cilta-cel. The overall response rate per independent review committee (primary endpoint) was 97% (95% CI, 91–99), with 67% of patients achieving stringent complete response. The median time to first response was 1 month (range, 1–9), and median time to complete response or better was 2 months (range, 1–15). Responses deepened over time, and the median duration of response was not reached. Of 57 patients who were evaluable for minimal residual disease (MRD) assessment, 93% were MRD-negative at 10^{-5}. The 12-month progression-free survival (PFS) and overall survival rates were 77% (95% CI, 66–84) and 89% (95% CI, 80–94), respectively; the median PFS was not reached. Grade 3/4 hematologic adverse events (AEs) that occurred in ≥20% of patients included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of patients (4% were grade 3/4), with median time to onset of 7 days (range, 1–12) and median duration of 4 days (range, 1–14, excluding 1 patient with duration of 97 days). CRS resolved in all patients except one with grade 5 CRS/haemophagocytic lymphohistiocytosis. CAR-T cell neurotoxicity occurred in 21% of patients (10% were grade ≥3). A total of 14 patients died during the study after cilta-cel infusion: no deaths occurred within the first 30 days, 2 deaths occurred within 100 days; and 12 deaths occurred more than 100 days post infusion, of which 5 were from disease progression, and 4 from treatment-related AEs.
Summary/Conclusion: A single infusion of cilta-cel yielded early, deep, and durable responses in heavily pretreated patients with MM, with a manageable safety profile at the RP2D. Investigation of cilta-cel in other

MM populations in earlier lines of therapy and in outpatient settings is under investigation.

EP965 FCRH5 TARGET EXPRESSION IN PATIENTS WITH RELAPSED REFRACTORY MULTIPLE MYELOMA (RRMM) TREATED WITH CEVOSTAMAB IN AN ONGOING PHASE I DOSE ESCALATION STUDY

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Background: Fc receptor-homolog 5 (FcRH5), an immunoglobulin (Ig) domain-containing type I membrane protein, is expressed exclusively in the B-cell lineage; and has been identified as a desirable target for the treatment of MM [1]. The humanized IgG-based T-cell-engaging bispecific antibody cevostamab (anti-FcRH5xCD3; BFCR4350A) binds to the most membrane-proximal domain of FcRH5 on myeloma cells and to cluster of differentiation 3 (CD3) on T cells resulting in efficient immunological synapse formation and potent T-cell-directed killing of myeloma cells. Cevostamab showed promising activity and manageable toxicity as monotherapy in the GO39775 Phase 1 dose escalation study (NCT03275103) enrolling RRMM patients (pts) [2].
Aims: To analyse pre-treatment FcRH5 target expression by response to therapy and pts baseline characteristics (prior therapy, cytogenetic risk status), in the cevostamab Phase I study.
Methods: Bone marrow aspirates (BMA) were collected prior to receiving cevostamab treatment. FcRH5 cell surface expression on myeloma cells was assessed using flow cytometry and the levels of expression (reported as molecules of equivalent soluble fluorochrome [MESF]) were compared between pts by prior therapy and stratified by cytogenetic risk status (determined by FISH). The clinical cut-off date (CCOD) used for the current analyses was August 18, 2020.
Results: As of CCOD, 53 pts (median age: 62.0 years [range: 33–80]) had enrolled in the study. Median number of prior lines of therapy was 6 (range: 2–15). Prior treatments included proteasome inhibitors (PIs), 100% (94.1% refractory); immunomodulatory drugs (IMiDs), 100% (98.0% refractory); anti-CD38 mAbs, 81% (92% refractory); and 86% of pts received autologous stem cell transplant. Overall, 72% of pts were triple-class refractory (≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb), and 94% of pts were refractory to their last therapy. In pts who received ≥3.6mg/20mg doses, the ORR was 53% (18/34); response was consistent in pts with exposure to prior daratumumab and anti-BCMA agents. FcRH5 expression was detected on myeloma cells in all pts with adequate BMA samples for biomarker evaluation (n=44). Prior therapy and the number of lines of treatment did not appear to affect FcRH5 expression. Of the pts with evaluable samples for cytogenetics (n=28), 25 pts were high risk [HR; 1q21, t(4;14), t(4,16) or del(17p)] and 3 standard risk (SR). Baseline FcRH5 expression stratified by cytogenetic risk showed a trend towards higher expression in pts with HR cytogenetics; median (min, max) MESF was 6329 (352, 44409) in HR and 2591 (766, 4560) in SR. Expression levels were consistent in HR pts with 1q21 vs no 1q21, t(4,14) vs no t(4,14) and d(17p) vs no d(17p). No clear correlations were observed between response to cevostamab and baseline expression levels of FcRH5.
Summary/Conclusion: Response to cevostamab was observed irrespective of FcRH5 expression levels in pts with RRMM assessed to date. Prior therapy did not affect the expression levels of FcRH5. There was a trend towards higher expression levels in pts with high-risk cytogenetics. These data further confirm FcRH5 as a promising target for MM therapeutics.
References: 1.Li et al. Cancer Cell 2017;31:383–95; 2.Cohen et al, ASH 2020

EP966 EFFECTS OF SELINEXOR ON PREVIOUSLY TREATED MULTIPLE MYELOMA (MM) WITH RAS-MUTATIONS

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Background: Activating mutations of the RAS genes *NRAS*, *KRAS*, and *HRAS* (*RAS*^{mut}) occur in up to 50% of MM and portend poor survival and high recurrence rates. MM cells with *RAS*^{mut} are susceptible to inhibition of germinal center kinase (GCK), resulting in IKAROS degradation independent of cereblon (CRBN). Selinexor is a selective inhibitor of nuclear export (SINE) compound that can induce IKAROS degradation through CRBN-independent pathways to overcome immunomodulatory drug resistance. We explored the benefit of selinexor treatment for pts with *RAS*^{mut} MM.
Aims: To evaluate the effect of NRAS, KRAS or HRAS mutations on outcomes in MM pts treated with a selinexor regimen.
Methods: In the randomized BOSTON study, pts with MM after 1-3 therapies received weekly XVd or twice weekly Vd. In the single-arm STORM study, pts with penta-treated, triple class refractory MM were treated with twice weekly Xd. Both treatment regimens are now FDA approved. Mutations were assessed post-hoc by exome sequencing of 119 and 52 pts from BOSTON and STORM, respectively. Pts were considered *RAS*^{mut} if their MM had *NRAS*, *KRAS* or *HRAS* mutations in codons 12, 13 or 61.
Results: There were 54 pts (45%) with *RAS*^{mut} in BOSTON (XVd=26, Vd=28), and 17 (33%) in STORM (all receiving Xd). In BOSTON, pts with *RAS*^{mut} MM treated with XVd had significantly longer progression-free survival (PFS) than those treated with Vd (median [med]=12.9 vs 6.7 months [mo], hazard ratio [HR]=0.48 [95% CI 0.24-0.97], p=0.039). For pts treated with Vd, those with *RAS*^{mut} had significantly shorter overall survival (OS) compared to *RAS*$^{wild\text{-}type\ (WT)}$ (med=16.8 mo vs not reached [NR], HR=2.87 [95% CI 1.03-7.99], p=0.035). PFS trended shorter in *RAS*^{mut} (med=6.74 vs 9.82 mo, HR=1.64 [95% CI 0.88-3.07], p=0.122). In contrast, amongst pts on XVd, there was no difference in survival between *RAS*^{mut} and *RAS*^{WT} pts (PFS: med=12.8 vs 12.9 mo, HR=1.08 [95% CI 0.52-2.26], p=0.83; OS: med=NR vs NR, HR=0.94 [95% CI 0.36-2.45], p=0.91). In STORM, pts with *RAS*^{mut} had shorter OS compared to *RAS*^{wt} pts (med=6.1 vs NR, HR=2.51 [95% CI 1.22-5.19], p=0.010). Preliminary studies to explore the mechanisms of action related to *RAS*^{mut} MM sensitivity to XVd demonstrated that selinexor treatment in vitro leads to downregulation of GCK.

	PFS		OS	
	p-value	HR (95% CI)	p-value	HR (95% CI)
BOSTON *RAS*^{mut} XVd vs Vd	0.039	0.48 (0.24-0.97)	0.22	0.57 (0.23, 1.41)
BOSTON XVd arm *RAS*^{mut} vs *RAS*^{WT}	0.83	1.08 (0.52, 2.26)	0.91	0.94 (0.36, 2.45)
BOSTON Vd arm *RAS*^{mut} vs *RAS*^{WT}	0.12	1.64 (0.88, 3.07)	0.035	2.87 (1.03, 7.99)
STORM (Xd) *RAS*^{mut} vs *RAS*^{WT}	0.28	1.58 (0.69, 3.63)	0.010	2.51 (1.22, 5.19)

Summary/Conclusion: Despite typically having the worst outcomes, pts with *RAS*^{mut} MM had a similar benefit from XVd as *RAS*^{WT} MM, showing that the XVd combination can overcome traditionally poor prognostic *RAS*^{mut}. Mechanistically, selinexor induced down regulation of GCK and enhanced killing of *RAS*^{mut} MM cells. With a manageable safety profile, the XVd regimen could provide a viable treatment option to improve PFS and OS in pts with MM with RAS mutations.

EP967 MODULATION OF SOLUBLE B-CELL MATURATION ANTIGEN LEVELS BY TECLISTAMAB AND TALQUETAMAB IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

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Background: B-cell maturation antigen (BCMA, CD269), a single transmembrane protein that is selectively expressed in the B-cell lineage, is a validated target for multiple myeloma (MM). BCMA can exists as both a surface protein and as a free soluble form (sBCMA). γ-secretase activity at the transmembrane domain leads to a shed BCMA protein fragment of approximately 6 kilodalton that can exist as free circulating sBCMA in blood. Teclistamab, a BCMA x CD3 bispecific antibody, and talquetamab, a GPRC5D x CD3 bispecific antibody, were developed to recruit $CD3^+$ T cells to $BCMA^+$ or $GPRC5D^+$ MM cells, respectively.
Aims: The objective of this study was to evaluate sBCMA levels in response to treatment with teclistamab or talquetamab in patients with relapsed and/or refractory MM.
Methods: Serum samples from patients with relapsed and/or refractory MM enrolled in the teclistamab and talquetamab phase 1 studies (64007957MMY1001 and 64407564MMY1001, respectively) were collected (at various timepoints between baseline and cycle 4 or end of treatment) and analyzed for sBCMA by an electrochemiluminescence ligand binding assay. Soluble BCMA data were quantitatively analyzed in reference to the patient's tumor burden and response, as well as to pharmacokinetic data. All patients enrolled in the phase 1 studies provided written informed consent.
Results: Teclistamab and talquetamab modulated levels of sBCMA in patients with high (≥ 50%) and low (< 50%) frequency of tumor plasma cells (TPCs), as well as in high and low risk cytogenetic groups. In cycle 3, the majority of the responders had reductions in sBCMA compared to baseline: 88% (50 out of 57) for teclistamab and 98% (49 out of 50) for talquetamab. In contrast, non-responders (patients who had progressive disease, stable disease, or minimal response) seemed to show an increase in sBCMA compared to baseline: 80% (33 out of 41) for teclistamab and 49% (24 out of 49) for talquetamab. Patients with deep responses tended to have a higher magnitude of sBCMA reduction compared to others. Based on the few patients who initially responded to teclistamab or talquetamab but then relapsed, sBCMA seemed to have an initial reduction followed by an increase in the levels. Soluble BCMA correlated with % bone marrow TPCs. The majority of patients with plasmacytoma (limited data were available) seemed to have high sBCMA, suggesting that sBCMA could be a comprehensive marker for tumor burden. Preliminary teclistamab population pharmacokinetic analysis showed that sBCMA did not appear to impact teclistamab exposure, suggesting that sBCMA was not acting as a sink for teclistamab.
Summary/Conclusion: Teclistamab and talquetamab induced changes in sBCMA levels that correlated with clinical activity, further supporting clinical development of these bispecific antibodies. Lastly, the findings provide support for sBCMA as a potential surrogate marker of myeloma tumor burden, and as a valuable marker for response in patients with MM.

EP968 SUBGROUP ANALYSIS ON RESPONSE TO INDUCTION THERAPY WITH BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE WITH OR WITHOUT ELOTUZUMAB FOR NEWLY-DIAGNOSED, TRANSPLANT-ELIGIBLE MULTIPLE MYLEOMA

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Background: Quadruplet treatment regimens including a proteasome inhibitor, immunomodulating agent and a monoclonal antibody are playing an emerging role in front-line treatment of multiple myeloma (MM). Recently, a randomized phase II trial (SWOG-1211, Usmani SZ et al., Lancet Haematology, 2021) comparing lenalidomide, bortezomib and dexamethasone (RVD) with or without the anti-SLAMF7 monoclonal antibody (moAb) elotuzumab (Elo) found no significant differences in response rates, progression-free survival (PFS) nor overall survival (OS) in high-risk newly diagnosed patients with high-risk MM.
Aims: We aimed to compare available response rates after induction therapy with RVD vs. Elo-RVD according to high-risk subgroups from our randomized phase III HD6 trial (NCT 02495922).
Methods: The German-speaking Myeloma Multicenter Group (GMMG) HD6 trial is a randomized multicenter phase III treatment protocol including 559 and 555 newly diagnosed transplantation-eligible MM patients in the intention-to-treat (ITT) and safety population, respectively. Induction therapy consisted of four 21-day cycles of RVD (arms A1+A2, n=280) or Elo-RVD (arms B1+B2, n=279). Exploratory analyses on response rates (very good partial response or better, ≥VGPR) according to predefined subgroups comparing RVD vs. Elo-RVD induction therapy will be presented.
Results: Median patient age was 59 (27-70) years at trial inclusion. Revised International Staging System (R-ISS), ISS stages, adverse cytogenetics (at least one of the following: del17p13, t(4;14), t(14;16) and the proportion of patients with renal impairment (either serum creatinine >2 mg/dl or glomerular filtration rate <40 ml/min) were equally distributed among the RVD and Elo-RVD groups. Revised ISS stages I / II / III were noted in 29.9% / 59.3% / 10.9% of patients in the RVD cohort vs. 28.1% / 58.1% / 13.8% in the Elo-RVD group. At least four cycles of preplanned RVD or Elo-RVD induction therapy were completed by 264 (94.3%) and 258 (92.5%) patients. The overall response rates (ORR, ≥PR) after the fourth cycle of induction therapy were 85.6% in the RVD group and 82.4% in the Elo-RVD group (Fisher p=0.53). Deep responses (very good partial response rates or better, ≥VGPR) were reached by 54.0% in the RVD group vs. 58.3% in the Elo-RVD group (Fisher p=0.22). The rates of ≥VGPR between RVD and Elo-RVD were significantly different in patients with R-ISS stage II (50.8% vs. 64.5%, Fisher p=0.03; odds ratio [OR]=1.83, 95% confidence interval [95% CI]: 1.09-3.07, Wald p=0.02). Borderline significant results were observed for patients with normal renal function (52.9% vs. 59.8%, Fisher p=0.07; OR=1.40, 95% CI: 0.98-2.01, Wald p=0.06). No differences were observed in other prognostically important subgroups such as in patients with renal impairment at baseline, with or without adverse cytogenetics, good (0-1) or poor (>1) World Health Organization (WHO) performance status or R-ISS stages I and III. Further analyses on toxicities and dose intensities of RVD vs. Elo-RVD are planned.
Summary/Conclusion: Addition of Elo to RVD improves the rate of deep responses (≥VGPR) post induction therapy in patients with R-ISS stage II, prognostically a rather heterogenous group of MM. Further subgroups that benefit from Elo-RVD vs. RVD regarding response post induction therapy could not be identified. However, benefit by the addition of monoclonal antibodies often becomes obvious during further treatment course (Moreau P et al., The Lancet, 2019). Final results for the primary endpoint of the HD6 trial (PFS) will be reported in late 2021.

EP969 DARATUMUMAB PLUS CYCLOPHOSPHAMIDE, BORTEZOMIB, AND DEXAMETHASONE INDUCTION THERAPY IN MULTIPLE MYELOMA FOLLOWED BY DARATUMUMAB MAINTENANCE: END-OF-STUDY RESULTS FROM LYRA

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Background: The safety and efficacy of daratumumab (DARA) plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) as an immunomodulatory drug-sparing regimen in newly-diagnosed patients with multiple myeloma (NDMM) and relapsed MM (RMM) were demonstrated in a primary analysis of LYRA, a phase 2, single-arm, community practice-based study (NCT02951819). An updated analysis of the study further showed that responses deepened with DARA maintenance therapy.

Aims: To report the final end-of-study analysis of LYRA.

Methods: Adult patients (aged ≥18 years) from the United States with MM (International Myeloma Working Group criteria) and no more than 1 prior line of therapy received 4–8 induction cycles of DARA plus CyBorD (oral cyclophosphamide 300 mg/m^2 once weekly [QW]; subcutaneous bortezomib 1.5 mg/m^2 on Days [D] 1, 8, and 15; oral or intravenous (IV) dexamethasone 40 mg QW every 28 days; DARA IV, 8 mg/kg on D1 and D2 of cycle [C] 1, 16 mg/kg QW on C1D8–C2, 16 mg/kg Q2W in C3–C6, and 16 mg/kg Q4W in C7–C8). Written informed consent was obtained from all patients. Following induction, eligible patients were allowed to receive autologous stem cell transplantation (ASCT). Patients received ≤12 maintenance cycles of DARA 16 mg/kg IV Q4W and were then followed up for ≤36 months after induction.

Results: Of 101 patients (NDMM, 87; RMM, 14), 36% had high-risk cytogenetics. Patients with NDMM received a median of 6 induction cycles; those with RMM received 8. Of 87 patients with NDMM, 39 (44.8%) received ASCT and 63 (72.4%) completed 12 months of maintenance therapy. Of 14 patients with RMM, 1 (7.1%) received ASCT and 7 (50.0%) completed 12 months of maintenance therapy. A higher proportion of patients with NDMM who received ASCT achieved very good partial response or better (≥VGPR; 82.1%) and complete response or better (≥CR; 48.7%) vs patients who did not receive ASCT (70.2% and 29.8%, respectively; Table). For patients with NDMM, median progression-free survival (PFS) and overall survival (OS) were not reached (median follow up, 35.7 months). Estimated 3-year PFS rates were 69.3% for patients with NDMM who received ASCT and 72.6% for those who did not; estimated 3-year OS rates were 94.9% and 84.3%, respectively. Efficacy outcomes for patients with RMM are reported in Table. Overall, 62.0% of patients experienced grade 3/4 treatment-emergent adverse events (TEAEs), and neutropenia (14.0%) was most common (≥10%). Serious TEAEs were observed in 33.0% of patients, and pneumonia (4.0%) and pulmonary embolism (3.0%) were most common. TEAEs leading to death occurred in 2.0% of patients (all unrelated to study treatment). Nearly half of patients (56.0%) experienced infusion-related reactions; most were mild (4.0% had grade 3/4 events).

	NDMM who received ASCT (n=39)	NDMM who did not receive ASCT (n=47)	RMM (n=14)
ORR, %	97.4	83.0	85.7
sCR	23.1	17.0	28.6
≥CR	48.7	29.8	64.3
≥VGPR	82.1	70.2	71.4
	(n=39)	(n=48)	(n=14)
Estimated 3-year PFS, % (95% CI)	69.3 (43.0-85.3)	72.6 (54.0-84.7)	31.7 (5.6-63.4)
Estimated 3-year OS, % (95% CI)	94.9 (81.0-98.7)	84.3 (69.8-92.2)	50.0 (22.9-72.2)
ORR, overall response rate; sCR, stringent complete response			

Summary/Conclusion: In patients with NDMM or RMM, induction with DARA plus CyBorD followed by DARA alone as maintenance therapy resulted in durable and deep responses, with a 3-year PFS rate of 70%, regardless of ASCT status. No new safety concerns were identified with longer follow up.

EP970 ANCHOR (OP-104): MELFLUFEN PLUS DEXAMETHASONE AND BORTEZOMIB IN RELAPSED/REFRACTORY MULTIPLE MYELOMA—OPTIMAL DOSE AND UPDATED EFFICACY AND SAFETY RESULTS

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Background: The development of resistance to standard treatments for relapsed/refractory multiple myeloma (RRMM) highlights the need for novel therapies. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and thereby delivers and rapidly releases alkylating agents inside tumor cells. Melflufen plus dexamethasone showed clinical activity and an acceptable safety profile in RRMM in the phase 2 HORIZON study (Richardson PG, et al. *J Clin Oncol*. 2020 Dec 9 [Epub]).

Aims: To provide an update of the phase 1 dose-finding part of the bortezomib arm of the phase 1/2a ANCHOR study of melflufen plus dexamethasone in combination with bortezomib or daratumumab in patients with RRMM (NCT03481556).

Methods: Eligible patients with RRMM were refractory to (or intolerant of) a prior IMiD, with 1-4 prior lines of therapy. Prior treatment with a proteasome inhibitor (PI) was allowed, but patients could not be refractory to PIs in the last line of therapy. Melflufen (30, 40, or 20 mg intravenously; day 1 of each 28-day cycle) was administered with bortezomib (1.3 mg/m^2 subcutaneous; days 1, 4, 8, and 11) plus oral dexamethasone (20 mg on days 1, 4, 8, and 11 and 40 mg on days 15 and 22; dexamethasone dose reduced for patients aged ≥ 75 years). The primary objective in phase 1 was to determine the optimal phase 2 dose of melflufen for this combination.

Results: As of the data cutoff date (October 19, 2020), 13 patients received melflufen (30 mg, n = 6; 40 mg, n = 7) plus dexamethasone and bortezomib. In the 30-mg and 40-mg cohorts, respectively, the median age was 78.5 years (range, 70-82) and 70.0 years (range, 61-76); the median prior lines of therapy was 3.5 (range, 2-4) and 2.0 (range, 1-4); 33% and 50% of evaluable patients had high-risk cytogenetics; 83% and 71% were refractory to the last line of therapy; 100% and 86% received a prior PI; and 33% and 14% were refractory to PIs. In the 30-mg and 40-mg cohorts, respectively, the median treatment duration was 6.5 months (range, 1.4-29.0) and 8.7 months (range, 2.1-19.6); 4 patients (67%) and 4 patients (57%) were still on treatment; and 2 patients and 3 patients discontinued study treatment. Reasons for discontinuation included progressive disease (PD; n=1) and other (n=1) in the 30-mg cohort and adverse event (AE; n=1), lack of efficacy (n=1), and PD (n=1) in the 40-mg cohort. The confirmed overall response rate in the 30-mg and 40-mg cohorts, respectively, was 50% (1 very good partial response [VGPR] and 2 partial response [PR]) and 71% (1 complete response, 3 VGPR, and 1 PR). The most common grade 3/4 treatment-related AEs (TRAEs) were thrombocytopenia (30 mg, 50%; 40 mg, 100%) and neutropenia (30 mg, 33%; 40 mg, 71%); grade 3/4 nonhematologic TRAEs were infrequent. Three patients discontinued study treatment due to treatment-emergent AEs (30 mg, cardiac failure chronic [n=1] and osteolysis [n=1]; 40 mg, thrombocytopenia [n=1]). Serious TRAEs occurred in 2 patients (33%) in the 30-mg cohort (neutropenia and pneumonia [n=1], syncope [n=1]) and 1 patient (14%) in the 40-mg cohort (thrombocytopenia and neutropenia). No dose-limiting toxicities occurred at either dose level. A fatal AE occurred in 1 patient in the 30-mg cohort (cardiac failure chronic; considered unrelated to study treatment).

Summary/Conclusion: ANCHOR determined that the optimal dose of melflufen is 30 mg and results showed clinical activity in heavily pretreated patients with RRMM and poor prognostic factors. Recruitment in phase 2 is ongoing; updated data will be presented.

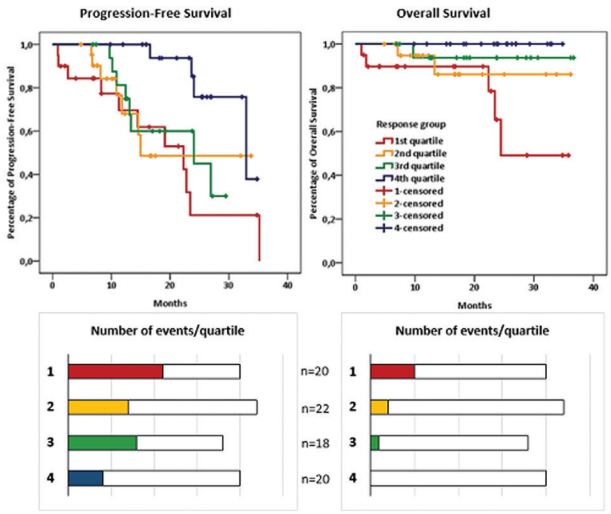
EP971 TIME TO BEST RESPONSE CORRELATES WITH OUTCOME IN THE RANDOMIZED COMPARISON BETWEEN KRD AND KTD FOLLOWED BY K MAINTENANCE OR OBSERVATION (AGMT-MM02 TRIAL)

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Background: Rapid induction of remission is a favorable prognostic factor in several cancers (Hodgkin's and aggressive lymphomas). In multiple myeloma, only few data are available on response kinetics and outcome.
Aims: Here, we evaluated the association between time to best response in patients with transplant non-eligible, newly diagnosed multiple myeloma (TNE NDMM) enrolled in a randomized phase II study comparing KRd with KTd for induction and K with observation for maintenance therapy.
Methods: At time of data-cut (July 9, 2020), 91 patients were randomized and 80 patients with TNE NDMM received at least one cycle (=per protocol group) and have been analyzed so far in this still ongoing study. Median age was 75 years, ISS stage I/II/III: 21 (26.3%)/26 (32.5%)/33 (41.2%), ECOG stage 0/1: 40 (50%)/40 (50%). Patients were randomized for 9 cycles of KRd or KTd. After end of induction, those with SD or better were randomized to K maintenance (day 1 and 15) for 12 cycles or observation. MRD was assessed by NGF with a sensitivity of 10^{-6} in patients with ≥VGPR. To investigate whether time to best response influences survival, patients were assigned into quartiles. Response rates were evaluated by descriptive statistics, survival estimates calculated according to Kaplan-Meier and survival curves compared using the log-rank test. Fisher test was used for comparison of individual groups.
Results: Median follow-up was 19.2 months. As the trial is still ongoing, response rates and survival data are given for both arms combined. Twenty-seven patients (33.8%) achieved CR, 33 patients (41.3%) VGPR, and 14 patients PR (17.5%). Six patients (7.5%) showed only minor or no response [MR: 3 (3.7%), SD: 2 (2.5%), PD: 1 (1.2%)]. Eleven patients discontinued therapy within the first cycle due to investigator decision [4 (4.4%)], patient's decision [3 (3.3%)], development of AE/unacceptable toxicity [2 (2.2%)], and death or other reason [1 each (1.1%)], respectively. Eighteen of 40 patients (45%) tested were found to be MRD negative. The time to best response varied between 26 and 675 days. Quartile 1: 20 patients, days 26-42 days, quartile 2: 22 patients (43-112 days), quartile 3: 18 patients (113-253 days), quartile 4: 20 patients (254-675 days). The proportion of patients with progression or death declined from quartile 1 (55%) to quartile 2 (31.8%) and quartile 4 (20%). Only quartile 3 showed a rise up to 44.4% compared to quartile 2. Median progression-free survival was similar for patients of quartiles 1-3 (1: 22.3, 2: 15.0, 3: 24.0 months, p=0.645) but was significantly longer in those of quartile 4 (33.0 months, p=0.024, Fig. 1). Similar findings were observed for overall survival. There was a steady decrease in the proportion of death from quartile 1-4 (Fig. 1) and survival curves were similar for quartile 1-3 (p=0.143), but significantly superior for those of quartile 4 (p=0.019). Additional evaluations regarding high-risk cytogenetics, MRD negativity, depth of response or age did not reveal statistically significant differences, but showed tendencies that early responders include a higher proportion of patients with high-risk cytogenetics (presence of t(4;14) and/or del(17p)), MRD positivity and higher age. Updated results will be presented.

Figure 1: Progression-free survival and overall survival according to quartiles of time to best response. Number of events/quartile are shown separately.



Summary/Conclusion: In conclusion, our data show that slow response kinetics are associated with prolonged progression-free and overall survival in patients randomized to either KRd or KTd induction therapy followed by one year of carfilzomib maintenance or observation.

EP972 CILTACABTAGENE AUTOLEUCEL FOR TRIPLE-CLASS EXPOSED MULTIPLE MYELOMA: ADJUSTED COMPARISON OF CARTITUDE-1 OUTCOMES VERSUS REAL WORLD CLINICAL PRACTICE OBSERVED IN GERMAN REGISTRY

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Background: Patients with relapsed/refractory multiple myeloma (RRMM) who are triple-class exposed to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and anti-CD38 monoclonal antibodies (MoABs) have few treatment options available and poor outcomes (Gandhi et al., Leukemia, 2019). Ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T-cell (CAR-T) therapy, is studied in CARTITUDE-1, an open-label, single arm phase 1b/2 clinical trial assessing safety and efficacy of cilta-cel in adult patients with triple-class exposed RRMM. In absence of a comparator arm in CARTITUDE-1, comparison of trial outcomes versus an external cohort of similar patients allows to quantify clinical benefits relative to treatments used in current clinical practice.
Aims: To compare overall survival (OS) and time to next treatment (TTNT) in triple-class exposed patients with RRMM treated with cilta-cel vs. therapies as currently used in real world clinical practice (RWCP).
Methods: Individual patient data (IPD) for baseline risk factors and outcomes on OS/TTNT were available for cilta-cel patients from CARTITUDE-1 (September 2020) and for triple-class exposed RRMM patients treated with RWCP therapies from a German registry (OIs). This

registry includes around 3,400 RRMM patients captured from a representative sample of 108 centers collected between January 2016 and March 2020. Patients with ECOG score 0 or 1 and ≥ 3 prior therapy lines, who received at least 1 subsequent active MM therapy after becoming triple-class exposed were selected from the registry. Hazard ratios (HR) with 95% confidence intervals (CI) for cilta-cel vs. RWCP were estimated for OS and TTNT using IPW weighted (Li et al., FJAjoe, 2019; Austin et al., PCJSim, 2016) and multivariable Cox proportional hazards regression models, adjusting for differences in commonly available baseline characteristics. Patients with multiple treatment lines initiated after fulfilling the inclusion criteria, contributed multiple times to the analyses, with line of therapy and its follow-up (observations) as unit of analysis and baseline information defined specific at initiation of each treatment line. Correlation of observations within patients was corrected using robust standard errors.
Results: Patients enrolled in CARTITUDE-1 (113 patients) and observations from RWCP (258 observations from 192 patients) were used for comparison. Cilta-cel patients had more advanced disease in terms of higher refractoriness, shorter time to progression on most recent prior line, higher number of prior lines, and shorter average duration of prior lines. RWCP included more patients with R-ISS stage III and ECOG score 1. Overlap weights analyses led to well-balanced cohorts and HR estimates for OS (HR 0.18, 95% CI 0.09-0.38) and TTNT (HR 0.19, 95% CI 0.09-0.39) were statistically significant in favor of cilta-cel. Multivariable regression analyses including baseline characteristics as covariates showed similar results confirming findings using IPW.
Summary/Conclusion: Comparative analyses using PLD, adjusting for differences in patient characteristics between both cohorts, shows that cilta-cel patients had significantly longer OS and TTNT compared to patients treated with therapies used in current clinical practice in Germany. These findings highlight cilta-cel's potential as an effective treatment option to address currently unmet treatment needs in triple-class exposed patients with RRMM.

EP973 MELFLUFEN PLUS DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA EXPOSED AND/OR REFRACTORY TO PRIOR ALKYLATORS – A POOLED ANALYSIS OF THE O-12-M1 AND HORIZON STUDIES

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Background: Therapies for multiple myeloma (MM) combine multiple drug classes including IMiDs, proteasome inhibitors, monoclonal antibodies, alkylators, histone deacetylase inhibitors, XPO1 inhibitors, and anti-B cell maturation antigen therapies (Legarda et al. *Cancer.* 2020;12:3576). Despite advances in therapy, outcomes remain poor for patients with relapsed/refractory MM (RRMM). Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and thereby rapidly delivers and releases alkylating agents inside tumor cells. Melflufen has a mechanism of action (MOA) distinct from other alkylating agents (Slipicevic et al. AACR 2020. Abs. 1843). In the O-12-M1 (NCT01897714) and HORIZON (OP-106; NCT02963493) studies, melflufen plus dexamethasone showed meaningful efficacy and a clinically manageable safety profile in patients with RRMM (Richardson et al. *Lancet Haematol.* 2020;7:5; Richardson et al. *J Clin Oncol.* 2020;Dec 9 [Epub]).
Aims: To examine the clinical activity of melflufen in patients from the O-12-M1 (phase 2 only) and HORIZON studies who were exposed to alkylators in prior lines of therapy (LoTs).
Methods: Patients in the phase 2 portion of the O-12-M1 study and HORIZON had RRMM with ≥2 prior LoTs and received melflufen 40 mg plus dexamethasone 40 mg (20 mg if aged ≥75 years). Both studies had a primary endpoint of overall response rate (ORR); secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Data from the 2 studies were pooled and analyzed according to prior exposure and refractory status to alkylators before study entry. Refractory status to prior alkylator therapy was defined as failure to achieve a minimal response or progression while on therapy, or within 60 days of last dose of alkylator therapy.
Results: A total of 202 patients were included in the analysis (HORIZON: n=157; O-12-M1: n=45); of these, 24 (12%) had not been exposed to an alkylator and 178 (88%) had been exposed to alkylators in ≥1 prior LoT (see **Table** for prior alkylator exposure/refractory status). Patients without prior exposure to an alkylator had the best response to therapy (ORR, 50.0% [95% CI, 29.1-70.9]; PFS, 7.1 months [95% CI, 3.7-9.0]). However, meaningful responses were also seen among patients exposed and refractory to prior alkylators (**Table**). PFS and OS were better or similar to that in the overall population in patients exposed to an alkylator in ≥1 prior LoT but not refractory and in patients exposed to an alkylator in 1 prior LoT and refractory, respectively. PFS and OS were shortest when both exposed and refractory to an alkylator in ≥2 prior LoTs; this group had more patients refractory to an alkylator in their last LoT (61%) and 82% were refractory to an alkylator within 12 months of study entry. Results should be interpreted with caution due to limited patient numbers. Grade 3/4 adverse events (AEs) were similar among patients exposed to prior alkylators (O-12-M1: 85%; HORIZON: 89%) and the overall population (O-12-M1: 84%; HORIZON: 89%). The most common AEs were hematologic but were mostly reversible and clinically manageable. Nonhematologic AEs were infrequent and primarily grade 1/2.

Table. Efficacy by Exposure and/or Refractoriness to Prior Alkylator Therapy

Patients	n	ORR, % (95% CI)	PFS, Median (95% CI), mo	OS, Median (95% CI), mo
Total	202	29.7 (23.5-36.5)	4.4 (3.7-5.1)	13.6 (11.2-17.6)
No prior alkylator exposure	24	50.0 (29.1-70.9)	7.1 (3.7-9.0)	22.4 (9.6-NE)
Exposed to alkylator in ≥1 prior LoT	178	27.0 (20.6-34.1)	4.2 (3.7-4.9)	11.8 (10.0-16.5)
Exposed in ≥1 prior LoT, not refractory	62	33.9 (22.3-47.0)	5.3 (4.2-7.9)	21.1 (17.2-33.2)
Exposed in 1 prior LoT and refractory	43	23.3 (11.8-38.6)	4.6 (3.0-6.5)	11.6 (7.7-18.9)
Exposed in ≥ 2 prior LoT, refractory in 1 LoT	40	35.0 (20.6-51.7)	3.7 (2.4-4.9)	10.1 (5.3-13.9)
Exposed and refractory in ≥2 prior LoTs	33	9.1 (1.9-24.3)	3.1 (1.7-4.0)	7.2 (4.8-13.6)

LoT, line of therapy; NE, not estimable.

Summary/Conclusion: Melflufen in combination with dexamethasone showed meaningful efficacy in heavily pretreated patients with RRMM including those exposed and/or refractory to prior alkylators and is in line with pre-clinical studies showing that melflufen has an MOA distinct from that of other alkylating agents.

EP974 EFFICACY AND SAFETY OF SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE BASED ON REFRACTORY STATUS TO LENALIDOMIDE IN PATIENTS WITH PREVIOUSLY TREATED MULTIPLE MYELOMA: A POST-HOC ANALYSIS OF THE BOSTON STUDY

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Background: Lenalidomide (LEN) is typically a frontline therapy for newly diagnosed MM. Patients (pts) with MM refractory to LEN are less likely to respond to other IMiDs and represent a signification area of unmet medical need. In the ITT population of the BOSTON study, selinexor, bortezomib, and dexamethasone (XVd) was associated with significant improvements in median progression-free survival (PFS), overall response rate (ORR), and rates of peripheral neuropathy, with trends in overall survival (OS) favoring XVd.
Aims: This study aimed to evaluate if PFS, overall response rate (ORR), time to next treatment (TTNT) and tolerability were influenced by prior treatment with LEN when comparing XVd with Vd.
Methods: The BOSTON trial (NCT03110562) is a Phase 3 randomized, controlled, open-label study of once weekly XVd vs twice weekly bortezomib and dexamethasone (Vd) in pts with MM and 1-3 prior therapies. We performed post-hoc analyses on two different subgroups to compare outcomes based on refractory status to LEN and immunomodulatory drug (IMiD) therapy.
Results: Amongst the 402 pts in BOSTON, 160 had MM refractory to any IMiD (XVd=74, Vd=86). Of those, 106 were documented to be refractory to LEN (XVd=53, Vd=53) and 296 were not refractory to LEN (XVd=142, Vd=154). Baseline characteristics were generally well balanced between subgroups. In these subgroups based on refractory status to IMiD or LEN, median PFS was significantly longer in the XVd arm as compared to Vd (IMiD refractory: 13.9 vs. 8.4 months (mo), p=0.005; LEN refractory: 10.2 vs. 7.1 mo, p=0.012; not LEN refractory, 15.4 vs 9.6 mo, p=0.014). Significant increases in TTNT were observed with XVd treatment in pts with MM that was: IMiD refractory (14.8 vs. 10.2 mo, p=0.003), LEN refractory (13.0 vs. 7.6 mo, p=0.015), and LEN not refractory (19.1 vs 12.9 mo, p=0.005). ORR was improved with XVd compared to Vd regardless of refractory status (IMiD refractory: 68.9% vs 55.8%, p=0.045; LEN refractory: 67.9% vs. 47.2%, p=0.016; and LEN not refractory: 79.6% vs 67.5%, p=0.010). The most common treatment-emergent AEs for the XVd/Vd arms for all subgroups were thrombocytopenia (66.2/30.6%; 71.7/40.4%; 55.6/22.4%), nausea (48.6/11.8%; 50.9/11.5%; 50.0/9.2%) and fatigue (40.5/20.0%; 45.3/21.2%; 40.8/17.1%) for IMiD, LEN, and not LEN refractory, respectively. Incidence of PN AEs of any grade were reduced with XVd compared to Vd: IMiD refractory: 27% vs. 42.4%; LEN refractory: 30.2% vs 36.5%; LEN not refractory: 33.1% vs 50.7%.
Summary/Conclusion: In pts with previously treated MM, PFS, ORR, and TTNT were significantly improved regardless of documented refractory status to LEN or to any IMiD. These analyses support the use of the XVd combination for pts with disease refractory to LEN and likely to any IMiD.

EP975 SUBGROUP ANALYSIS: EFFICACY AND SAFETY OF ORAL PANOBINOSTAT IN COMBINATION WITH SC BORTEZOMIB AND ORAL DEXAMETHASONE IN RELAPSED OR RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS > 75 YEARS OF AGE

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Background: Panobinostat (Pano), a pan-histone deacetylase inhibitor, is approved for the treatment of relapsed or relapsed/refractory multiple myeloma (RRMM) in combination with BTZ and dex (FVd) in patients who received ≥2 prior lines of therapy, including BTZ and an IMiD. The pivotal phase 3 PANORAMA 1 trial, which used IV BTZ, demonstrated significant PFS benefit with FVd compared with placebo-Vd; however, AEs were more frequent. The randomized phase 2 PANORAMA 3 study was conducted to optimize FVd by comparing three varying regimens and by incorporating SC BTZ. This study demonstrated that 20 mg TIW provides favorable outcomes, more durable responses, and a favorable AE profile compared to those seen in PANORAMA 1. Here we present data indicating that response outcomes and AE rates in the subset of patients >75 in PANORAMA 3 were similar to those of the general trial population and to those of patients ≤75 years of age.
Aims: To evaluate the overall response rate (ORR; IMWG 2011 criteria) after up to 8 treatment cycles by Independent Review Committee assessment. Secondary endpoints included in this abstract are duration of response (DOR) and safety.
Methods: PANORAMA 3 (NCT02654990) was a randomized, open-label, international, multicenter phase 2 study. Eligible patients were ≥18 years old with 1–4 prior lines of therapy, including an IMiD. Patients primarily refractory to BTZ were excluded. Patients were randomized 1:1:1 to Pano 20 mg TIW (d 1, 3, 5, 8, 10, 12), Pano 20 mg BIW (d 1, 4, 8, 11), or Pano 10 mg TIW (d 1, 3, 5, 8, 10, 12), all administered in 21-day cycles. Randomization was stratified by age at screening (≤75 vs >75 years). For Cycles 1–4, patients ≤75 years old received SC BTZ 1.3mg/m(2) BIW (d 1, 4, 8, 11) and oral dex 20mg d 1, 2, 4, 5, 8, 9, 11, 12. Patients aged ≤75 years from cycle 5 onwards, and patients > 75 years for all cycles, received BTZ 1.3 mg/m(2) weekly (d1 and 8) and dex 20mg on d 1, 2, 8, and 9.
Results: In total, 248 patients were randomized and 241 patients received treatment. Of the patients who received treatment, 211 patients were ≤75 years of age and 30 patients were >75 years of age. In the overall patient population, across the 3 arms, the ORR after 8 cycles was 62.2%, and the median duration of response for the 20mg TIW arm, across all age groups, was 22 months. Median DOR in patients >75 years of age for each specific treatment arm could not be calculated and will be presented subsequently. Across the general study population, treatment-related Grade ≥3 AEs were reported in 78%, 72%, and 54% of patients in the 20 TIW, 20 BIW, and 10 TIW arms respectively; serious AEs were reported in 54%, 48%, and 44% of patients respectively; and discontinuations due to AEs occurred in 29.5%, 28%, and 15% of patients respectively. See Table 1 for response rates and Table 2 for adverse events for patients ≤75 and >75 years of age.

Table 1

Response Rates	Patients ≤75 Years of Age n=216			Patients >75 Years of Age n=32		
	20mg TIW N=72	20mg BIW N=73	10mg TIW N=71	20mg TIW n=10	20mg BIW n=10	10mg TIW n=12
ORR for up to 8 cycles	62.5%	68.4%	54.9%	60%	40%	25%

Table 2

Adverse Events	Patients ≤75 Years of Age n=211			Patients >75 Years of Age n=30		
	20mg TIW n=69	20mg BIW n=73	10mg TIW n=69	20mg TIW n=9	20mg BIW n=10	10mg TIW n=11
Serious AEs, all Grades	53.6	49.3	44.9	55.6	40	36.4
Serious AEs ≥ Grade 3 (%)	49.3	45.2	40.6	44	20	36.4
Diarrhea ≥ Grade 3 (%)	11.6	11	5.8	11.1	0	0
Thrombocytopenia ≥ Grade 3 (%)	40.6	32.9	26.1	55.6	20	9.1
Serious Infections ≥ Grade 3 (%)	24.6	23.3	21.7	11.1	0	36.4

Summary/Conclusion: In PANORAMA 3, SC BTZ improved the tolerability of FVd relative to that seen with IV BTZ in PANORAMA 1. Across the entire patient population, the most durable and deepest responses were observed in the 20 mg TIW arm, which yielded a median DOR of 22 months. In PANORAMA 3, the efficacy outcomes seen in the subset of patients >75 years of age were similar to those of the general study population and to those of the group ≤75. Importantly, in patients >75 years of age, rates of high-grade AEs, including diarrhea, were similar to those seen in the general study population and to those seen in the group ≤75.

EP976 SURVIVAL AMONG OLDER PATIENTS WITH PREVIOUSLY TREATED MULTIPLE MYELOMA TREATED WITH SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE (XVD) IN THE BOSTON STUDY

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Background: Multiple myeloma (MM) typically affects older patients (pts) who are more vulnerable to toxicity with anti-MM treatments. These pts have significant morbidities resulting in a need for dose modifications or alternative suboptimal treatment options. Significant improvements were observed in the BOSTON study with XVd vs Vd in progression-free survival (PFS), overall response rate (ORR) and rates of peripheral neuropathy (PN); median overall survival (OS) trended in favor of XVd.
Aims: Here we report survival outcomes in the BOSTON study population based on age.
Methods: The phase 3 randomized BOSTON trial (NCT03110562) is a controlled, open-label study of once weekly XVd vs. twice weekly standard Vd in pts with MM and 1-3 prior treatment regimens. We performed post-hoc analyses to compare survival benefits in pts ≥65 vs <65 years of age.
Results: The BOSTON study enrolled a total of 402 pts between June 2017 and February 2019 who were randomized into XVd or Vd arms. The numbers of pts treated with XVd or Vd who were ≥65 were 109/132 and 86/75 who were <65, respectively. Baseline characteristics were similar by age although pts ≥65 years were less likely to have received ASCT than those <65 years (48.4% vs. 25.3%). Median PFS was prolonged with XVd compared with Vd across both age groups: ≥65 (HR, 0.55 [95% CI, 0.37-0.83] P=0.002) and <65, (HR, 0. 74 [95% CI, 0.49-1.11], P=0.07). Vd was associated with a lower ORR (64.4%) than treatment with XVd (76.1%) (OR, 1.77 [95% CI, 1.00-3.11], P=0.024) in pts ≥65, while the ORR in those <65 was 76.7% with XVd and 58.7% (OR, 2.33 [95% CI, 1.18-4.59], P=0.007) with Vd. As of Jan 2021, the median OS for the overall population was not reached for both arms (HR=0.86; p=0.193), with 61 and 75 deaths in the XVd and Vd arms, respectively. Median OS was not reached in pts ≥65 with XVd and was 28.6 months with Vd (HR=0.60; 95% CI, 0.38-0.94; p=0.012), while OS was similar for pts <65 (p=0.926). Pts ≥65 had a lower incidence of death on XVd as compared to Vd (29 vs 56) and there were 32 deaths with XVd and 19 with Vd in pts <65. Grade ≥3 treatment emergent adverse events (AEs) were not observed more often in older compared to younger pts. Amongst pts ≥65, PN of any grade was lower with XVd (32.1%) compared to Vd (46.5%); (OR 0.57 [95% CI 0.34-0.97], p=0.017), including a lower incidence of grade ≥3 PN (XVd 4.6% vs. Vd 11.6%). Pts <65 followed a similar trend of PN AEs of any grade: XVd, 32.6%; Vd, 48.0% (OR 0.42 [95% CI 0.21-0.82], p=0.006).
Summary/Conclusion: In an older patient population with a poor prognosis, XVd was associated with a significant survival benefit, improved PFS and ORR with reduced PN, and requires relatively short and infrequent clinic visits. XVd may be a simple, effective regimen for pts with previously treated MM including those ≥65 years of age.

EP977 COMPARISON OF OUTCOMES WITH CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) IN CARTITUDE-1 VERSUS STANDARD OF CARE IN TRIPLE-CLASS EXPOSED MULTIPLE MYELOMA PATIENTS IN CLINICAL TRIALS OF DARATUMUMAB

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Background: Triple-class exposed relapsed/refractory multiple myeloma (RRMM) patients (ie, those exposed to a proteasome inhibitor [PI], immunomodulatory drug [IMiD], and an anti-CD38 monoclonal antibody) tend to relapse, leading to progressively worse outcomes, including shorter progression-free survival (PFS) with each subsequent relapse. CARTITUDE-1 (NCT03548207) is a single-arm, phase 1b/2 study evaluating the efficacy and safety of cilta-cel, a chimeric antigen receptor T-cell therapy with 2 B-cell maturation antigen-targeting single-domain antibodies, in heavily pretreated patients with RRMM. The CARTITUDE-1 study enrolled patients who received ≥3 prior lines of therapy [LOT] or were double refractory to a PI and IMiD, received a PI, IMiD, and anti-CD38 antibody, had an Eastern Cooperative Oncology Group performance status score of ≤1, and documented disease progression ≤12 months after the last LOT.
Aims: To compare efficacy outcomes in triple-class exposed RRMM patients treated with cilta-cel from CARTITUDE-1 (N=97) versus standard of care (SOC) in a cohort of patients who participated in global daratumumab clinical trials.
Methods: Triple-class exposed patients with RRMM who met CARTITUDE-1 eligibility criteria were identified from the follow-up data from 3 global trials of the anti-CD38 monoclonal antibody, daratumumab: POLLUX (phase 3 study of daratumumab-lenalidomide-dexamethasone vs lenalidomide-dexamethasone; NCT02076009), CASTOR (phase 3 study of daratumumab-bortezomib-dexamethasone vs bortezomib-dexamethasone; NCT02136134), and EQUULEUS (phase 1b study of daratumumab plus standard MM regimens; NCT01998971). In these trials, patients were followed for overall response, PFS, and overall survival (OS) on subsequent treatments (per physician's choice) after discontinuation of the study treatment. These trial data were used to identify an SOC patient cohort who met CARTITUDE-1 (Sept 2020 data cutoff) eligibility criteria, including organ function. Outcomes were compared between the cilta-cel and SOC cohorts, adjusting for unbalanced prognostic baseline covariates, using inverse probability of treatment weighting (IPTW) propensity scores with logistic regression for overall response rate (ORR), and Cox models for PFS and OS to estimate the average treatment effect in the CARTITUDE-1 population. Sensitivity analyses were performed using multivariate Cox regression models and propensity score matching.
Results: In all, 267 triple-class exposed patients with RRMM from the European Union (70.0%), North America (14.2%), Asia/Pacific (12.7%), and other regions (3.0%) met the inclusion criteria. Baseline characteristics were similar between the 2 cohorts after propensity score weighting (Table). Treatment regimens in the SOC cohort primarily included pomalidomide (26%), cyclophosphamide (26%), lenalidomide (20%), bortezomib (20%), carfilzomib (17%), and thalidomide (10%). Patients had significantly improved ORR, PFS, and OS with cilta-cel

(N=97) versus SOC (N=267) (table). Cilta-cel treatment benefit was robust across the sensitivity analyses.

	CARTITUDE-1 (N=97)	SOC Cohort Observed (N=267)	SOC Cohort IPTW-Adjusted
Baseline characteristic, %			
Age <65 years	64	42	53
<6 years since MM diagnosis	46	45	47
High-risk cytogenetics*	24	15	15
ISS stage III	14	10	15
Prior LOT >4	66	31	67
Time to progression on last LOT (≤4 months)	50	30	58
Triple-class refractory† and quad-drug refractory	45	82	47
Penta-drug refractory‡	42	13	37
Outcomes			
ORR, % OR (95% CI)§	97	43.1 41.41 (15.05, 171.45)¶	43.2 41.11 (14.04, 176.02)¶
PFS, HR (95% CI)		HR 0.24 (0.16, 0.35)¶	HR 0.19, (0.11, 0.32)¶
OS, HR (95% CI)		HR 0.30 (0.17, 0.52)¶	HR 0.23 (0.12, 0.43)¶

*del17p, t(14;16), t(4;14); †≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody; ‡≥2 PI, ≥2 IMiD, and 1 anti-CD38 antibody; §CARTITUDE-1 vs SOC cohort; ¶P <0.0001.

CI, confidence interval; HR, hazard ratio; IMiD, immunomodulatory drug; IPTW, inverse probability of treatment weighting; ISS, international staging system; LOT, line of therapy; MM, multiple myeloma; OR, odds ratio; ORR, overall response rate; PI, proteasome inhibitor; SOC, standard of care.

Summary/Conclusion: Cilta-cel shows significantly better efficacy outcomes over SOC in patients previously treated with a PI, IMiD, and daratumumab, highlighting its potential as an effective treatment option in triple-class exposed patients with RRMM.

EP978 MATCHING ADJUSTED INDIRECT COMPARISON OF CILTACABTAGENE AUTOLEUCEL VERSUS BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) TREATED WITH ≥3 LINES OF PRIOR THERAPY

K. Weisel [1,*], A. Krishnan [2], K. Yong [3], J. M. Schecter [4], M. Vogel [5], C. C. Jackson [4], W. Deraedt [6], H. Tian [4], T.-M. Yeh [4], A. Banerjee [7], M. J. Carrasco-Alfonso [8], X. Wu [8], T. Nesheiwat [8], S. Van Sanden [5], J. Diels [5], S. Valluri [5], S. Z. Usmani [9], J. G. Berdeja [10], S. Jagannath [11], T. Martin [12]

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Background: Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor (CAR) T-cell therapy with two BCMA–targeting, single-domain antibodies designed to confer avidity. In the phase 1b/2 CARTITUDE-1 single arm study (NCT03548207), a single infusion of cilta-cel yielded early, deep, and durable responses with a manageable safety profile in heavily pretreated triple-class exposed (to immunomodulatory drugs [IMiDs], proteasome inhibitors [PIs], and anti-CD38 antibodies) RRMM patients. In the absence of head-to-head trials, matched adjusted comparison methods may be helpful to compare the relative efficacy of different treatment regimens. A systematic literature review using PRISMA guidelines identified belantamab mafodotin as a potential BCMA-targeting non-CAR T-cell comparator in the triple-class exposed RRMM patient population.
Aims: To compare efficacy outcomes for cilta-cel from the CARTITUDE-1 study to the approved 2.5 mg/kg (every 3 weeks) dose of belantamab mafodotin from the DREAMM-2 trial (NCT03525678).
Methods: CARTITUDE-1 included triple class exposed patients who received ≥3 prior lines of therapy or were double refractory to an IMiD and PI, had ECOG score of ≤1, and disease progression ≤12 months after the last line of therapy. Unanchored matching-adjusted indirect treatment comparisons (MAIC) were performed based on individual patient-level data from 97 infused patients in CARTITUDE-1 and published aggregate-level data from DREAMM-2 (N=97). Patients from CARTITUDE-1 (N=85) who matched the eligibility criteria for DREAMM-2 (≥ triple-class refractory and refractory to last line of treatment) were included in the analysis. Individual patient data for time-to-event outcomes from DREAMM-2 were simulated based on the published Kaplan-Meier curves. Matching of CARTITUDE-1 patients to the DREAMM-2 population was based on propensity score weighting methods, using available prognostic factors identified from the literature and based on clinical expertise. Outcomes included overall response rate (ORR), complete response or better (≥CR), progression free survival (PFS), and overall survival (OS). For ORR and ≥CR, the relative effects of cilta-cel versus belantamab mafodotin were quantified using an odds ratio (OR) and 95% confidence interval (CI) derived from a weighted logistic regression analysis, while time to event endpoints were analyzed using a weighted Cox proportional hazards model. A similar comparative analysis was performed including all enrolled patients from CARTITUDE-1.
Results: Cilta-cel was associated with significantly higher ORR and ≥CR, and improved PFS and OS compared with belantamab mafodotin in a population matched to DREAMM-2 (Table). Similarly, higher efficacy was associated with cilta-cel in the comparative analysis which included all patients enrolled in CARTITUDE-1.

Outcome*	Cilta-cel vs. belantamab mafodotin 2.5 mg/kg
ORR, OR (95% CI)	270.65 (74.64, 981.41)†
≥CR, OR (95% CI)	59.17 (15.17, 230.76)†
PFS, HR (95% CI)	0.21 (0.11, 0.40)†
OS, HR (95% CI)	0.22 (0.10, 0.46)†

*Patient populations from CARTITUDE-1 (N=85, ≥ triple-class refractory and refractory to last line of treatment) and DREAMM-2 (N=97) were matched on refractory status, cytogenetic risk, EMD, and ISS; †P<0.0001.
CR, complete response; CI, confidence interval; EMD, extramedullary disease; HR, hazard ratio; ISS, international staging system; OR, odds ratio; OS, overall survival; PFS, progression-free survival.

Summary/Conclusion: These analyses demonstrated improved efficacy with cilta-cel versus belantamab mafodotin for ORR, ≥CR, PFS, and OS, highlighting its potential in patients with triple-class exposed RRMM.

EP979 FIRST-LINE THERAPY WITH LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE PATIENTS WITH MULTIPLE MYELOMA: FINAL RESULTS OF THE OBSERVATIONAL STUDY FIRST-NIS

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Background: Lenalidomide plus low-dose dexamethasone (Rd) is an established standard of care for transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM) of all ages. Approval was based on the results of the pivotal phase III FIRST trial showing a significantly prolonged progression-free (PFS) and overall survival (OS) in pts treated with Rd compared with melphalan-prednisone-thalidomide (MPT) (Facon et al., Blood 2018). Since MM is a diagnosis of advanced age and only 35% of pts were age older than 75 years in the FIRST trial, the results are difficult to extrapolate to a real-world (RW) setting. Besides, RW data of this commonly used regimen are still scarce.
Aims: The focus of the final analysis part one of the FIRST-NIS is to evaluate effectiveness and safety of first-line Rd therapy in NDMM pts in a RW setting.
Methods: The prospective, multicenter, non-interventional, observational FIRST-NIS study collected data on 172 MM pts receiving Rd first-line therapy from 41 sites across Germany. Primary objective was to evaluate effectiveness of Rd assessed by 24-month PFS rate (PFS24). Secondary endpoints included OS, PFS, objective response rate (ORR), duration of response, quality of life (QoL) and safety. Descriptive statistics were used to analyze the data. Time-to-event analyses were performed using the Kaplan-Meier method. Final survival analysis will be performed 60 months after last patient in (LPI) in 2023 (final analysis part two).
Results: Of 172 pts enrolled, 164 pts qualified for effectiveness and 168 pts for safety analyses. Baseline characteristics of all pts and pts stratified

by age (≤75, >75 years) are presented in Table 1. With a median follow-up of 18.7 months at data base cut (4th November 2020), PFS24 rate was 48.0% for the total cohort, 65.5% for pts ≤75 years and 40.1% for pts >75 years. The median PFS was 22.9 months for all pts, 31.5 months for pts ≤75 years and 19.3 months for pts >75 years. The ORR was 59.1% in all pts, 70.8% in pts ≤75 years and 54.3% in pts >75 years. In total, 98.2% of pts developed adverse events (AEs). Grade 3/4 AEs were detected in 63.1% of pts, of which the most common were anemia (8.3%), thrombocytopenia (4.8%), dyspnea (4.8%) and pneumonia (4.8%).

Table 1: Baseline characteristics

	All (N=164)	≤75 years (N=48, 29.3%)	>75 years (N=116, 70.7%)
Age, years			
Median, range	77.7, 53.6-91.3		
Sex, n (%)			
Female	91 (55.5)	22 (45.8)	69 (59.5)
Male	73 (44.5)	26 (54.2)	47 (40.5)
ECOG Performance Status, n (%)			
0-1	126 (76.8)	39 (81.3)	87 (75.0)
≥2	29 (17.7)	7 (14.6)	22 (19.0)
Missing	9 (5.5)	2 (4.2)	7 (6.0)
International Staging System Stage, n (%)			
I	38 (23.2)	14 (29.2)	24 (20.7)
II	60 (36.6)	23 (47.9)	37 (31.9)
III	40 (24.4)	8 (16.7)	32 (27.6)
Unknown	26 (15.9)	3 (6.3)	23 (19.8)
Creatinine clearance, n (%)			
<30 ml/min	16 (9.8)	2 (4.2)	14 (12.1)
<60 ml/min	87 (53.0)	12 (25.0)	75 (64.7)
≥60 ml/min	77 (47.0)	36 (75.0)	41 (35.3)
High-risk cytogenetic profile (t(4;14) or t(14;16) or del17p), n (%)			
Yes	12 (7.3)	3 (6.3)	9 (7.8)
No	97 (59.1)	28 (58.3)	69 (59.5)
Unknown	52 (31.7)	17 (35.4)	35 (30.2)
Missing	3 (1.8)	0 (0.0)	3 (2.6)

Summary/Conclusion: Although the FIRST-NIS represents an elderly RW pts population with approximately 70% of pts aged >75 years, the results revealed a favorable risk-benefit profile for Rd in NDMM pts. In elderly pts >75 years, however, PFS results were lower compared to younger pts ≤75 years. Reasons might be the higher rates of advanced-stage disease and renal impairment observed in the elderly pts. Overall, the Rd combination seems to be a reasonable and orally available treatment option also for elderly pts with NDMM in the RW setting.

EP980 ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE VERSUS CARFILZOMIB AND DEXAMETHASONE IN ELDERLY PATIENTS WITH RELAPSED MULTIPLE MYELOMA: IKEMA SUBGROUP ANALYSIS

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Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*=0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile.
Aims: This subgroup analysis of IKEMA examined efficacy and safety in pts aged <70 and ≥70 years.
Methods: Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). The primary end point was PFS, as assessed by an independent response committee. We compared outcomes in pts <70 vs ≥70 years; division into different or additional age groups resulted in smaller sample sizes.
Results: Of the 302 randomized pts, 71.5% were aged <70 years (Isa-Kd: 70.9%; Kd: 72.4%) and 28.5% were aged ≥70 years (Isa-Kd: 29.1%; Kd: 27.6%). Consistent with the significant improvement of PFS in the overall population, the addition of Isa to Kd resulted in improved PFS independently of age (Table). The CR, ≥very good partial response (VGPR), and MRD- rates were higher with Isa-Kd vs Kd. Within the Isa-Kd arm, CR rate and ≥VGPR rate were similar in elderly and younger pts. MRD- was observed in 32.3% of younger pts and 23.1% of elderly pts with Isa-Kd. In both arms, Grade ≥3 and serious treatment-emergent adverse events (TEAEs) were more frequently reported in elderly pts vs pts <70 years old (Table). For both age groups, the incidence of Grade ≥3 TEAEs was higher whereas the incidence of serious TEAEs was similar between Isa-Kd and Kd. In the elderly subgroup, 3 (5.9%) pts receiving Isa-Kd and 1 (2.9%) receiving Kd had fatal TEAEs (Isa-Kd, infection; Kd, general health deterioration due to progressive disease). The most common Grade ≥3 TEAEs in pts aged <70 and ≥70 years treated with Isa-Kd vs Kd were hypertension (18.3% vs 17.0% [<70 years] and 25.5% vs 26.5% [≥70 years]) and pneumonia (14.3% vs 9.1% [<70 years] and 21.6% vs 20.6% [≥70 years]).

	<70 Years		≥70 Years	
	Isa-Kd (n=127)	Kd (n=89)	Isa-Kd (n=52)	Kd (n=34)
PFS HR (95% CI)	0.609 (0.384–0.968)		0.364 (0.176–0.751)	
CR, %	40.2	29.2	38.5	23.5
≥VGPR, %	72.4	56.2	73.1	55.9
MRD-, %	32.3	13.5	23.1	11.8
Grade ≥3 TEAEs, %*	71.4	63.6	90.2	76.5
Serious TEAEs, %*	54.0	52.3	72.5	70.6
Fatal TEAEs, %*	2.4	3.4	5.9	2.9
TEAEs leading to definitive discontinuation, %*	7.1	10.2	11.8	23.5

*n=126; n=88; n=51; n=34

Summary/Conclusion: The addition of Isa to Kd improved PFS and quality of response in elderly pts, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd provides a potential new treatment option for elderly pts with RMM.

EP981 ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED MULTIPLE MYELOMA PATIENTS WITH HIGH-RISK CYTOGENETICS: IKEMA SUBGROUP ANALYSIS

I. Spicka [1,*], P. Moreau [2], T. Martin [3], T. Facon [4], G. Martinez [5], A. Oriol [6], Y. Koh [7], A. Lim [8], G. Mikala [9], L. Rosiñol [10], M. Yağci [11], M. Cavo [12], M.-L. Risse [13], G. Asset [14], S. Macé [13], H. van de Velde [15], K. Yong [16]

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Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*=0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile.
Aims: This subgroup analysis of IKEMA examined efficacy and safety in pts with high-risk cytogenetics [t(4;14), del(17p), and t(14;16)] and/or gain(1q21).
Methods: Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). High-risk cytogenetics was assessed by central laboratory analysis and defined as ≥1 of the following: del(17p): 50% cutoff; t(4;14) or t(14;16): 30% cutoff. Assessment of gain(1q21) was prespecified as ≥3 copies: 30% cutoff.
Results: Of the randomized pts, 23.5% (Isa-Kd) and 25.2% (Kd) had ≥1 high-risk cytogenetic abnormality (CA); 26.3% (Isa-Kd) and 25.2% (Kd) had isolated gain(1q21). The addition of Isa to Kd improved PFS for pts with ≥1 high-risk CA and standard-risk pts (Table); pts with t(4;14) (HR 0.549; 95% CI, 0.232–1.301) had a more pronounced treatment effect than pts with del(17p) (HR 0.837; 95% CI, 0.281–2.496). A clear PFS benefit with Isa-Kd was also seen for pts with isolated gain(1q21) and gain(1q21) combined with other high-risk CA (Table). The trend toward improved CR, ≥very good partial response (VGPR), and MRD- rates with the addition of Isa was more pronounced in pts with gain(1q21) than in pts with high-risk CA alone. Grade ≥3 treatment-emergent adverse events (TEAEs) were more common with Isa-Kd vs Kd, but the incidence of serious and fatal TEAEs was similar with both arms for high-risk pts (Table).

%	High-Risk		Standard Risk		Isolated Gain(1q21)		Gain(1q21) + High-Risk CA	
	Isa-Kd n=42	Kd n=31	Isa-Kd n=114	Kd n=77	Isa-Kd n=47	Kd n=31	Isa-Kd n=25	Kd n=19
PFS HR vs Kd (95% CI)	0.724 (0.361–1.451)		0.440 (0.266–0.728)		0.462 (0.219–0.972)		0.678 (0.299–1.537)	
CR	23.8	22.6	46.5	26.0	46.8	22.6	32.0	26.3
≥VGPR	57.1	54.8	78.9	54.5	80.9	51.6	64.0	52.6
MRD-	21.4	22.6	36.0	11.7	36.2	9.7	28.0	21.1
Grade ≥3 TEAEs	85.7	63.3	76.1	76.6	78.3	67.7	88.0	66.7
Serious TEAEs	64.3	66.7	57.5	59.7	63.0	51.6	60.0	66.7
Fatal TEAEs	0	0	4.4	5.2	6.5	3.2	0	0
TEAEs leading to definitive discontinuation	4.8	10.0	9.7	18.2	10.9	19.4	0	0

Summary/Conclusion: The addition of Isa to Kd improved PFS in pts with high-risk CA and disease response in pts with gain(1q21) isolated or combined with high-risk CA, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA population. Isa-Kd is a potential new treatment option for the difficult-to-treat subgroup of pts with RMM and high-risk cytogenetics.

EP982 CARFILZOMIB, DEXAMETHASONE, AND DARATUMUMAB (KDD) VS KD IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: ANALYSIS OF TIME TO NEXT TREATMENT, TIME TO PROGRESSION, AND PROGRESSION-FREE SURVIVAL FOR NEXT THERAPY

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Background: Lenalidomide (Len)- and bortezomib-based treatments are standard frontline therapies for multiple myeloma (MM). Many patients discontinue these drugs due to progression or toxicity, resulting in a need for bortezomib- and len-sparing treatment combinations for relapsed or refractory (RR) patients. After approximately 27 months of median follow-up in the phase 3, randomized CANDOR study, median progression-free survival was 29 months in patients treated with carfilzomib, dexamethasone, and daratumumab (KdD) vs 15 months in patients treated with carfilzomib and dexamethasone (Kd) (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.45–0.78) (Dimopoulos et al., *Blood* 2020).
Aims: To compare time to next treatment (TTNT), time to progression (TTP), and time to second objective disease progression (PFS2) in patients treated with KdD vs Kd in the CANDOR study.
Methods: The study design of CANDOR (NCT03158688) has been previously published (Dimopoulos et al., *Lancet* 2020). This post hoc analysis used a planned interim readout from CANDOR (data cutoff: June 15, 2020). TTNT was defined as the time from randomization to initiation of subsequent MM treatments. Patients who did not move on to a next treatment were censored. TTP was defined as the time from randomization to disease progression as assessed by a validated computer algorithm (Onyx Response Computer Algorithm). PFS2 was defined as the time from randomization to second disease progression or death, whichever occurred first. Since the date of the second disease progression was not collected in CANDOR, for patients who had progressive disease (PD), the start date of the next line of therapy was used as a surrogate for the PFS2 event; for patients who had not had a PD, the start date of the third line of therapy was used as a surrogate for the PFS2 event. TTNT, TTP, and PFS2 were compared between KdD and Kd arms using a stratified log-rank test and HRs were estimated by a stratified Cox proportional hazards model with stratification factors of International Staging System stage (1 or 2 vs 3), prior proteasome inhibitor (PI) exposure, and number of prior lines of therapy.
Results: Patients treated with KdD had longer TTNT compared with patients treated with Kd (HR: 0.473; 95% CI: 0.354–0.633), with median TTNT for patients in the KdD arm not estimable (NE) (95% CI: 30–NE) vs 18 months (95% CI: 14–25) in the Kd arm. Treatment with KdD improved TTP compared with Kd treatment (HR: 0.497; 95% CI: 0.370–0.667); median TTP was NE (95% CI: 28–NE) in the KdD arm vs 16 months (95% CI: 12–22) in the Kd arm. Median PFS2 was NE (95% CI: NE–NE) in the KdD arm vs 33 months (95% CI: 33–NE) in the Kd arm (HR: 0.729; 95% CI: 0.526–1.012). The observed improvements in TTNT, TTP, and PFS2 for KdD vs Kd-treated patients were consistent regardless of prior lines of therapy, prior PI exposure, prior len exposure, and len-refractoriness (Figure).

Figure. Subgroup analysis of (A) TTNT, (B) TTP, and (C) PFS2.

A.

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median TTNT, mo	Kd (n = 154) Events/ Patients	Kd (n = 154) Median TTNT, mo	Favors KdD / Favors Kd	Hazard ratio for KdD vs Kd (95% CI)
All patients	107/312	NE	84/154	18.1		0.473 (0.354–0.633)
1 prior line	45/133	NE	31/67	25.6		0.579 (0.365–0.918)
≥ 2 prior lines	62/179	NE	53/87	16.2		0.414 (0.284–0.602)
Prior PI exposure	96/279	NE	77/139	17.8		0.461 (0.340–0.625)
No prior len exposure	62/189	NE	37/80	25.6		0.537 (0.353–0.817)
Prior len exposure	45/123	30.1	47/74	15.2		0.396 (0.256–0.611)
Not refractory to len	71/213	NE	49/99	19.0		0.522 (0.360–0.758)
Refractory to len	36/99	28.8	35/55	14.1		0.338 (0.202–0.568)

B.

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median TTP, mo	Kd (n = 154) Events/ Patients	Kd (n = 154) Median TTP, mo	Favors KdD / Favors Kd	Hazard ratio for KdD vs Kd (95% CI)
All patients	111/312	NE	78/154	15.7		0.497 (0.370–0.667)
1 prior line	43/133	NE	27/67	24.0		0.601 (0.369–0.977)
≥ 2 prior lines	68/179	NE	51/87	14.6		0.443 (0.306–0.642)
Prior PI exposure	101/279	NE	74/139	15.3		0.473 (0.348–0.641)
No prior len exposure	65/189	NE	34/80	22.2		0.555 (0.361–0.854)
Prior len exposure	46/123	NE	44/74	12.0		0.408 (0.264–0.631)
Not refractory to len	74/213	NE	45/99	20.3		0.543 (0.371–0.795)
Refractory to len	37/99	NE	33/55	11.1		0.371 (0.222–0.619)

C.

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median PFS2, mo	Kd (n = 154) Events/ Patients	Kd (n = 154) Median PFS2, mo	Favors KdD / Favors Kd	Hazard ratio for KdD vs Kd (95% CI)
All patients	98/312	NE	58/154	33.2		0.729 (0.526–1.012)
1 prior line	31/133	NE	20/67	NE		0.660 (0.374–1.165)
≥ 2 prior lines	67/179	NE	38/87	33.2		0.766 (0.513–1.143)
Prior PI exposure	93/279	NE	55/139	33.2		0.733 (0.524–1.026)
No prior len exposure	58/189	NE	26/80	NE		0.759 (0.473–1.218)
Prior len exposure	40/123	NE	32/74	33.2		0.688 (0.430–1.101)
Not refractory to len	68/213	NE	33/99	33.2		0.820 (0.537–1.251)
Refractory to len	30/99	NE	25/55	NE		0.620 (0.360–1.067)

0 1 2

CI, confidence interval; len, lenalidomide; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; mo, months; NE, not estimable; PFS2, time to second objective disease progression; PI, proteasome inhibitor; TTNT, time to next treatment; TTP, time to progression.

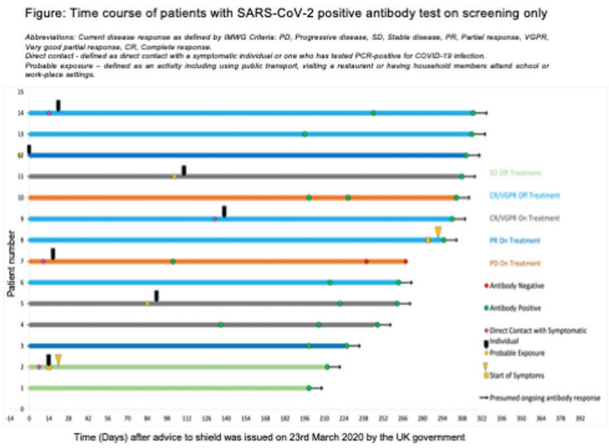
Summary/Conclusion: Patients receiving KdD vs Kd had improvements in time to their next treatment, time to disease progression, and time to second disease progression or death following subsequent therapies. These data confirm and expand upon previously reported results of CANDOR, indicating the robust efficacy benefit of KdD across clinically relevant subgroups, including in those exposed and/or refractory to len. These findings reinforce the clinical value of KdD as an emerging standard of care in the management of RRMM for patients with 1–3 prior lines of therapy.

EP983 DEVELOPMENT OF ANTIBODY RESPONSE TO SARS-COV-2 FOLLOWING ASYMPTOMATIC INFECTION IN PATIENTS WITH PLASMA CELL DISORDERS ON IMMUNOMODULATORY THERAPY

W. Y. Chan [1,2,*], E. Sanchez [3], S. Chavda [1,2], C. Lecat [1,2], L. Ainley [1,2], K. Xu [1], B. Wisniowski [1], S. Mahmood [1], X. Papanikolaou [1], C. Kyriakou [1], J. Sive [1], A. Wechalekar [1], R. Popat [1], N. Rabin [1], L. Lee [1,2], E. Nastouli [3], K. Yong [1,2]

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Background: Plasma cell disorder (PCD) patients are extremely vulnerable to SARS-CoV-2 infection due to disease-related impaired humoral and cellular immunity as well as the receipt of immunosuppressive therapy. Reported mortality in a large cohort of patients with plasma cell disorders is 33%. The roll out of the COVID-19 vaccine is welcomed in this population, however there is concern of suboptimal antibody responses, from previous experience with the influenza vaccine. There is urgent need to understand the humoral response to SARS-CoV-2 infection in these patients, in the context of systemic anti-cancer therapy (SACT).
Aims: We aimed to investigate the presence of SARS-CoV-2 antibodies in a cohort of PCD patients, the relationship with symptomatic infection, PCD characteristics and receipt of SACT.
Methods: SARS-CoV-2 antibody screening with the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics, Basel, Switzerland), a semi-quantitative assay of IgG and IgM against the nucleocapsid (N) antigen was introduced for PCD patients at our institution in July 2020. Clinical information was retrieved from the medical records. Patients with unexpected positive antibody tests were asked about possible past contacts and exposure to SARS-CoV-2.
Results: We report on a six-month period of routine SARS-CoV-2 antibody screening. Two-hundred and forty-three PCD patients had one antibody test, 106 had serial samples. Total seroprevalence was 10.7% (26/243), of which 12 were patients with known PCR-swab positive COVID-19 disease. In a separate but overlapping cohort, 41 patients have had PCR confirmed COVID-19 disease; 20 of these patients were tested, and 12 (60%) had seroconverted. Median time to testing from positive PCR test in the antibody positive patients was 86.5 days (range 22-256) and in antibody negative patients, 30.5 days (range 5-176 days). No PCD or COVID-19 disease factors were found to influence the likelihood of mounting an antibody response after PCR-confirmed COVID-19 disease in these 20 patients. In our screened cohort, 14 (6.3%) patients were unexpectedly antibody positive. Their clinical course is summarised in the included figure. The majority 85.7% (12/14) of patients described no COVID-19 symptoms. Seven (50%) patients were on SACT (including ixazomib, pomalidomide, lenalidomide and dexamethasone combinations) throughout the period from possible exposure to positive antibody test, with no interruption to their ongoing oral immunomodulatory treatment. Ten antibody positive patients had serial positive results at median 45 days (range 21-119) apart, demonstrating persistence, but some decline in titre over time.



Summary/Conclusion: Our seroprevalence of 10.7% is lower but not dissimilar to that reported in the London population over a similar time period reflecting shielding behaviours in our patients but also the challenges of protecting them during high SARS-CoV-2 incidence in the community. Nevertheless, PCD patients retain the ability to seroconvert, even with asymptomatic COVID-19 disease and while on immunomodulatory therapy. Seroconversion rates following symptomatic infection appear lower however, with evidence of delay compared to the general population. These data support the advice for COVID-19 vaccination to be offered to all PCD patients although the suboptimal humoral response calls for close antibody monitoring of all vaccinated PCD patients and timely booster doses.

EP984 CHARACTERISTICS OF NEUROTOXICITY ASSOCIATED WITH IDECABTAGENE VICLEUCEL (IDE-CEL, BB2121) IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA IN THE PIVOTAL PHASE 2 KARMMA STUDY

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Background: Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, showed promising efficacy in patients with relapsed and refractory multiple myeloma (RRMM) in the KarMMa study with an overall response rate (ORR) of 73% and a complete response rate (CRR) of 33% across the target dose range of 150–450 × 10^6 CAR+ T cells (Munshi NC, et al. *N Engl J Med* 2021;384:705-716). CAR T cell therapies have been associated with potentially severe adverse events, including cytokine release syndrome (CRS) and neurotoxicity (NT). Improved understanding of these adverse events may allow for better management of such toxicities.
Aims: To examine associations of NT with patient and disease characteristics, describe patient management, and evaluate the impact of NT on outcomes in the KarMMa study.
Methods: Patients enrolled in the KarMMa study had received ≥3 prior regimens, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and were refractory to their last regimen per IMWG criteria (NCT03361748). Ide-cel target doses of 150, 300, or 450 × 10^6 CAR+ T cells were given after 3 d of lymphodepletion with cyclophosphamide (300 mg/m^2/d) and fludarabine (30 mg/m^2/d) followed by 2 d of rest. Endpoints included ORR (primary), CRR (key secondary), duration of response (DOR), progression-free survival, and safety. Investigator-identified NT events were captured under the single preferred term of neurotoxicity and graded according to NCI CTCAE v4.03. Events were managed with corticosteroids, anakinra, and tocilizumab as needed.
Results: Of 128 patients treated with ide-cel, NT was reported in 23 (18%); 12 patients (9%) had maximum grade 1 NT, 7 (5%) had grade 2, and 4 (3%) had grade 3. No grade 4 or 5 NT occurred. Most baseline characteristics were similar in patients with and without NT, including R-ISS disease stage III (22% and 15%), high-risk cytogenetics (39% and 34%), and extramedullary disease (35% and 40%); exceptions were high tumor burden (65% and 48%) and sex (48% and 62% men). NT (any grade/grade 3) occurred in 0%/0%, 17%/1%, and 20%/6% of patients at target doses of 150, 300, and 450 × 10^6 CAR+ T cells. Median time to onset was similar regardless of grade, and there were no late-onset events (**Table**). NT was managed with corticosteroids in 10 patients (43%), tocilizumab in 3 (13%), and anakinra in 1 (4%). Median (range) time to first use of corticosteroids was 2 d (1–6). ORR and DOR were similar in patients with and without NT (**Table**). All NT occurred in the proximity of CRS events with the start date of NT events either overlapping with or occurring within 1 wk of the start of a CRS event.

NT events	Grade 1 (n=12)	Grade 2 (n=7)	Grade 3 (n=4)	Any grade (n=23)
Time to onset, median (range), d	2 (1–10)	2 (1–4)	3 (1–4)	2 (1–10)
No. of events	13	7	4	24
Duration/event, n (%)				
1–5 d	9 (69)	3 (43)	1 (25)	13 (54)
6–10 d	4 (31)	2 (29)	0	6 (25)
>10 d	0	1 (14)	3 (75)	4 (17)
Ongoing	0	1 (14)	0	1 (4)
Median (range), d[a]	3 (1–9)	6 (1–26)	14 (2–22)	3 (1–26)
Corticosteroids, n (%)	2 (17)	4 (57)	4 (100)	10 (43)
Tocilizumab, n (%)	1 (8)	0	2 (50)	3 (13)
Anakinra, n (%)	0	0	1 (25)	1 (4)
Efficacy	**No NT (n=105)**		**NT, any grade (n=23)**	
Response, % (95% CI)				
ORR	73 (64.9–81.8)		74 (56.0–91.9)	
CRR	35 (26.1–44.4)		22 (4.9–38.6)	
PFS, median (95% CI), mo	8.9 (5.7–11.9)		6.1 (3.0–11.1)	
DOR, median (95% CI), mo[b]	11.0 (8.0–11.3)		10.0 (4.0–NE)	
OS, median (95% CI), mo	19.4 (18.0–NE)		NE (12.3–NE)	

Data cutoff: 14 Jan 2020. NE, not estimable; OS, overall survival; PFS, progression-free survival
[a]Ongoing NT excluded. [b]Among responders.

Summary/Conclusion: NT occurred early in the KarMMa study, was generally of short duration, and was mostly grade 1/2 with no grade ≥4 events. All NT was proximal to CRS. Patients with NT had a favorable ORR after ide-cel treatment. These results continue to demonstrate the durable efficacy and tolerability of ide-cel in patients with RRMM.

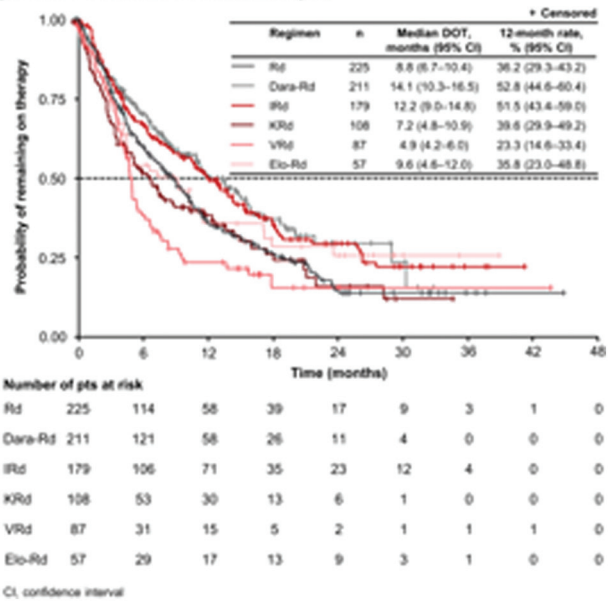
EP985 REAL-WORLD DURATION OF TREATMENT (DOT) WITH LENALIDOMIDE-DEXAMETHASONE (RD)-BASED REGIMENS IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): OUTCOMES FROM THE GLOBAL INSIGHT MM STUDY

N. Puig [1,*], R. Abonour [2], F. E. Davies [3], A. Chari [4], J. G. Berdeja [5], M. Boccadoro [6], R. Hájek [7], R. M. Rifkin [8], X. Leleu [9], E. Terpos [10], C. L. Costello [11], K. C. Weisel [12], S. Z. Usmani [13], F. van Rhee [14], J. A. Zonder [15], M. A. Thompson [16], J. Omel [17], A. Spencer [18], V. T. M. Hungria [19], G. Cook [20], J. Vela-Ojeda [21], M. Armour [22], K. Ren [23], D. Cherepanov [23], D. M. Stull [23], H. C. Lee [24]

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Background: Daratumumab (Dara), ixazomib (I), carfilzomib (K), bortezomib (V), and elotuzumab (Elo) plus Rd, as well as Rd alone, are among the standards of care for RRMM treatment. In phase 3 RRMM trials, these regimens have been given as long-term/continuous therapy, with median DOTs ranging from 10.1 to 34.3 months. Longer DOT is associated with improved outcomes; however, the lengthy DOTs seen in clinical trials do not always translate to the real-world setting due to multiple pt- and treatment-related factors, emphasizing the importance of real-world data collection to aid in treatment decisions.
Aims: To estimate DOT with Rd-based regimens in RRMM pts in the global, prospective, observational INSIGHT MM study (NCT02761187).
Methods: From July 2016 to June 2019, INSIGHT MM enrolled 4307 pts from 15 countries, including 1939 pts with ≥2 prior lines of therapy (LOT). Prospective follow-up of ≥2 years/pt is ongoing. DOT was defined as time from Rd-based treatment initiation within a LOT (index regimen) to time of discontinuation of index regimen. Kaplan-Meier analyses were used to determine DOT for each Rd-based regimen reported, overall, and by LOT and region (Europe+Israel [EUR]; North America [NA]). Exposure to prior therapies and reasons for treatment discontinuation were also examined.
Results: In total, 821 pts received 867 Rd-based LOT for RRMM (225 Rd, 211 Dara-Rd, 179 IRd, 108 KRd, 87 VRd, and 57 Elo-Rd; pts could be included more than once if they received an Rd-based treatment in >1 LOT), including 464/262/150 in 2nd/3rd/≥4th line (134/70/24 Rd, 115/58/39 Dara-Rd, 58/82/40 IRd, 67/25/18 KRd, 57/16/15 VRd, and 33/11/14 Elo-Rd; 9 pts received the same regimen >once). Overall, median DOT was longest with Dara-Rd and IRd (14.1 and 12.2 months); the proportions of pts in treatment at 12 months (12-month DOT rate) were 52.8% and 51.5%, respectively (Figure). Analysis by region showed higher 12-month DOT rates in EUR vs NA with Dara-Rd (57.1 vs 43.7%), IRd (55.3 vs 34.2%), and KRd (41.0 vs 30.7%), a lower rate in EUR with VRd (11.0 vs 30.7%), and similar rates with Rd (40.8 vs 40.0%) and Elo-Rd (37.0 vs 33.6%). These rates were not analyzed in Latin America and Asia-Pacific regions due to small pt numbers. Among 2nd/3rd/≥4th-line pts, 12-month DOT rates with Dara-Rd were 58.8%/56.1%/31.1%; with IRd, 49.8%/56.6%/47.4%; with KRd, 41.3%/44.3%/35.3%; with Elo-Rd, 40.8%/30.0%/27.7%; with Rd, 36.8%/36.2%/28.1%; and with VRd, 25.0%/40.0%/0%. Most regimens received immediately prior to Rd-based treatment were V-based (n=504, 58.1%). Overall, common prior regimens received included VCd (20.6%), VRd (10.3%), VTd (9.1%), Vd (8.9%), Rd (6.6%), and VMP (5.9%), used primarily as 1st and 2nd line. Prior therapies were more diverse in pts receiving Rd-based treatment beyond 3rd vs in earlier lines. Overall, 555/867 (64.0%) of the reported LOT were in R-naïve pts and 312 (36.0%) were in pts exposed to R in any line prior to Rd-based treatment. At data cutoff, 530/867 (61.1%) Rd-based individual LOT had been discontinued; overall reasons for discontinuation (multiple reasons could be provided per LOT) included relapse in 224 pts (42.3% of 530), adverse events in 78 (14.7%), death in 33 (6.2%), and other reasons in 207 (39.1%).

Figure. Kaplan Meier analysis of DOT by index regimen in RRMM patients treated with Rd-based therapies



Summary/Conclusion: DOT with Rd-based treatment in the real-world setting of INSIGHT MM generally appeared shorter than in clinical trials. The longest DOTs were seen in 2nd and 3rd LOT with Dara-Rd and IRd. Thirty six percent of the reported LOT were in pts who received R in any prior line, while the most common therapies immediately prior to Rd-based therapy were V-based.

EP986 ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN PATIENTS WITH RELAPSED MULTIPLE MYELOMA ACCORDING TO PRIOR LINES OF TREATMENT AND REFRACTORY STATUS: IKEMA SUBGROUP ANALYSIS

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Background: Patients (pts) with multiple myeloma (MM) often relapse and become refractory to successive lines of therapy, warranting better treatment options. The Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd in pts with relapsed MM (RMM) (HR 0.53; 99% CI 0.32–0.89; *P*=0.0007).
Aims: Evaluate the efficacy and/or safety of Isa-Kd by number of prior lines of therapy (1 vs >1) and refractoriness to lenalidomide (Len) or bortezomib (Bor).
Methods: Pts were randomized (3:2) to Isa-Kd (n=179) or Kd (n=123). Isa (10 mg/kg IV) was given weekly for 4 weeks, then every 2 weeks. K (20 mg/m^2 days 1-2, then 56 mg/m^2) was given twice-weekly 3 of 4 weeks, and d (20 mg) twice-weekly. The primary endpoint was PFS; key secondary endpoints were very good partial response or better (≥VGPR), minimum residual disease negativity (MRD-), and complete response (CR) rates.
Results: Of the 302 randomized pts, 44.7% had 1 prior line, 55.3% had >1 prior line, 32.8% were Len-refractory, and 30.1% were Bor-refractory. PFS was improved with Isa-Kd vs Kd in pts who received 1 prior line and >1 prior line, as well as in pts refractory to Len, Len at last regimen, Bor, or Bor at last regimen (Table). The addition of Isa to Kd improved depth of response (≥VGPR, MRD-, and CR rates) in all subpopulations analyzed by prior treatment. Grade ≥3 treatment-emergent adverse events (TEAEs) were generally similar between the prior line subgroups (77.2% [Isa-Kd] vs 64.8% [Kd], 1 prior line; 76.5% [Isa-Kd] vs 69.1% [Kd], >1 prior line) and the overall safety population (76.8% [Isa-Kd] vs 67.2% [Kd]). Serious AEs were 62.0% vs 48.1% in the 1 prior line subgroup, and 57.1% vs 64.7% in the >1 prior line subgroup; TEAEs leading to discontinuations were 8.9% vs 11.1%, 1 prior line and 8.2% vs 16.2%, >1 prior line.

		n		PFS, HR (95% CI)	≥VGPR,%		MRD-, %		CR, %	
		Isa-Kd	Kd	-	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
Overall		179	123	0.53 (0.32-0.89)*	72.6	56.1	29.6	13.0	39.7	27.6
Number of prior lines as per randomization	1	80	55	0.59 (0.31-1.12)	75.0	61.8	33.8	18.2	41.3	36.4
	>1	99	68	0.48 (0.29-0.78)	70.7	51.5	26.3	8.8	38.4	20.6
Refractory to Len	Yes	57	42	0.60 (0.34-1.1)	66.7	35.7	24.6	9.5	38.6	11.9
Refractory to Len at last regimen	Yes	36	31	0.69 (0.35-1.39)	72.2	38.7	27.8	9.7	47.2	12.9
Refractory to Bor	Yes	52	39	0.62 (0.33-1.16)	55.8	51.3	17.3	10.3	28.8	17.9
Refractory to Bor at last regimen	Yes	32	23	0.38 (0.16-0.92)	62.5	47.8	25.0	8.7	31.3	17.4

*99% CI

Summary/Conclusion: The addition of Isa to Kd improved PFS and depth of response, irrespective of prior lines of therapy or refractory status, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd had a manageable safety profile regardless of number of prior lines. Isa-Kd is a potential new treatment option for pretreated pts with RMM.

EP987 A PROSPECTIVE, NON-INTERVENTIONAL, MULTINATIONAL STUDY OF REAL-LIFE STANDARD OF CARE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH ≥3 PRIOR LINES OF THERAPY: INTERIM DATA FROM LOCOMMOTION

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Background: Despite advances in medical treatments that have improved patient survival, multiple myeloma (MM) remains an incurable disease. Most patients with MM eventually progress through standard drug classes of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 monoclonal antibodies (mAbs), and others. There are currently no prospective data on real-world standard of care in patients who progress after PIs, IMiDs, and anti-CD38 mAbs.
Aims: To describe the interim results from LocoMMotion (NCT04035226), the first prospective study on the efficacy and safety of real-life standard of care in patients with relapsed/refractory MM.
Methods: Between August 2019 and October 2020, eligible patients who were aged ≥18 years and had a diagnosis of MM were enrolled in 75 sites across 9 European countries and the US. Patients were included if they had received 3 or more prior lines of therapy or were double-refractory to a PI and IMiD, had measurable disease at screening, received at least a PI, an IMiD, and anti-CD38 mAb with documented progressive disease since their last line of therapy, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1. All patients provided informed consent prior to enrollment in the study. Responses were assessed per International Myeloma Working Group response criteria. The overall response rate (ORR) of real-life current standard of care (primary objective of the study) was assessed by a Response Review Committee. Secondary objectives of the study included additional efficacy and safety evaluation of real-life standard of care.
Results: The data cut-off was November 4, 2020 for the first interim analysis of 225 patients (203 [90.2%] from Europe and 22 [9.8%] from the US) with a median follow-up of 3.7 months (range: 0–12.7). The median age was 68 years (range: 41–89), 124 (55.1%) patients were male, 162 (72.0%) had a baseline ECOG PS score of 1, and median time since initial MM diagnosis was 6.0 years (range: 0.3–22.8). Patients had received a median of 4.0 (range: 2–13) prior lines of therapy; all patients were triple-class exposed, 166 (73.8%) were triple-class refractory, and 208 (92.4%) were refractory to their last line of therapy. The ORR with real-life standard of care salvage therapy was 20.1% (95% CI: 15.0–26.0) in the response-evaluable population (n=219). Treatment-emergent adverse events (TEAEs) were reported in 148 (65.8%) patients, 95 (42.2%) were grade 3 or higher. The most common grade ≥3 TEAEs were anemia, thrombocytopenia, and neutropenia. Fifteen deaths (6.7%) occurred due to TEAEs during the study. Treatment is ongoing in 121 (53.8%) patients.
Summary/Conclusion: The interim results of this first, prospective study of real-life standard of care treatment demonstrate that heavily pretreated, triple-class exposed patients with relapsed/refractory MM continue to progress after multiple lines of therapy and have poor outcomes. Therefore, new treatments with novel mechanisms of action are needed for this patient population.

EP988 POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE AFTER 1 PRIOR LINE OF THERAPY IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA: A SAFETY SUBANALYSIS OF THE PHASE 3 OPTIMISMM TRIAL

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Background: Patients (pts) with newly diagnosed multiple myeloma (MM) are routinely treated with lenalidomide (LEN) until disease progression. Thus, at the time of first relapse, many pts will have LEN-refractory disease. These pts need proven effective therapies that not only help achieve disease control but also have a manageable safety profile. Pts with relapsed or refractory MM (RRMM) who were treated with pomalidomide (POM), bortezomib (BORT), and dexamethasone (DEX; PVd) at first relapse in OPTIMISMM (phase 3, NT01734928) had a significantly improved median PFS (20.7 vs 11.6 mo; HR, 0.54; 95% CI, 0.36-0.82; *P* = .0027) vs Vd; all pts were previously treated with LEN, and 57% were LEN refractory (Richardson PG, et al. *Lancet Oncol* 2019;20:781-794). Adverse events reported with PVd in the overall population were consistent with the individual safety profiles for POM, BORT, and DEX.

Aims: To report a safety analysis of treatment-emergent adverse events (TEAEs) in the events of interest (EOI) category for PVd vs Vd administered at first relapse in OPTIMISMM.

Methods: In 21-day cycles, pts received PVd or Vd (1:1). POM 4 mg/d was given on d 1-14 (PVd arm only); BORT 1.3 mg/m^2 was given on d 1, 4, 8, and 11 of cycle 1-8 and d 1 and 8 of cycle 9+; and DEX 20 mg/d (10 mg/d for pts aged > 75 yr) was given on the days of and after BORT. Key eligibility criteria included ≥ 2 cycles of prior LEN; LEN-refractory pts were allowed. Adverse events were graded according to the NCI CTCAE (version 4.0) and were summarized by system organ class and preferred term. All pts provided informed consent.

Results: 226 of 559 pts (40%) in OPTIMISMM had 1 prior line of therapy (LOT) and 221 (PVd, n=111; Vd, n=110) were included in the safety analysis population (all pts who received ≥1 dose of study drug). Baseline characteristics were generally well balanced between Tx arms. All pts had prior LEN Tx and 57% (126/221) were LEN refractory; 59% (131/221) had prior BORT Tx. Median duration of treatment was longer in the PVd vs Vd arm: 47.4 wk (4.7-147.0) vs 27.1 wk (0.4-162.0). Grade (Gr) 3/4 TEAEs EOI occurred in 57.5% of pts (PVd, 69.4%; Vd, 45.5%; **Table**). Overall, the most common Gr 3/4 TEAEs EOI were neutropenia (24.4%), infections and infestations (22.2%), and thrombocytopenia (20.4%). Gr 3/4 TEAEs EOI more common in the PVd vs Vd arm included neutropenia (36.9% vs 11.8%), infections and infestations (28.8% vs 15.5%), and peripheral neuropathy (11.7% vs 4.5%). Onset of neutropenia was mostly in the first 3 cycles and primarily Gr 3/4. Onset of infections and infestations commonly occurred during cycles 1-9 and were mostly Gr 1/2. Onset of peripheral neuropathy commonly occurred in the first 6 cycles; instances were mostly Gr 1/2. See table for median time to onset and duration of selected TEAE EOIs. TEAE EOIs were mainly managed with dose reductions and interruptions (**Table**). POM discontinuations due to ≥1 TEAE EOI of any grade were low (9.0%). In the PVd arm, 62% (31/50) of pts with any-grade neutropenia received G-CSF support. No pt discontinued POM due to neutropenia. Infections and infestations were the primary cause of PVd dose interruptions (54.1%). Peripheral neuropathy was the most common TEAE EOI leading to dose reduction (32.4%) and drug discontinuation (16.2%) with PVd.

Table. Summary of incidence, time to onset, duration, and dose modifications for TEAE EOIs

TEAE EOI	Grade 3/4 TEAE EOI, n (%)[a]		Grade 3/4 TEAE EOI, incidence rate per 100 person-years[b]		Median time to onset of any-grade TEAE EOI/median duration, d	
	PVd (n = 111)	Vd (n = 110)	PVd (n = 111)	Vd (n = 110)	PVd	Vd
≥ 1 Specified event	77 (69.4)	50 (45.5)	-	-	-	-
Neutropenia	41 (36.9)	13 (11.8)	46.25	18.14	23.1/ 8.0 (n=50)	46.0/ 5.0 (n=21)
Thrombocytopenia	22 (19.8)	23 (20.9)	21.30	32.96	11.0/ 15.0 (n=31)	30.4/ 14.0 (n=32)
Infections and infestations	32 (28.8)	17 (15.5)	32.91	23.71	63.9/ 12.0 (n=91)	57.5/ 12.0 (n=74)
Peripheral neuropathy	13 (11.7)	5 (4.5)	11.31	6.39	42.1/ 19.0 (n=69)	53.9/ 22.5 (n=52)
Summary of dose modifications						
	Any drug dose reduction due to TEAE EOI, n (%)		Any drug dose interruption due to TEAE EOI, n (%)		Any drug discontinuation due to TEAE EOI, n (%)	
	PVd (n = 111)	Vd (n = 110)	PVd (n = 111)	Vd (n = 110)	PVd (n = 111)	Vd (n = 110)
≥ 1 TEAE EOI leading to dose modification of any drug	65 (58.6)	43 (39.1)	88 (79.3)	60 (54.5)	24 (21.6)	17 (15.5)
Neutropenia	13 (11.7)	1 (0.9)	22 (19.8)	2 (1.8)	0	0
Thrombocytopenia	12 (10.8)	6 (5.5)	11 (9.9)	13 (11.8)	1 (0.9)	1 (0.9)
Infections and infestations	8 (7.2)	4 (3.6)	60 (54.1)	40 (36.4)	4 (3.6)	1 (0.9)
Peripheral neuropathy	36 (32.4)	29 (26.4)	24 (21.6)	18 (16.4)	18 (16.2)	11 (10.0)
Somnolence, including dizziness and confusion	8 (7.2)	1 (0.9)	8 (7.2)	3 (2.7)	1 (0.9)	1 (0.9)

[a]Occurring in >10% of pts in either treatment arm. [b]Incidence rate per 100 person-years was calculated as 100 × n/T, where n equals the number pts with the selected AE and T equals the total person-years.

Summary/Conclusion: The safety profile for PVd at first relapse in pts with MM is consistent with that in previous reports. TEAEs EOI generally occurred in early cycles of treatment and could be managed with dose modifications or appropriate treatment for infections.

EP989 SURVIVAL AND OUTCOMES OF NEWLY-DIAGNOSED MULTIPLE MYELOMA PATIENTS STRATIFIED BY TRANSPLANT STATUS DIAGNOSED BETWEEN 2007-2018: REAL-WORLD ANALYSIS FROM THE CANADIAN MYELOMA RESEARCH GROUP DATABASE

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Background: Considerable progress has been made in therapeutic options for multiple myeloma (MM). However, data confirming translation of these successes into routine clinical settings, as well as outcomes from large data sets spanning multiple lines of therapy, are limited. Understanding such real-world data can provide key insights into knowledge and clinical gaps which could be targeted for future optimization. The Canadian Myeloma Research Group Database (CMRG-DB) is a prospectively maintained disease-specific database with >7500 patients from 15 academic sites across Canada with legacy data from 2007.

Aims: The aim was to provide high-level outcomes for all patients within the database, stratified by frontline autologous stem cell status (ASCT), in order to: 1) evaluate the rates of early mortality (<6 months and <1 year); 2) understand the trends in overall survival (OS) over time; and 3) evaluate OS by line of treatment.

Methods: All patients in the database diagnosed with MM from 2007-2018 who received therapy for active MM were included in this analysis. Rates of early mortality (<6 months and <1 year) were summarized for

the cohort stratified by the use of frontline ASCT. Patients were analyzed by period of treatment in 3-year increments beginning in 2007 and by line of therapy. OS was measured from the time of therapy initiation to death or last follow-up and was analyzed using the Kaplan-Meier method.
Results: We identified 5154 patients meeting the study entry criteria. Of these, 3030 patients (58.79%) received an upfront ASCT and 2124 (41.21%) did not. At diagnosis, the median age for the entire cohort was 64 years (range 26-98) and 58.6% were males. The presenting features of anemia, lytic bone disease, renal failure and hypercalcemia were noted in 57.6%, 46.5%, 18.7% and 12.4% of patients, respectively. A total of 28.3%, 36.3% and 35.4% had ISS stage I, II and III disease, respectively. High-risk cytogenetics by FISH [t(4;14), t (14;16) and 17p deletion] were present in 33% of patients.
The 6-month and 1-year mortality rates were 0.2% and 2.0% for ASCT patients and higher at 7.8% and 13.8% for non-ASCT patients. The median OS was 125.3 months and 54.3 months for those that did and did not receive frontline ASCT, respectively. OS increased over time among the ASCT cohort with a clear change after 2013 (Figure 1A). Improvements were also noted among the non-ASCT cohort after 2010 (Figure 1B). When the cohort was stratified by line of treatment, OS decreased from 1st - to 3rd - line, with a notable drop in OS noted in 4th line and beyond among both the ASCT and non-ASCT cohorts (Figure 1C and 1D). Further details regarding the spectrum of regimens at each line will be provided.
Summary/Conclusion: The CMRG-DB is one of the largest prospectively maintained real-world MM data sets. Advancements in outcomes are notable, coinciding with the widespread adoptions of novel agents in frontline therapy (~2010) and routine lenalidomide maintenance (~2013) in Canada. Most of the improvement has been in lines 1-3 after which survival remains relatively short. Although notable gains have been made for ASCT patients with low rates of early mortality and improvements in OS, outcomes for non-ASCT patients lag and are targets for future optimization. The database serves as a useful tool to measure the impact of novel treatment approaches as they are introduced in routine clinical use, especially in advanced disease which continues to represent an area of unmet need.

EP990 COMPARISON OF CILTACABTAGENE AUTOLEUCEL VERSUS CONVENTIONAL TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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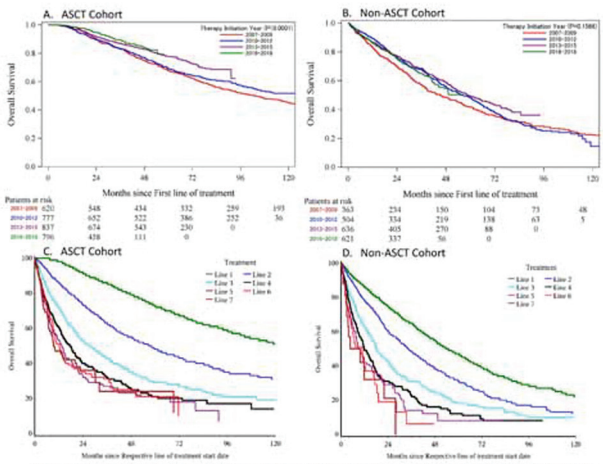


Figure 1: Overall survival by A) year of therapy initiation, ASCT cohort B) year of therapy initiation, non-ASCT Cohort C) line of treatment, ASCT cohort D) line of treatment, Non-ASCT cohort

Background: Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T (CAR-T) cell therapy with two B-cell maturation antigen-targeting single-domain antibodies designed to confer avidity. CARTITUDE-1 (NCT03548207) is a single arm, phase 1b/2 study conducted to evaluate cilta-cel therapy in US patients with relapsed/refractory multiple myeloma (RRMM). Patients in CARTITUDE-1 were refractory to both an immunomodulatory imide drug (IMiD) and proteasome inhibitor (PI) or had received ≥3 prior lines of therapy and previous exposure to anti-CD38 monoclonal antibody (MoAb). While recent reports of cilta-cel efficacy were encouraging, it is unknown how they compare with similar patients receiving conventional (non CAR-T) treatment.
Aims: To compare the efficacy of cilta-cel versus conventional treatment in patients with RRMM.
Methods: A contemporary US-based dataset of patients with MM who were refractory to anti-CD38 MoAb (MAMMOTH study) was utilized to identify patients who would meet eligibility for CARTITUDE-1 and who received conventional therapy. Analyses were performed on the intent-to-treat (ITT) population in CARTITUDE-1, defined as patients who underwent apheresis (N=113), and a modified ITT (mITT) population, defined as the subset of patients who received cilta-cel at the recommended phase 2 dose (N=97). From the MAMMOTH dataset, we identified a population corresponding to CARTITUDE-1 ITT (N=190) and a mITT population, patients without death or progression within 47 days (median time between apheresis and cilta-cel infusion) from onset of therapy (N=122). Propensity scores (PS) were calculated with demographics, number of prior therapies, cytogenetics, and refractoriness to MM agents as covariates. Nearest neighbor 1:1 PS matching was performed by an analyst who was blinded to outcomes. The overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were evaluated for ITT and mITT populations in CARTITUDE-1 vs. matching MAMMOTH cohorts.
Results: A total of 95 ITT (75 received bridging therapy, 82 received cilta-cel) and 69 mITT (54 received bridging) CARTITUDE-1 patients matched MAMMOTH patients (Table). Among the patients in the MAMMOTH ITT cohort, 34% had received pomalidomide, 24% anti-CD38 MoAb, 19% carfilzomib, and 35% cytotoxic chemotherapy in next therapy. ORR in the ITT cohorts was higher in CARTITUDE-1 than in MAMMOTH (84% vs. 28%). Compared with their MAMMOTH counterparts, patients in CARTITUDE-1 ITT cohort had improved PFS (12 months, 73% vs. 12%) and OS (12 months, 83% vs. 39%). Between the mITT cohorts, CARTITUDE-1 patients had superior ORR (96% vs. 30%), PFS (12 months, 79% vs. 15%), and OS (12 months, 88% vs. 41%).

	ITT (apheresis) CARTITUDE-1 (N=95)	ITT matches, MAMMOTH (N=95)		mITT (treated) CARTITUDE-1 (N=69)	mITT matches, MAMMOTH (N=69)	
Mean Age -years (sd)	62.4 (8.5)	62 (8.5)		62.6 (7.7)	62.7 (9.4)	
High cytogenetic risk	22%	24%		25%	23%	
Mean N lines of therapy (sd)	6.2 (3.0)	6.3 (2.4)		5.9 (2.9)	6 (1.9)	
Triple-class refractory	97%	96%		96%	96%	
Penta exposed	80%	76%		75%	75%	
Penta refractory	43%	42%		35%	42%	
ORR	84%	28%	P<0.001	96%	30%	P<0.001
PFS	HR=0.11, 95% C.I. 0.05-0.22		P<0.001	HR=0.02, 95% C.I. 0.01-0.14		P<0.001
OS	HR=0.20, 95% C.I. 0.10-0.39		P<0.001	HR=0.05, 95% C.I. 0.01-0.22		P<0.001

C.I., confidence interval; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat; N, number; ORR, overall response rate; OS, overall survival; PFS, progression free survival; sd, standard deviation.

Summary/Conclusion: In patients with RRMM beyond therapy with IMiD, PI, and anti-CD38 MoAb, treatment with cilta-cel is associated with higher response rate and superior PFS and OS when compared with conventional treatment.

EP992 A MULTINATIONAL CHART REVIEW OF REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background: Approvals of new agents have changed the treatment landscape for multiple myeloma (MM) in recent years, but real-world (RW) data on treatment patterns and clinical outcomes in patients with relapsed/refractory multiple myeloma (RRMM) outside of clinical trial settings remain limited.
Aims: To assess RW treatment patterns and clinical outcomes of patients with RRMM in Canada, France, Spain, and UK.
Methods: This retrospective, observational chart abstraction study recruited oncologists, hematologists and hemato-oncologists in Canada, France, Spain and the UK, who reviewed deidentified medical records from adult patients with a diagnosis of RRMM between Jan 1, 2012–Dec 31, 2016. RRMM was defined by disease progression during or after first-line (1L) therapy for MM (date of 1L MM progression was study index). Treatment regimens were described, and progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan–Meier estimation from start of each line of therapy (LoT), 1L–3L.
Results: A total of 412 patient records were included (Canada: n=101; France: n=101; Spain: n=104; UK: n=106). Mean (SD) age of patients at index was 65.4 (10.5) years, 59.2% of participants were male, median duration of follow-up from index was 37.7 months; and median number of LoT received was 3. At index, a higher proportion of patients in the UK (53.8%) had at least one gene translocation associated with high risk MM including del(17/17p), t(4;14), t(14;16), t(14;20), compared with other countries (34.6–39.6%). Median Charlson Comorbidity Index score at index was 1.0 in Canada, France and the UK, and 2.0 in Spain. Rates of MM-related symptoms were broadly comparable but with some country variation for some symptoms: proportion of patients with anaemia ranged from 24.8–51.9%, renal impairment from 5.9–24.0%, hypercalcemia 6.6–12.5%, and skeletal-related events 4.7–22.1%. Bortezomib-based regimens were most frequently used in 1L (**Table**), both in patients who did and who did not have stem cell transplant (SCT). Lenalidomide-based regimens were frequently used in 2L (particularly Rd, KRd, VRd, and NRd); carfilzomib (KRd, Kd) and daratumumab (DaraVd) were among the most frequently used regimens in 2L in France and Spain, but not Canada and the UK. In the 3L setting, pomalidomide (Pd, PCd), carfilzomib (Kd), and daratumumab (Dara monotherapy, DaraVd) were frequently used in most countries except the UK. Following 1st relapse, almost all patients received 2L therapy (>93% in all countries); while a lower proportion received 3L therapy following 2nd relapse (36.6%–64.2%). Median PFS ranged from 20.7 months (UK) to 33.9 months (Canada) in 2L, and from 12.0 months (France) to 22.5 months (UK) in 3L. Median OS was not reached for any LoT from 1L–3L. From start of 2L, 2-y OS rate ranged from 82% (Spain) to 92% (UK); from start of 3L, 2-y OS ranged from 65% (Spain) to 89% (UK).

Table: Most frequent treatment regimens and survival outcomes in 1L–3L.

	Canada (N=101)	France (N=101)	Spain (N=104)	UK (N=106)
1L no SCT	*n=60*	*n=58*	*n=65*	*n=59*
1	VCD (31.7)	VMP (43.1)	VMP (55.4)	CTD (28.8)
2	Rd (15)	MPT (22.4)	VD (10.8)	VD (11.9)
3	TD (11.7)	Rd (12.1)	VCD (9.2)	VCD (10.2)
4	VMP (8.3)	VD (5.2)	Rd (7.7)	VTD (10.2)
5	MP (6.7)	RVD (5.2)	Benda (4.6)	MP (8.5)
Median PFS, months (95% CI)	18.4 (11.3–22.9)	21.6 (17.7–24.8)	13.9 (10.9–19.5)	18.9 (13.1–22.5)
2-y OS	93%	98%	89%	85%
1L SCT	*n=41*	*n=43*	*n=39*	*n=47*
1	VCD (68.3)	VTD (55.8)	VTD (56.4)	VTD (48.9)
2	Rd+Benda (7.3)	VD (7.0)	VCD (12.8)	CTD (40.4)
3	VD (4.9)	VCD (7.0)	VD (10.3)	VCD (6.4)
4	MPR (4.9)	VRD (7.0)	VRD (5.1)	VD (4.3)
5	VD+Doxo (2.4)	MPT (4.7)	VD+Doxo (2.6)	–
Median PFS, months (95% CI)	23.8 (18.3–28)	32.6 (18.8–40.7)	21.3 (17.4–31.9)	24.8 (19.7–30.3)
2-y OS	98%	98%	90%	100%
2L	*n=88*	*n=92*	*n=101*	*n=103*
1	Rd (54.4)	Rd (47.8)	Rd (53.4)	Rd (21.7)
2	VD (8.7)	KRD (7.6)	KRD (11.7)	VD (18.9)
3	Pan (6.5)	KD (5.4)	VRD (5.8)	CTD (15.1)
4	VCD (3.3)	VCD (4.4)	VD (3.9)	VCD (13.2)
5	NRD (3.3)	NRD (4.4)	DaraVD (2.9)	NRD (4.7)
Median PFS, months (95% CI)	33.9 (25.7–40.6)	27.8 (23.2–36.2)	23.0 (18.2–31.6)	20.7 (18.0–24.7)
2-y OS	88%	87%	82%	92%
3L	*n=35*	*n=48*	*n=42*	*n=68*
1	PomCD (20.0)	PomD (40.4)	KD (19.5)	Rd (42.7)
2	DaraVD (14.3)	KD (8.5)	PomD (19.5)	NRD (35.3)
3	KD (14.3)	Dara (8.5)	PomCD (12.2)	KD (5.9)
4	Rd (8.6)	PomCD (8.5)	DaraVD (9.8)	RCD (5.9)
5	PomD (8.6)	NRD (6.4)	Dara+D (9.8)	PanVD (4.4)
Median PFS, months (95% CI)	20.8 (9.0–62.1)	12.0 (7.8–14.0)	15.0 (9.8–17.9)	22.5 (17.1–30.1)
2-y OS	69%	75%	65%	89%

Benda, bendamustine; C, cyclophosphamide; Dara, daratumumab; D/d, dexamethasone; Doxo, doxorubicin; K, carfilzomib; M, melphalan; N, ixazomib; Pan, panobinostat; P, prednisolone; Pom, pomalidomide; R, lenalidomide; T, thalidomide; V, bortezomib

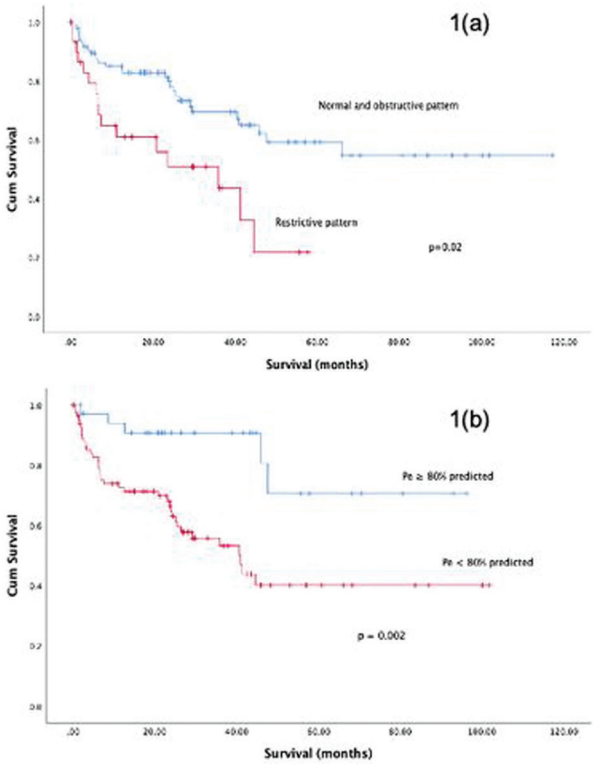
Summary/Conclusion: Newer therapies for RRMM began to be commonly used in 2L and became more frequent in 3L. Following first relapse, a substantial proportion of patients with RRMM received 2L but not 3L therapies. PFS in 2L and 3L was longer than in clinical trials but comparable with other RW studies, suggesting that patients with RRMM have longer than expected treatment-free interval instead of continuous treatment until disease progression. These findings also suggest there may be country variations in the implementation of approved new therapies in routine clinical practice.

EP993 PULMONARY FUNCTION TESTS REVEAL UNRECOGNIZED LUNG DYSFUNCTION AND HAVE INDEPENDENT PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH SYSTEMIC AL AMYLOIDOSIS

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Background: Dyspnea in patients with AL amyloidosis is a common symptom usually attributed to cardiac dysfunction. Lung involvement is not a common feature of the disease and requires histopathological verification and a symptomatic presentation or typical radiographic changes of diffuse interstitial lung disease. However, post-mortem data and some retrospective studies suggest that lung involvement is likely underrecognized. A systematic functional approach of lung function in these patients is lacking.
Aims: To perform a comprehensive evaluation of lung function in consecutive patients with newly diagnosed AL amyloidosis.
Methods: This non-interventional, prospective study included 139 consecutive patients with systemic AL amyloidosis treated in the Department of Clinical Therapeutics (Athens, Greece). Patients with localized lung amyloidosis were excluded. Pulmonary function tests (PFTs) were performed in a Master screen Body (Jaeger, Germany). Spirometry, lung volume measurements, carbon monoxide diffusion capacity (DLCO) corrected for hemoglobin, maximal expiratory (Pe) and inspiratory (Pi) pressures were measured in a sitting position. Patient's age, height and weight were recorded for use in the calculation of reference values.
Results: Median age was 65 years, 59% of patients were male; 65% had renal, 79% cardiac, 24% liver, 22% peripheral/autonomic and 2% lung involvement. Mayo stage distribution was as follows; 10% stage I, 52% stage II, 31% stage IIIa and 7% stage IIIb. Among patients, 68% had a normal breathing pattern, 9% obstructive and 23% restrictive. A restrictive pattern was associated with advanced Mayo stage (p=0.034); there was no association with free light chain (FLC) levels. One-year mortality for patients with a normal pattern was 14% versus 18% with obstructive and 38% for patients with a restrictive pattern. In univariate analysis, a restrictive breathing pattern was associated with worse survival (28.6 vs 76 months for patients with obstructive/normal pattern, p=0.002) and remained significant even after adjustment for Mayo stage (HR: 2.01, p=0.034). Certain indices of PFTs which reflect neuromuscular fitness and not breathing pattern (Pi and Pe), were severely affected in the majority of patients (93% for Pi and 61% for Pe had <80% of predicted values). Among PFT indices, FEV%, FVC1%, TLC, DLCO and Pe% were all associated with survival. Importantly, each of FEV1%<80%, FVC1%<80% and Pe% <80% of predicted remained significant for survival when adjusted individually for Mayo stage (FEV1%<80%, HR:2.1, p=0.016, FVC1%<80% HR:2.8, p<0.001, Pe% <80%, HR: 4.6, p=0.002). Low Pe% remained an independent prognostic factor for survival (HR 3.1, p=0.005) even when adjusted for the breathing pattern (restrictive versus normal/obstructive). Furthermore, among patients with stage IIIb disease, a low Pe% could further identify and ultra-high risk subgroup with even worse outcome (p=0.033).



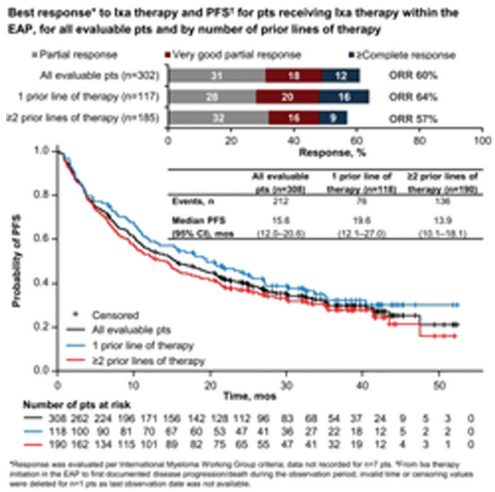
Summary/Conclusion: In this comprehensive evaluation of lung function by PFTs we found that a restrictive breathing pattern is common in patients with systemic AL amyloidosis. Importantly, indices of PFTs associated with neuromuscular function are severely affected in most patients and are associated with prognosis, independently of the degree of cardiac dysfunction. Our results point to the presence of unrecognized pulmonary dysfunction, despite the absence of typical imaging findings, with prognostic and potentially therapeutic implications.

EP994 EFFECTIVENESS AND SAFETY OF IXAZOMIB-BASED THERAPY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (MM) OUTSIDE OF A CLINICAL TRIAL: FINAL ANALYSIS OF THE 'USE VIA EARLY ACCESS TO IXAZOMIB' (UVEA IXA) STUDY

H. Ludwig [1,*], E. Terpos [2], M.-V. Mateos [3], M. Boccadoro [4], B. Kishore [5], K. Ramasamy [6], P. Krhovska [7], M. Streetly [8], V. Gergely [9], M. Ladicka [10], S. Fernandez [11], L. Simoni [11], N. Bent-Ennakhil [12], A. Zomas [12], F. Gavini [12], R. Hájek [13]

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Background: In MM treatment, it is important to improve our understanding of routine clinical practice and the effectiveness of new agents outside of clinical trials. Ixazomib (Ixa) is approved for MM patients (pts) who have received ≥1 prior therapy on the basis of TOURMALINE-MM1 study data.
Aims: Report data from the final analysis of UVEA-IXA, a European, multicenter, observational, longitudinal cohort study of pts receiving Ixa via an Early Access Program (EAP) in the Czech Republic, Greece, Hungary, Italy, Slovakia, Slovenia, Spain, and United Kingdom.
Methods: UVEA-IXA comprised a retrospective chart review from Ixa therapy initiation in the EAP and a prospective 1-year (yr) follow-up period from chart review initiation, with quarterly data capture. Eligible pts were in biochemical and/or symptomatic relapse after 1–3 prior lines of therapy, had not received anti-MM therapy for >3 cycles (except steroids) at the start of Ixa therapy, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Lenalidomide (R)- or proteasome inhibitor-refractory pts were ineligible. Primary endpoints were response and progression-free survival (PFS).
Results: 309/357 enrolled pts were evaluable; 54% were male; median age at enrollment was 68 yrs (range 36–92), 40% aged ≥70 yrs. At the start of Ixa therapy, 37/123 pts (30%; n=186 unknown [unk]) had International Staging System (ISS) stage III MM, 62/308 (20%; n=1 unk) had ECOG PS 2, and 13/279 (5%; n=30 unk) had an estimated glomerular filtration rate (eGFR) <30 mL/min. Of 309 pts, 61% had ≥1 comorbidity, including hypertension (26%), renal disease (23%), and diabetes (9%). Median time from diagnosis was 37.2 months (mos; range 4.9–232.8); 39%, 43%, and 18% of pts had received 1, 2, and 3 prior lines of therapy, respectively. Median observation period (n=306; n=3 not available) was 25.5 mos (range 0.8–54.1). Pts received Ixa for a median of 10.5 mos (range 0.2–52.3); most pts also received R (98%) and dexamethasone (97%). Overall response rate (ORR) on Ixa therapy was 60%; median PFS (mPFS) was 15.6 mos (Figure). Risk of progression/death was significantly greater in pts with ECOG 2 vs 0–1: 87% vs 64% had PFS events (p=0.0004). Overall, median time to next therapy after stopping Ixa was 21.4 mos. Median overall survival was 35.5 mos (95% confidence interval [CI] 28.0–44.4) overall, and 43.1 vs 31.4 mos (95% CI 31.2–not evaluable vs 21.5–47.5) in pts with 1 vs ≥2 prior lines of therapy. Ixa dose was reduced in 57/307 pts (19%; n=2 not recorded); 246/309 pts (80%) discontinued Ixa, most frequently due to: progression in 37% of pts, adverse events (AEs) in 19%, and loss/lack of response in 10%. Among 215 pts who received ≥4 cycles of Ixa, rates of any-grade (G) and G≥3 AEs were 62% and 37%; most common any-G AEs were thrombocytopenia (15%) and diarrhea (13%); the most common G≥3 AE was thrombocytopenia (6%).



Summary/Conclusion: UVEA-IXA data show that Ixa therapy is an effective, tolerable treatment option outside the clinical trial setting. Outcomes were favorable in pts with 1 vs ≥2 prior lines of therapy and ECOG PS 0–1 vs 2. Although UVEA-IXA data derive from retrospective chart review/infrequent prospective data capture and thus cannot be directly compared to clinical trial data, compared with TOURMALINE-MM1 pts (Ixa arm; ORR 78%, mPFS 20.6 mos), UVEA-IXA pts had higher rates of ECOG PS 2 (20 vs 5%), ISS stage III MM (30 vs 12%), and eGFR <30 mL/min (5 vs 1%), and had received more prior lines of therapy (61 vs 38% had ≥2). Most common AEs were gastrointestinal and hematologic, consistent with the safety profile in TOURMALINE-MM1.

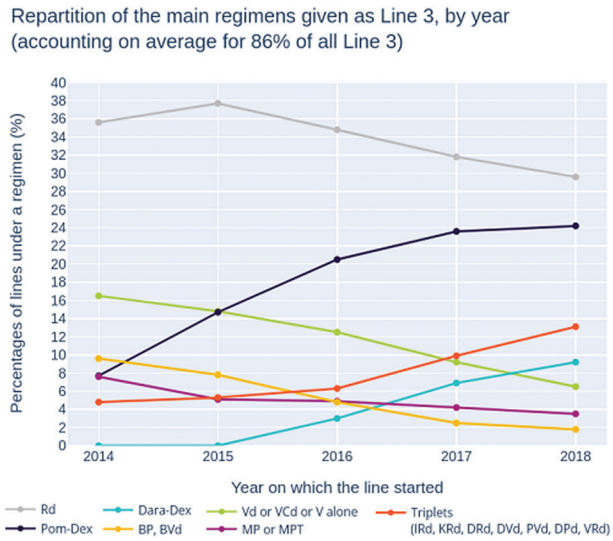
EP995 OVERVIEW AND EVOLUTION OF TREATMENT LINES IN MULTIPLE MYELOMA FROM 2014 TO 2018: A RETROSPECTIVE STUDY USING THE FRENCH NATIONAL CLAIM DATABASE (SNDS)

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France, Issy-les-moulineaux, [4]HEVA, Lyon, [5]Department of Biostatistics and Epidemiology, Gustave Roussy, University Paris-Saclay, Villejuif, France, Oncostat U1018, Inserm, Université Paris-Saclay, Équipe Labellisée Ligue Contre le Cancer, Villejuif, France, GRADES, Université Paris-Saclay, Chatenay-Malabry, [6]Centre Hospitalier Universitaire de Nantes, Nantes, France

Background: Multiple Myeloma (MM) disease course is a succession of remissions and relapses, which define lines of treatment. For each line, several regimens can be used. Although guidelines provide recommendations on the disease management, real world data are missing to describe which regimens are used in the daily practice. Regarding recent changes due to the introduction of new drugs (e.g., daratumumab, carfilzomib and ixazomib), an accurate and updated overview of MM treatment management is needed. This study provides a comprehensive overview of these recent changes based on the nationwide French National Health Insurance (NHI) databases, called SNDS ("Système National des Données de Santé"). These databases include hospital records, primary and secondary care of 66 million people.
Aims: To describe the evolution over time of MM treatment management by line and treatment sequencing in practice in France, in the context of a new therapeutic landscape.
Methods: This is a retrospective observational cohort study including all cases of multiple myeloma from 2014 to 2018 identified through the French NHI databases (SNDS). Cases were detected using a validated algorithm which was expanded to consider recent evolutions of MM therapeutic management. Treatment lines were re-constructed through ATLAS, a published adaptation of the Smith-Waterman alignment sequence algorithm, by scanning day-by-day patient claims. This innovative algorithm gave the temporal flexibility needed, and impossible with a solely rule-based identification, to identify lines considering the possible deviations between theoretical regimens and patient reality, and between reality and claim data. For each year (2014-2018) and for each line, the number and percentage of patients starting a regimen was assessed and protocols detailed.
Results: 36,208 prevalent patients treated for a MM between 2014 and 2018 were included. As expected, the main regimen for L1 without transplant changed from VMP (2014: 32%) to Rd (2018: 30%), the place of VRd regimen rapidly increased (2017: 4%, 2018: 10%), whereas MPT and MP regimens decreased (together, 2014: 19%, 2018: 4%). For L1 with transplant, VTd remains the main regimen (2014: 59%; 2018: 61%). Same for Rd on L2 and L3 (L2 - 2014: 47%, 2018: 54%; L3 - 2014: 36%; 2018: 30%), although we observed a shifting of some standards from doublet to triplet therapy (IRd, KRd, DRd, DVd, DPd, PVd, and VRd) with the newest drugs, as presented in the attached figure. Moreover, L4+ landscape is broadly evolving with a main regimen changed from Pom-Dex (2014: 21%) to Dara-Dex (2018: 21%). The rapidly acquired place of Pom-Dex in L3 (2018: 24%) can be related to the shift to the use of lenalidomide in earlier lines (L1, L2), hence inducing more lenalidomide-refractory patients. Regarding treatment sequences, the main course of patients having a L4+ in 2018 was as follows: L1: V-based regimen (VMP for non-transplant; VTd for transplant); L2: Rd; L3: Pom-Dex; L4+: Dara-Dex. All these results will be updated (Q2-2021) and presented with 2019 data.



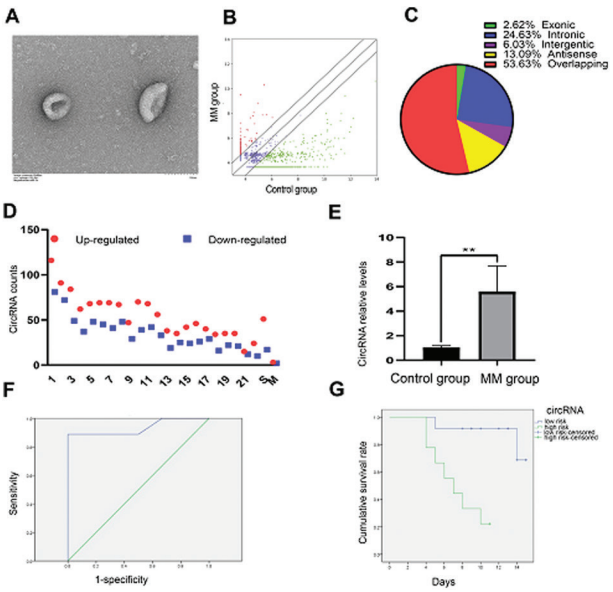
Summary/Conclusion: This study demonstrates the fast evolution of treatment management of MM patients, due to new drug marketing authorizations. The study also showed that real-world data are a powerful tool to study treatment lines at a national scale and lead the way to more precise analyses of optimal therapeutic sequences, including their impact on the overall survival.

EP996 EXOSOMAL CIRCRNA CACNG2 IS A NOVEL BIOMARKER FOR MM-RELATED CARDIAC DISEASES

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Background: Cardiac disease is one of the most common complications of multiple myeloma (MM), which seriously affects the survival and prognosis of patients. Several studies have revealed that circular RNAs (circRNAs) might play some roles in the initiation and progression of MM. Exosomes participate in the growth and drug resistance of many tumors via delivering bioactive molecules contained in them. However, the clinical significance of most serum exosome-derived circRNAs (exo-circRNAs) in MM-related cardiac complications is rarely studied.
Aims: To provide evidence for exo-circRNAs as novel potential diagnostic and therapeutic targets for MM-related cardiac diseases.
Methods: We collected serum samples from 21 MM patients which cardiac complications and 5 matched healthy control people as total samples. Then, we used the ExoQuick exosome precipitation kit to separate the exosomes, after which transmission electron microscopy (TEM) was applied to observe the precipitates. Subsequently, 6 serum samples from MM patients and 5 control samples were sent for high-throughput sequencing. According to p value and fold changes, the top 6 significantly up-regulated and 10 down-regulated exo-circRNAs were selected for quantitative real-time PCR (qRT-PCR) in total samples. Finally, we statistically analyzed the data with SPSS STATISTICS 26.0. ROC curves and Kaplan Meier survival curves were performed to evaluate the diagnostic and prognostic performance of the relative circRNA in MM-related cardiac diseases.
Results: 1.Characterization of serum exosomes
Under the TEM, oval extracellular vesicles less than 100 nm diameter were observed (Fig 1A), which demonstrated that the separated granules were true exosomes.
2. High throughput RNA sequencing
We identified 16106 differentially expressed exo-circRNAs via high-throughput sequencing. Taking FC ≥ 2.0 and $P \leq 0.05$ as the criteria, 2,052 exo-circRNAs were selected with significant differences compared with the control group. Then they were visualized by a Scatter plot (Fig 1B). Further analysis showed that most of the up-regulated ones were sense overlapping, while most of the down-regulated ones were exonic (Fig 1C), and they were widely distributed in 22 pairs of autosomes, sex chromosomes and mitochondria (Fig 1D).
3.qRT-PCR validation
The results showed that one of the up-regulated circRNAs chr22: 37076154-37076351 - was derived from the intron of CACNG2 locus, named it as "circ-CACNG2", with the data of 5.55 ± 2.15 in MM, which was more than five times that in the control group (Fig 1E, $P<0.01$). It proved that circ-CACNG2 was highly expressed in the exosomes of MM patients.
4.Correlation between circ-CACNG2 and clinicopathological characteristics
The receiver operating characteristic curve (ROC) analysis indicated that circ-CACNG2 had high sensitivity and specificity as a prognostic indicator. The area under the ROC curve (AUC) was 0.935 (P=0.001, Fig 1F), and the optimal critical value of circ-CACNG2 is 4.95 (sensitivity = 88.9% and specificity =100%, Fig 1F). Furthermore, Kaplan Meier survival curve analysis demonstrated that there was a significant difference in survival time between circ-CACNG2 high risk (≥ 4.95) and low risk (< 4.95) (P = 0.001, Fig 1G).



Summary/Conclusion: Exosome-derived circ-CACNG2 has the potential to be a novel independent diagnostic factor and prognostic indicator of MM-related cardiac diseases. And it may be an effective therapeutic target in the future.

EP997 AUTOLOGOUS TRANSPLANT IN MULTIPLE MYELOMA: IMPROVEMENT IN IMMEDIATE RESULTS USING NON-CRYOPRESERVED STEM CELLS

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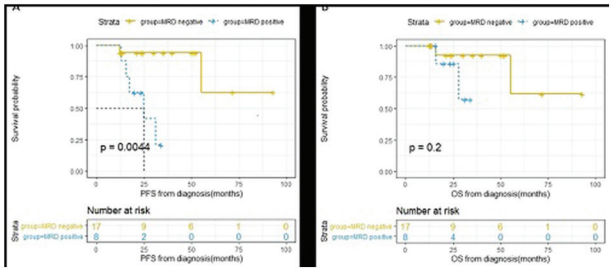
Background: Patients with diagnosis of multiple myeloma (MM) who are candidates to receive an autologous hematopoietic stem cell transplant (Auto-HSCT) are stimulated to harvest stem cells from the peripheral blood. These cells can be either cryopreserved with Dimethyl sulfoxide (DMS) for later use or stored in liquid state at 4ºC for up to 5 days to be reinfused after a 48-hours- conditioning regimen with a total dose of 200mg/m2 of Melphalan. Potential advantages of non-cryopreserved stem cells are a decrease in apoptotic progenitors, the avoidance of DMS toxicity, and a reduction in the use of economic resources.
Aims: To compare acute complication, transfusional requirement, and time to hematologic recovery between patients with MM that receive cryopreserved (CRYO) and non-cryopreserved (non-CRYO) autologous stem cells.
Methods: Observational, retrospective trial that included pacientes with MM who received Auto-HSCT between January 2018 to January 2021 at a high complexity center.
Results: 62 pacientes received transplant on the study period. 4 were excluded due to missing important data. 21 patients received non-CRYO cells whereas 37 received CRYO products. Median age was 55±9.53 years; 59% were males. Median number of chemotherapy cycles was 6 cycles; 47% were on complete remission, 21% very good partial remission, and 33% on partial remission. Before harvesting, 52% versus 75% patients require addition of plerixafor in the non-CRYO and CRYO groups, respectively (p=0.72). The mean amount of CD34+/kg infused cells was 7.7±1.6 x106 for the non-CRYO patients versus 6.6±2.4 x106 for the CRYO group (p=0.44).
Incidence of febrile neutropenia was 61% non-CRYO vs 91% CRYO (p=0.01). There were no cases of severe sepsis nor dialysis requirements. Incidence of grade IV mucositis was 19% non-CRYO vs 45% CRYO (p=0.08). Requirement of parental nutricion was 42% non-CRYO vs 78% CRYO (p=0.01).
Platelet transfusion requirement was 10.05±10.70 units for non-CRYO and 11.68±8.27 units for the CRYO group (p=0.18). The median amount of red blood cells units was 0.67±2.22 units in the non-CRYO group versus 0.62±1.52units in the CRYO group (p=0.55).
Time in days to neutrophil recovery (>500/mm3 for 2 consecutive days) was 10.52±1.29 non-CRYO vs 12.89±2.23 CRYO (p>0.001). In the case of platelet recovery (>30.000/mm3 without transfusion in the last 3 days), it took 13.14±7.25 days non-CRYO versus 15.51±4.19 days CRYO (p<0.001). Median hospital stay was 13 ±2.55 non CRYO versus 16±4.11 CRYO (p<0.001). There were no transplant-related deaths in either group.
Summary/Conclusion: Auto-HSCT in MM using non-cryopreserved cells is a safe and effective technique associated with a decrease in febrile neutropenia incidence, lower parenteral nutrition requirement, faster hematologic recovery and shorter hospital stay, making it more cost-effective. Besides, it showed a tendency to a lower incidence of severe mucositis. There was no significant impact on transfusion requirement and on mortality associated with the transplant. Further studies are needed to evaluate long-term outcomes.

EP998 CLINICAL VALUE OF MINIMAL RESIDUAL DISEASE ASSESSED BY MULTIPARAMETER FLOW CYTOMETRY IN AMYLOID LIGHT CHAIN AMYLOIDOSIS

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Background: Amyloid light chain (AL) amyloidosis, as a clonal plasma cell disorder, is characterized by organ dysfunction secondary to deposition of misfolded monoclonal light chains and most commonly involves the heart, kidney, and liver. AL amyloidosis is typically associated with a lower indolent clonal plasma cell burden within the bone marrow than multiple myeloma (MM). However, even low levels of unstable light chains secreted by these plasma cells can deposit in organs, resulting in organ dysfunction. Thus, the treatment of the disease aims to target the plasma cell clone and completely eliminate toxic light chain production. With the development of novel therapies, deep responses, as assessed by serum- or urine-based methods such as immunofixation electrophoresis and free light chain (FLC) quantification, can be achieved in a significant proportion of patients with AL amyloidosis. However, there are several limitations inherent to FLC assays and immunofixation electrophoresis. Hematologic relapses still occur, and organ function may continue to deteriorate due to small residual clones. The small amounts of light chains produced by these plasma clones may not be detectable by conventional techniques. In MM, multiparameter flow cytometry (MFC) is being used to detect the presence of minimal residual disease (MRD), and the absence of detectable MRD has been associated with improved survival outcomes across different therapeutic regimens and lines of therapy. Such data are sparse in patients with AL amyloidosis. Some studies have shown that the absence of MRD detected by MFC is associated with superior outcomes in patients with AL amyloidosis, but these studies have limitations given the heterogeneity of patients tested and the lack of predefined time points for MRD assessment.
Aims: To assess the feasibility and prognostic value of minimal residual disease (MRD) evaluated by multiparameter flow cytometry (MFC) in newly diagnosed amyloid light chain (AL) amyloidosis patients.
Methods: Clinical data from 25 consecutive newly diagnosed AL amyloidosis patients with MRD data tested 3 months after first-line therapy completion were retrospectively analyzed in a single center from 2012 to 2019. First-line therapy included 8 courses of VD or 4 courses of VD and sequential autologous stem cell transplantation (ASCT), both without maintenance therapy.
Results: Of 25 patients with very good partial response (VGPR) or better, 19 (76%) achieved MRD negativity. There were no differences in baseline characteristics between MRD-negative and MRD-positive patients. More ASCT patients than non-ASCT patients (90.0% vs 53.3%, P=0.043) achieved MRD negativity. In the MRD-negative and MRD-positive groups, renal response was observed in 82% vs 50% (P=0.116), cardiac response in 93% vs 25% (P=0.019), liver response in 100% vs 50% (p=0.286), and any organ response in 94% vs 50% (P=0.023) of patients. At a median follow-up of 25.1 months, MRD-negative patients showed significantly longer progression-free survival (PFS) from diagnosis than MRD-positive patients (24.52 vs 76.39 months, P= 0.004) (Figure 1).



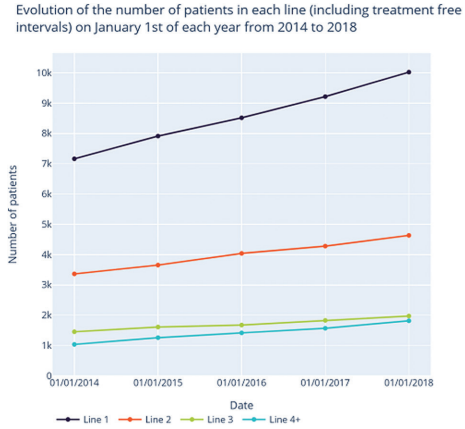
Summary/Conclusion: MRD negativity measured by MFC at 3 months after first-line therapy completion in patients with AL amyloidosis is measurable and associated with improved organ response rates and PFS over a long follow-up.

EP999 EPIDEMIOLOGY OF MULTIPLE MYELOMA: DATA FROM THE FRENCH NATIONAL HEALTH INSURANCE DATABASE (SNDS)

C. Touzeau [1,*], M. Pierres [2], M. Javelot [2], C. Guilmet [2], L. Lamarsalle [3], F. Raguideau [3], I. Borget [4], V. Augusto [5], A. Perrot [6]

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Background: Multiple myeloma (MM) is considered as an incurable hematologic disease. Net cancer-specific survival at 5 years after diagnosis of MM was estimated at 47% between 2005 and 2010. Thanks to significant improvements of the MM therapeutic management in the past decades, the overall survival of MM patients tends to increase, and some patients now achieve long-term remission. This directly impacts the dynamic of MM epidemiology. The world age-standardized MM incidence rate in France was estimated at 4.1/100 000/year in 2020, based on extrapolations from available regional data. For the first time, this study provides updated and comprehensive epidemiological data by line of treatments based on the nationwide French National Health Insurance (NHI) databases, called SNDS ("Système National des Données de Santé"). These databases include hospital records, primary and secondary care for 66 million people.
Aims: To estimate incidence, prevalence of multiple myeloma and mortality of these patients, each year and for each line from 2014 to 2018, based on secondary use of data from the French NHI databases.
Methods: This is a retrospective observational cohort study of multiple myeloma patients identified through the French NHI databases, SNDS from 2014 to 2018. To identify patients with MM, a published algorithm was used as a base and was expanded to consider recent evolutions of MM therapeutic management. The rates were standardized using the age distribution in the world population. Treatment lines were re-constructed through ATLAS, a published adaptation of the Smith-Waterman alignment sequence algorithm, by scanning day-by-day patient claims.
Results: 56,247 prevalent MM patients were identified from 2014 to 2018. Among them, 36,208 patients (64.4%) were treated for MM. The world age-standardized prevalence rates tend to regularly increase every year (from 19.6/100,000/year in 2014 to 23.6 in 2017, 2018 to be consolidated). In 2017, the 23,496 prevalent patients presented a median age of 70 years old. In average, they started their first treatment for MM 3.2 years (+/- 2.9) ago. The standardized incidence rate tends to increase over the years from 2014 to 2017. In 2017 the incidence rate was 4.7 (4.5-4.8)/100 000 person-years and was slightly higher among men (5.4 (5.2-5.6)) than women (4.0 (3.8-4.2)), and much higher in patients ≥ 65 years old (31.7 (30.6-32.9)). Standardized mortality rate was estimated at 3.2 (2.5-3.9) in 2017, respectively 3.6 (2.5-4.6) in men and 2.8 (1.9-3.6) in women, with a tendency to decrease slowly over the years. Moreover, as displayed on the figure attached, the number of treated patients for each line tends to increase overtime going for instance from 7,163 in 2014 to 10,022 in 2018 for patients in L1. The number of patients receiving a L4+ increased between 2014 (N=1040) and 2018 (N=1818).



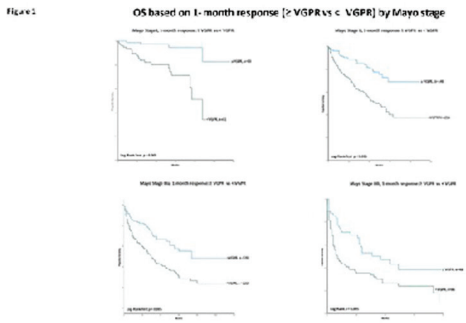
Summary/Conclusion: This study expands existing epidemiological data on MM patients in France and is the first to present recent nationwide results by line of treatment. Incidence rates are in accordance with the estimations from French network of cancer registries confirming that the French health insurance databases are a valuable source of data to further study the therapeutic management of multiple myeloma.

EP1000 IMPACT OF EARLY RESPONSE ON OUTCOMES IN AL AMYLOIDOSIS FOLLOWING TREATMENT WITH FRONTLINE BORTEZOMIB

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Background: The outcomes in systemic AL amyloidosis are dependent on the depth of haematologic response. However, there is limited data on the impact of the speed response on outcomes.
Aims: Here we report the impact of speed of response in a cohort of AL patients treated with upfront Bortezomib.
Methods: Patients seen from February 2010 until August 2019 are included in the present analysis.
Results: 1194 & 1133 patients comprised the ITT and 1-month landmark cohorts. In the landmark cohort, 137 (11.5%), 270 (22.6%), 252 (21.1%), and 352 (31.1%) patients had a CR, VGPR, PR and NR at 1-month. Patients with ≥ VGPR at 1-month had significantly better survival (median not reached; at the end of 1, 2, 5,10 years, 87%/92%, 83%/87%, 68%/72% & 63%/58% of patients in CR/VGPR respectively were alive) compared to those with a PR (median OS 60 months) or NR (median OS 32 months) (p<0.005). At 1-month, patients with CR and iFLC < 20 mg/l had a significantly better survival compared to CR and iFLC > 20 mg/l (p=0.005). Reaching ≥ VGPR at 1-month significantly improved survival in all Mayo disease stages.



Summary/Conclusion: In conclusion, patients achieving an early deep haematologic response have a significantly superior survival irrespective of cardiac involvement.

EP1001 RELATIONSHIP BETWEEN CORNEAL EXAM FINDINGS, BEST-CORRECTED VISUAL ACUITY (BCVA), AND OCULAR SYMPTOMS IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM) RECEIVING BELANTAMAB MAFODOTIN

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Background: Belantamab mafodotin (GSK2857916; belamaf) is a B-cell maturation antigen (BCMA)-targeting antibody–drug conjugate approved in the US and EU as a monotherapy for the treatment of adult patients with RRMM. Ocular events (OEs) during the pivotal DREAMM-2 trial (NCT03525678) included corneal exam findings (punctate keratopathy and microcyst-like epithelial changes), BCVA changes, and ocular symptoms. Dose reductions or delays based on corneal exam findings and BCVA were used to manage OEs. Here we performed a *post hoc* investigation of relationships between corneal exam findings, BCVA changes, and patient-reported ocular symptoms to explore if BCVA changes and symptoms could guide dosing, rather than corneal exams.

Aims:.

Methods: Eye evaluations (including a corneal exam and BCVA assessment of Snellen visual acuity) were performed on all patients receiving single-agent belamaf (2.5 mg/kg) by ophthalmologists at baseline and prior to each belamaf dose. Changes in the corneal epithelium (Ker) and BCVA were both assessed as per protocol-defined criteria and assessment of grade (Gr) was based on the worse eye. BCVA grading was relative to baseline. Patient-reported ocular symptoms were reported as per the Common Terminology Criteria for Adverse Events.

Results: In 12.5% of eye evaluations Gr 3–4 Ker was associated with minimal or no (Gr ≤1) BCVA changes. When patient-reported ocular symptoms were also considered, only 7.5% of evaluations found Gr 3–4 Ker with Gr ≤1 BCVA changes or ocular symptoms. Mild or no (Gr ≤2) Ker was associated with Gr ≤1 BCVA changes in 59.5% of evaluations, or in 38.8% of evaluations with no ocular symptoms reported. Overall, Gr 3–4 Ker were found in 24.9% of evaluations; by contrast, patients had Gr 2–4 BCVA changes or ocular symptoms in 53.7% of evaluations.

Table. Association of corneal epithelium changes (Ker) with BCVA changes and ocular symptoms

Ker + BCVA changes only (evaluations, n=773); n (%)	
Gr 3–4 Ker & Gr ≤1 BCVA	97 (12.5)
Gr 3–4 Ker & Gr 2–4 BCVA	96 (12.4)
Gr ≤2 Ker & Gr ≤1 BCVA	460 (59.5)
Gr ≤2 Ker & Gr 2–4 BCVA	120 (15.5)
Ker + BCVA changes or ocular symptoms (evaluations, n=773); n (%)	
Gr 3–4 Ker & (Gr ≤1 BCVA, no symptoms)	58 (7.5)
Gr 3–4 Ker & (Gr 2–4 BCVA, or symptoms)	135 (17.4)
Gr ≤2 Ker & (Gr ≤1 BCVA, no symptoms)	300 (38.8)
Gr ≤2 Ker & (Gr 2–4 BCVA, or symptoms)	280 (36.2)

Summary/Conclusion: These findings highlight that BCVA changes and ocular symptoms should be further investigated to determine if they can be used as alternatives (eg, frequency of eye examinations based on symptoms) for the management of belamaf dosing to potentially reduce the burden on patients and healthcare professionals.

Funding Source: GSK (205678; NCT03525678). Drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa.

Encore statement: ©2021 American Society of Clinical Oncology, Inc. Reused with permission. All rights reserved. This abstract was previously submitted to the American Society of Clinical Oncology (ASCO) Annual Meeting, June 4–8, 2021, and is submitted on behalf of the original authors with their permission.

EP1002 SELINEXOR CONTAINING REGIMENS IN PATIENTS WITH MULTIPLE MYELOMA PREVIOUSLY TREATED WITH ANTI-CD38 MONOCLONAL ANTIBODIES

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins. XPO1 is required for multiple myeloma (MM) cell growth, is associated with poor prognosis and mediates resistance to standard MM therapies. Selinexor (SEL) is a first-in-class, oral selective inhibitor of nuclear export (SINE) compound approved in combination with dexamethasone (dex) ± bortezomib for patients (pts) with previously treated MM. Once MM becomes refractory to anti-CD38 monoclonal antibodies (αCD38 mAb), pts have limited effective treatment options and poor prognoses. With standard therapies, overall response rate (ORR) to the first regimen after refractoriness to an αCD38 mAb is 31%, median progression-free survival (PFS) is 3.4 months and median overall survival (OS) is 8.6 months (Gandhi et al, *Leukemia*, 2019). The doublet SEL-dex (Xd) has shown ORR ~26% in triple-class (IMID, PI, αCD38 mAb) refractory MM and improved OS over matched cohorts in community (Richardson et al, *eJHaem*, 2021) and academic (Cornell et al, *AJH*, 2020) settings. SEL-based triplets could be more effective in this triple class treated population.

Aims: To retrospectively analyze the efficacy and safety of SEL-containing triplets in pts in the STOMP study previously treated with αCD38 mAbs.

Methods: STOMP is a multi-arm, open-label, Phase 1b/2 study evaluating SEL in various triplet combinations (ClinicalTrials.gov: NCT02343042). Pts who entered the study received Xd plus pomalidomide (XPd, n=19), bortezomib (XVd, n=4), lenalidomide (XRd, n=4), daratumumab (XDd, n=2) or carfilzomib (XKd, n=18). ORR, OS, PFS and adverse events (AEs) were analyzed.

Results: Among the 47 pts, median age 64 yrs, female 53%, median time from diagnosis 5.1 yrs, median number of prior regimens 5 (range, 2–11). Prior daratumumab (96%), isatuximab (4%); 96% had MM documented to be refractory to αCD38 mAb, 81% had triple-class refractory MM, 74% and 47% were quad- and penta-treated, 43% (20/47) and 15% (7/47) had quad- and penta-refractory MM. αCD38 mAb was included in the immediate prior regimen of 57% of pts and median duration from end of most recent αCD38 mAb therapy to first dose of study treatment was 6.9 weeks (range, 2.6-114.9). ORR was 51% among the 45 evaluable pts; 59% in the XPd arm (n=17; 2 pts were not efficacy evaluable) and 67% in the XKd arm. ORR was 47% (9/19) among efficacy evaluable pts with quad-refractory MM. Among all evaluable pts, median PFS was 8.8 months (95% CI: 4.9, NE) and median OS was 20.4 months (95% CI: 9.6, NE). Among the 25 pts with αCD38 mAb in their immediate prior regimen, efficacy of SEL-containing triplets was similar to that of the prior regimen: ORR 52% vs. 45%, median PFS 8.8 vs. 9.3 months. The most common treatment emergent AEs were nausea (72%), anemia (64%), thrombocytopenia (60%), fatigue (57%), which were managed with standard

supportive care and dose modifications; cytopenias were infrequently symptomatic.
Summary/Conclusion: SEL-containing triplets in pts with MM previously treated with αCD38 mAbs, most of whom had triple-class refractory MM, exhibit tolerability and comparable effectiveness to their most recent αCD38 mAb-containing regimens. Compared to historical controls who received regimens with agents with which they were previously treated, OS on the SEL-containing triplets was much higher. These results suggest that the use of SEL-containing triplets can provide prolonged disease control with good tolerability rather than recycling previously utilized drugs/mechanisms. Further investigation is warranted.

EP1003 INCIDENCE, MITIGATION, AND MANAGEMENT OF NEUROLOGIC ADVERSE EVENTS IN THE PHASE 2 CARTITUDE-2 STUDY OF CILTACABTAGENE AUTOLEUCEL IN PATIENTS WITH MULTIPLE MYELOMA

H. Einsele [1,*], S. Parekh [2], D. Madduri [2], B. Santomasso [3], J. Gállego Pérez-Larraya [4], N. van de Donk [5], B. Arnulf [6], M.-V. Mateos [7], K. De Braganca [8], H. Varsos [8], M. Carrasco-Alfonso [9], M. Akram [9], N. Lendvai [8], C. Jackson [8], Y. Olyslager [10], E. Zudaire [11], C. Li [11], D. Geng [9], A. Jakubowiak [12], A. Cohen [13]

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Background: Ciltacabtagene autoleucel (Cilta-cel or JNJ-68284528) is a chimeric antigen receptor T (CAR-T) cell therapy with two B-cell maturation antigen (BCMA)-targeting, single-domain antibodies designed to confer high avidity binding. In the phase 2, multicohort, open-label CARTITUDE-2 (NCT04133636) study, the efficacy and safety of cilta-cel in patients with multiple myeloma (MM) were assessed in various clinical settings.
Aims: To describe the mitigation and management strategies implemented in order to identify and reduce the risk for neurologic adverse events (AEs) in Cohort A patients (progressive MM after 1–3 prior lines of therapy).
Methods: Eligible patients (≥18 years of age) had MM per International Myeloma Working Group criteria, measurable disease, Eastern Cooperative Oncology Group performance status ≤1, progressive MM after 1–3 prior lines of therapy (including a proteasome inhibitor and immunomodulatory drug), and were lenalidomide refractory (no prior BCMA-targeting agent). All patients provided informed consent prior to enrollment in the study. Patients received cilta-cel (0.75×10^6 [range: $0.5–1.0\times10^6$] CAR+ viable T cells/kg) as a single infusion 5–7 days after start of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily for 3 days). Monitoring and mitigation strategies for neurologic AEs included providing more effective bridging therapy to reduce tumor burden prior to lymphodepletion, frequent assessment of CAR-T-related immune effector cell-associated neurotoxicity syndrome (ICANS) using the immune effector cell-associated encephalopathy tool, regular handwriting assessments to detect micrographia, and neuroimaging (brain MRI) and EEG for patients with prior neurologic disease. Management strategies included evaluation of infectious and paraneoplastic etiologies upon observation of ICANS ≥ grade 1, administration of tocilizumab (if concurrent cytokine release syndrome [CRS], all grade of ICANS) and/or dexamethasone (grade 2/3) or methylprednisolone (grade 4). ICANS and CRS were graded by American Society for Transplantation and Cellular Therapy criteria; neurotoxicities not classified as ICANS were graded per Common Terminology Criteria for Adverse Events version 5.0.
Results: As of 15 Jan 2021 (median follow-up: 5.8 months [range: 2.5–9.8 months]), 20 patients in Cohort A received cilta-cel. The median age was 60 years (range: 38–75) and 65% of patients were male. Neurotoxicities occurred in 4 patients (20%). Three patients had ICANS (grade 1/2); the median time to onset of symptoms was 8 days (range: 7–11), and the median duration was 2 days (range: 1–2). Two of the 3 patients received supportive measures to treat ICANS, including levetiracetam and steroids; all 3 had concurrent CRS and all recovered. One patient developed isolated grade 2 facial paralysis on Day 29 after ciltacel infusion and recovered 51 days after the onset of event following treatment with dexamethasone for 28 days. No movement or neurocognitive disorders were reported.
Summary/Conclusion: Neurologic AEs were generally manageable in patients with MM following treatment with cilta-cel. With a median follow-up of 5.8 months, there were no movement or neurocognitive disorders in patients with progressive MM who had received 1–3 prior lines of therapy (Cohort A). These results suggest that early detection and management of neurologic AEs can lead to better treatment outcomes.

EP1004 VACCINATION AGAINST SEASONAL INFLUENZA AND PNEUMONIA IMPROVES CLINICAL OUTCOME IN MULTIPLE MYELOMA PATIENTS RECEIVING CONTINUOUS TREATMENT WITH LENALIDOMIDE: A REAL-LIFE SURVEY

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Background: Respiratory infections are common complications of multiple myeloma(MM),leading to increased risk of death within first 90 days from diagnosis.Despite proven efficacy of vaccination and guidelines,this supportive care is underutilized in MM patients.
Aims:
We report the results of a single-center, retrospective evaluation of rate of
hospitalization and infection in patients undergoing vaccination after start of anti-MM treatment,
based on lenalidomide or proteasome inhibitors, alone or in combination with monoclonal
antibodies.
We report results of a single-center, retrospective evaluation of rate of hospitalization and infection in patients undergoing vaccination after start of anti-MM treatment based on lenalidomide or proteasome inhibitors,alone or in combination with monoclonal antibodies.
Methods: We have retrospectively evaluated 290 consecutive MM patients from September 2019,distinguished in three cohorts: active disease requiring anti-MM treatment(group A, N=120),not active disease controlled by maintenance/continuous therapy(group B, N=107), and off-therapy due to stable disease remission(group C, N=63),who received vaccination against seasonal flu(FV)and/or pneumococcus(PV). We monitored the number of infections requiring hospitalization, including COVID-19,OS at 12 months,and MM and not-MM related factors associated to early death.
Results: Of 290 patients, 71% received FV and 45% PV, 44% both. FV was performed in A, B and C groups, respectively in 71%, 72% and 71% patients. Among group A, B and C 45%, 48% and 40% patients respectively received PV.The rates of infections at 12 months in A, B and C groups were respectively 40%, 20% and 6%. The rates of hospitalization for infections at 12 months among group A, B and C were respectively 18%, 4% and 27%.In A group, factors associated to development of infection were age>65 years(OR, 3.95, p=0.005),male gender(OR, 4.46, p=0.0004),high-risk FISH(OR, 5.68, p=0.0039),ALC<1100 cells/mmc(OR, 3.82, p=0.0085),ANC<1500 cells/mmc(OR, 26.42, p=0.03),and IgM<40(OR 2.78, p=0.006).Factors associated to hospitalization for infection were age>65 years(OR, 9.50, p=0.03), male gender (OR, 8.71, p=0.005), ALC<1100 cells/mmc (OR, 10.91, p=0.03),and IgM<40 (OR 5.71, p=0.007).Continuous treatment with lenalidomide based regimens was associated to increased infection(OR, 3.70, p=0.004)and hospitalization rates(OR, 21.11, p=0.0036).FV was associated to reduced number of infections at one year in patients

carrying high-risk cytogenetics or undergoing continuous treatment with daratumumab.PV reduced number of infections in patients carrying high-risk cytogenetics, ALC<1100/mmc, ANC<1500/mmc or who received ASCT before study entry. 29 patients(10%)died(6 for infection,23 for disease progression).Predictors at study entry of shorter 12-mOS were age≥65 yo(p=0.009), frailty score≥1(p=0.03),ANC<1500/mmc(p=0.0002),IgM<40mg/dL(p=0.01),active disease(p<0.0001),previous ASCT(p=0.002),occurrence of hospitalization(p<0.0001)or/and infections(p=0.001).Continuous therapy,including lenalidomide maintenance or daratumumab exposure did not affect 12-mOS in our cohort. In multivariable analysis active disease(HR 71.5, 95% CI 1.97 - 25.93, p=0.0028) and hospitalization for infection(HR 38.1,95% CI 1.27–11.37,p=0.0167)significantly impact on OS.

Summary/Conclusion: Vaccination coverage does not protect from infections patients with active MM, particularly when treated with lenalidomide.

EP1005 REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES IN MULTIPLE MYELOMA PATIENTS REFRACTORY TO LENALIDOMIDE

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Background: In recent years, lenalidomide (LEN) has become an increasingly common therapy of multiple myeloma (MM). However, once patients become refractory to LEN, they are generally considered harder to treat, with fewer treatment options available. Real world (RW) evidence on clinical management of LEN-refractory patients is lacking.

Aims: To describe clinical characteristics, treatment patterns, and clinical outcomes across lines of therapy (LoT) in patients who were refractory to LEN therapy for MM.

Methods: Using the Système National des Données de Santé in France, we identified a cohort of adult patients with an initial diagnosis of MM (index date) between Jan 1, 2010–Dec 31, 2018 who received at least one LoT for MM. Within this cohort, patients who were refractory to LEN (defined as having received only 1 LEN-based LoT, with no LEN in any subsequent LoT, and having initiated a new, non-LEN-based treatment regimen within 60 days of the LEN-containing LoT) were assessed. Baseline patient characteristics were captured in the 12 months before index, and symptoms and comorbidities within the 6 months prior to each LoT. The most frequently used regimens following the LEN-refractory LoT were described. Median overall survival (OS), duration of treatment (DoT) and time to next treatment (TTNT) from the start of each LEN-refractory LoT was assessed by Kaplan–Meier method, and 1–5-year landmark survival rates were calculated.

Results: In total, 25,323 patients received ≥1 LoT for MM, of whom 1907 patients were identified as having experienced a LEN-refractory LOT. During the study follow-up period (2010–2018), LEN-based regimens were among the most frequently used regimens in the overall cohort of MM patients, accounting for 14.9% of the 5 most common 1L regimens and 45.7% of the 5 most common 2L regimens. In recent years (2016–2018), LEN-based regimens accounted for 24.7% and 30.6% of the 5 most frequent regimens in 1L and 2L, respectively. Among patients who were refractory to LEN, mean (SD) age was 67.3 (10.7) years at index, and 70.5 (10.5) years when patients became LEN-refractory; 50.9% of LEN-refractory patients were male. Most patients (90.2%) had their LEN-refractory encounter in 2L–4L. The proportion of patients with CRAB symptoms and the median Charlson Comorbidity Index remained consistent across LoTs. After a LEN-refractory LoT, the most frequently used subsequent regimens were generally POM-based (**Table**). In LEN refractory patients, DoT continued to decrease across LoT (1L: 9.7 months; 2L: 8.4 months; 3L: 6.7 months; 4L: 6.7 months; 5L 7.2 months); similarly, TTNT decreased with advancing LoT (1L–2L: 18.0 months; 2L–3L: 12.0 months; 3L–4L: 9.0 months; 4L–5L: 9.0 months). Survival outcomes in patients following a refractory LEN regimen were poor, with a median OS ranging from 10.4–12.2 months across LoT. Less than a third of patients survived for at least 2 years following a LEN-refractory LoT.

Table. Survival outcomes and subsequent treatment regimens in patients who were LEN-refractory

	2L (n=498)	3L (n=652)	4L (n=388)	5L (n=118)
Most frequent regimens after LEN-refractory LoT, %				
1	POM (17.1)	POM (18.4)	POM (23.2)	POM (24.6)
2	BEN (10.2)	BOR (13.2)	CYCLO+POM (11.3)	DARA (7.6)
3	DARA (8.4)	CYCLO+POM (10.3)	DARA (9.3)	CYCLO+POM (7.6)
Median OS, months (95% CI)	13.4 (11.9–16.1)	13.6 (12.1–15.0)	12.4 (10.3–13.5)	12.4 (9.1–18.7)
1–y OS, % (95% CI)	54.6 (49.7–59.2)	54 (49.8–58)	50.9 (45.4–56)	53.2 (43.1–62.4)
2–y OS, % (95% CI)	33.7 (28.6–38.7)	33.8 (29.5–38.2)	26.5 (21.1–32.1)	30.3 (20.1–41.1)
3–y OS, % (95% CI)	25.9 (20.8–31.2)	20.6 (16.3–25.2)	14.5 (9.6–20.5)	17.4 (7.6–30.5)
4–y OS, % (95% CI)	21 (15.7–26.7)	15.6 (11.1–20.9)	9.7 (4.9–16.6)	11.6 (3–26.6)
5–y OS, % (95% CI)	15.2 (9.5–22.1)	9.3 (4.6–16)	9.7 (4.9–16.6)	Could not be estimated

BEN, Bendamustine; BOR, Bortezomib; CYCLO, Cyclophosphamide; DARA, Daratumumab; POM, Pomalidomide.

Summary/Conclusion: This large, national health database analysis demonstrated that in French RW clinical practice, LEN was frequently used as 1L and 2L therapy for MM, and use of LEN has increased in recent years. After becoming LEN-refractory, patients generally receive POM-based therapy. However, survival outcomes after LEN-refractory regimens were poor, with median survival of around a year and few patients surviving beyond 2 years, regardless of the LEN-refractory LoT. These observations highlight the need for new, efficacious LEN-free treatment options for this hard-to-treat patient population.

EP1006 ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN EAST ASIAN PATIENTS WITH RELAPSED MULTIPLE MYELOMA: IKEMA SUBGROUP ANALYSIS

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Background: The Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (hazard ratio [HR] 0.53; 99% confidence interval [CI] 0.32–0.89; *P*=0.0007).

Aims: To evaluate the efficacy and safety of Isa-Kd in the East Asian patients (19 Japanese, 27 Korean).

Methods: RMM pts who received 1-3 prior lines of therapy were stratified to receive Isa-Kd or Kd. Isa-Kd arm received Isa (10 mg/kg intravenously) weekly for 4 weeks, then every 2 weeks. Both arms received K (20 mg/m^2 days 1-2, 56 mg/m^2 thereafter) twice-weekly for 3 of 4 weeks, and d (20 mg) twice-weekly. Treatment continued until disease progression or unacceptable adverse events (AE). The primary endpoint was prolongation of PFS. Key secondary endpoints included; very good partial response or better (≥VGPR), complete response (CR) rate and minimal residual disease negativity (MRD–) rate.

Results: East Asian pts (25 Isa-Kd, 21 Kd) were randomized. Pt characteristics were similar in the East Asian subgroup compared with the intent to treat (ITT) population (N=302). Median age (Isa-Kd 64.0 [range 45–83] years vs Kd 60.0 [range 33–73] years); median prior lines Isa-Kd 2.0 (range 1–3) vs Kd 1.0 (range 1–3); refractory

to lenalidomide 16.0% Isa-Kd vs 47.6% Kd; refractory to PI 20.0% Isa-Kd vs 33.3% Kd; high-risk cytogenetics 48.0% Isa-Kd vs 42.9% Kd. After a median follow-up of 20.7 months, the addition of Isa to Kd improved ≥VGPR, CR and MRD– rates (Table). The HR 0.64 (95%CI: 0.231-1.764) for disease progression or death favored Isa-Kd. Grade ≥3 AEs were observed in 79.2% Isa-Kd vs 55.0% Kd pts, serious TEAEs in 45.8% Isa-Kd vs 50.0% Kd; TEAEs leading to treatment discontinuation were lower in the Isa-Kd group (4.2% Isa-Kd vs 10.0% Kd). Overall, 64.0% Isa-Kd vs 42.9% Kd pts were still receiving treatment.

	East Asia		ITT	
	Isa-Kd n=25	Kd n=21	Isa-Kd n=179	Kd n=123
PFS HR	0.638 (95% CI: 0.231-1.764)		0.531 (99% CI:0.318–0.889)	
≥VGPR rate, n (%)	20 (80.0)	11 (52.4)	130 (72.6)	69 (56.9)
CR rate, n (%)	11 (44.0)	5 (23.8)	71 (39.7)	34 (27.6)
MRD– rate, n (%)	11 (44.0)	2 (9.5)	53 (29.6)	16 (13.0)
≥Grade 3 TEAE, n (%)	19 (79.2)*	11 (55.0)**	136 (76.8)†	82 (67.2)††
Serious TEAE, n (%)	11 (45.8)*	10 (50.0)**	105 (59.3)‡	70 (57.4)††
Fatal TEAE, n (%)	0*	1 (5.0)**	6 (3.4)†	4 (3.3)††

*n=2, **n=20, †n=177, ††n=122

Summary/Conclusion: Efficacy and safety results of Isa-Kd in East Asian pts are consistent with the results of the overall IKEMA population, in which significantly better efficacy (PFS, CR, ≥VGPR and MRD– rate) was reported in favor of Isa-Kd without an increase in the number of patients with serious TEAEs or discontinuations. Isa-Kd is a potential treatment option for East Asian pts with RMM.

EP1007 TUMOR CHARACTERISTICS OF DISEASE PROGRESSION AFTER BCMA-CART TREATMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA WITH EXTRAMEDULLARY LESIONS

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Background: Although protease inhibitors, immunomodulators, and hematopoietic stem cell transplantation prolong the survival of patients with multiple myeloma, the disease is still incurable. BCMA-CART treatment can make patients with relapsed and refractory multiple myeloma (RR MM) obtain Re-remission, but RR MM patients with extramedullary lesions are prone to relapse or progress again after BCMA-CART. Exploring the mechanism of relapse and progress in these patients is conducive to the selection of maintenance programs after CART to prolong survival.
Aims: The purpose of this study is to explore the disease characteristics of the disease progression of RR MM with extramedullary lesions after BCMA-CART treatment, so as to clarify the mechanism of recurrence or progression in this type of patients, and provide evidence for the selection of the maintenance plan for the patients who are in remission after the BCMA-CART treatment.
Methods: The clinical and molecular characteristics of patients with RR MM with extramedullary lesions who underwent BCMA-CART treatment in our hospital from January 2019 to December 2020 were collected, For disease remission, compare the flow cytometry and immunohistochemical changes of tumor tissue in patients with extramedullary lesions before BCMA-CART treatment and after recurrence or progression, and compare the molecular characteristics of patients with different prognosis to clarify the mechanism of disease recurrence or progression.
Results: From January 2019 to December 2020, a total of 8 patients with RR MM with extramedullary lesions were treated in our department. Of the 8 patients with extramedullary recurrence, 6 (75%) patients relapsed or progressed within 1 year after BCMA-CART treatment. The 6 patients with recurrence or progression had a curative effect assessment of 1 at 3 months after BCMA-CART treatment. 1 case (16.7%) CR, 4 cases (66.7%) PR, 1 case (16.7%) SD; 2 cases of patients who did not relapse and progressed within 1 year after BCMA-CART had CR (3 months after BCMA-CART). 100%). The recurrence or progression sites were bone marrow, cerebrospinal fluid, right psoas major and erector spinae muscles, right eyelid mass, right shoulder soft tissue and elevated serum M protein;
Before treatment, 8 patients underwent flow cytometry and immunohistochemical BCMA antigen detection of tumor tissues. The results showed that BCMA antigen expression was positive, and 4 of the 6 patients who relapsed or progressed were re-exposed to BCMA of tumor cells. Antigen detection of the first patient with bone marrow recurrence showed negative BCMA by bone marrow flow cytometry; the second patient with recurrence of right psoas major and erector spinae had negative tumor tissue flow BCMA, and immunohistochemistry showed weak BCMA positive; Three patients had new lesions on the right eyelid. The tumor tissue flow cytometry showed negative BCMA, and immunohistochemistry showed weak BCMA; the fifth patient had a progression of the right shoulder tumor, and the tissue flow cytometry showed negative BCMA, and puncture tumor immunity histochemistry was negative for BCMA.
Summary/Conclusion: In patients with RR MM with extramedullary lesions, the negative or weak expression of tumor cell surface antigens after BCMA-CART treatment may be one of the mechanisms of disease recurrence or progression; if not achieving deep remission 3 months after BCMA-CART treatment, the possibility of recurrence or progression after 1 year is high.
Key words:
RR MM with extramedullary lesions, BCMA-CART, extramedullary lesions

EP1008 ORAL SELINEXOR, POMALIDOMIDE, AND DEXAMETHASONE (XPD) AT RECOMMENDED PHASE 2 DOSE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (MM)

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL is approved with low-dose dexamethasone (dex) ± bortezomib (BOR) for patients (pts) with previously treated MM. In the Phase 3 BOSTON study, once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS) and overall response rate (ORR) with marked reduction of peripheral neuropathy as compared to standard twice weekly BOR/dex (Vd), despite XVd utilizing 40% less BOR and 25% less dex than Vd. Pomalidomide (POM) plus dex (Pd) has an ORR of 31% and median PFS (mPFS) of 4 months in MM pts refractory to BOR and lenalidomide (LEN).
Aims: To determine if the addition of once weekly SEL to Pd (XPd) would be an active, all-oral combination with an acceptable safety profile in pts with LEN- and BOR-treated MM.
Methods: In the XPd arm of the multi-arm Phase 1b/2 STOMP study, SEL was evaluated at 60, 80, or 100 mg QW or 60 or 80 mg twice weekly in combination with Pd. Study objectives were to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) and to assess the safety and activity of the XPd regimen overall and at the RP2D.

Results: As of 4 Jan 2021, 65 pts (33 male) were enrolled with median age of 64 years (range 37-85 years) and median of 3 (range 1-10) prior lines of therapy. Previously treated/refractory rates were LEN 100%/85%, BOR 92%/49%, carfilzomib 43%/37%, POM 31%/29%, and daratumumab (dara) 26%/26%. RP2D was SEL 60 mg QW, POM 4 mg (days 1-21), dex 40 mg QW.

Common hematologic, treatment-related adverse events (TRAEs) included (all grades, grades ≥3) neutropenia (63%, 55%), anemia (58%, 32%), and thrombocytopenia (54%, 31%) which were typically asymptomatic. Non-hematologic TRAEs were reversible and included nausea (62%, 2%), fatigue (55%, 11%), and decreased appetite (45%, 2%).

Among pts with POM naïve or nonrefractory MM (N=44), ORR was 57% (1 sCR, 1 CR, 8 VGPR, 15 PR); mPFS was 12.2 months. In pts treated with RP2D (N=20), ORR was 65% (1 sCR, 5 VGPR, 7 PR); mPFS was not reached with a median follow-up time of 3.9 months. In pts with POM-refractory MM and those with prior dara, ORRs were 44% (7/16) and 60% (9/15), respectively.

Summary/Conclusion: SEL, once weekly, can be safely combined with Pd in pts with heavily pretreated MM. No new safety signals were identified. The all-oral combination of XPd is highly active with an ORR of 65% at RP2D (compared to expected ORR ~30% for Pd) and produces durable responses with a mPFS of 12.2 months overall. These data support a planned Phase 3 study with an all-oral combination of XPd vs elotuzumab-Pd in pts who have been previously treated with LEN, a PI, and an anti-CD38 mAb.

EP1009 IDECABTAGENE VICLEUCEL (IDE-CEL, BB2121), A BCMA-DIRECTED CAR T CELL THERAPY, IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA: UPDATED KARMMA RESULTS

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Background: Patients with relapsed and refractory multiple myeloma (RRMM) previously exposed to immunomodulatory agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) have poor outcomes with subsequent treatments. In the pivotal KarMMa trial, ide-cel, a BCMA-directed CAR T cell therapy, showed frequent, deep, and durable responses in heavily pretreated patients with RRMM (Munshi NC, et al. *N Engl J Med* 2021;384:705-716).

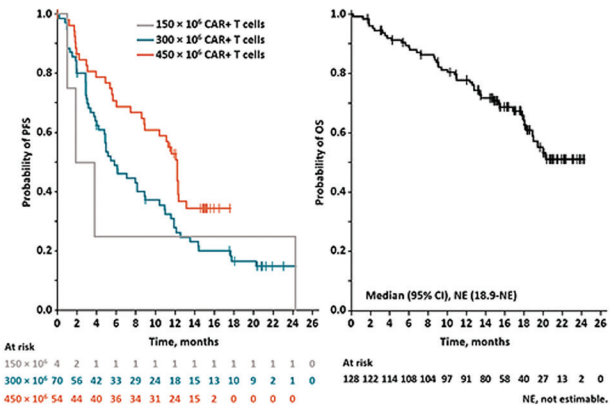
Aims: To report updated efficacy and safety data from the phase 2 KarMMa trial (NCT03361748).

Methods: Eligible patients had received ≥ 3 prior regimens (including an immunomodulatory agent, a PI, and an anti-CD38 mAb) and were refractory to their last regimen per IMWG criteria. After 3 days of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2), patients received 150—450 × 10^6 CAR+ T cells (target dose levels). The primary endpoint was overall response rate (ORR). The key secondary endpoints included complete response (CR) rate (CR + stringent CR [sCR]). Other secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Of the 140 patients enrolled in KarMMa, 128 received ide-cel. Data are presented for the treated patients, who had a median age of 61 years and had received a median of 6 (range, 3-16) prior regimens; 84% were triple-class refractory, and 26% were penta-refractory (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab). Most patients (88%) had received bridging therapy. At the data cutoff (7 April 2020), the median follow-up was 15.4 months. The ORR was 73% and the median PFS was 8.8 months; both increased with higher dose (**Table**). At the highest target dose (450 × 10^6 CAR+ T cells), the ORR was 81%, the CR rate was 39%, and the median PFS increased to 12.2 months with longer follow-up. Responses were observed in all subgroups, including difficult-to-treat subsets (eg, high tumor burden [ORR, 71%], extramedullary disease [70%], and R-ISS stage III disease [48%]). OS continues to mature, and the median has not been reached (**Figure**); the estimated 15-month OS rate was 71%. The most common any-grade toxicities were cytopenia (97%) and cytokine release syndrome (CRS; 84%). CRS was mostly grade 1/2; 5 patients (4%) had grade 3, 1 had grade 4 (at 300 × 10^6), and 1 had grade 5 (at 300 × 10^6) events. Investigator-identified neurotoxicity was reported in 23 patients (18%); 4 patients (3%) had grade 3 and 0 had grade ≥ 4 events. Tocilizumab was used in 67 and 3 patients with CRS and neurotoxicity, respectively. Similarly, steroids were used in 19 and 10 patients with CRS and neurotoxicity, respectively.

Dose, × 10^6 CAR+ T cells	150 (n = 4)	300 (n = 70)	450 (n = 54)	300-450 (n = 124)	Total (N = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	92 (74)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	41 (33)	42 (33)
Median DOR, mo*	†	9.9	11.3	10.7	10.7
Median PFS, mo*	†	5.8	12.2	8.8	8.8

*Kaplan-Meier estimate. †Not reported due to small n.



Summary/Conclusion: Updated results from the KarMMa trial continue to demonstrate deep, durable responses with ide-cel in heavily pretreated, triple-class–exposed patients with RRMM. Efficacy and safety reflect prior reports and support a favorable clinical benefit-risk profile for ide-cel across the target dose levels.

EP1010 ANALYSIS OF A PHASE 2 MINIMAL RESIDUAL DISEASE (MRD)-ADAPTIVE TRIAL OF ELOTUZUMAB, CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (ELO-KRD) FOR NEWLY DIAGNOSED MULTIPLE MYELOMA (MM)

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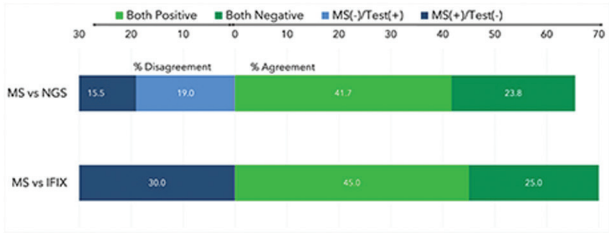
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Background: The addition of a monoclonal antibody to triplet induction regimens in patients (pts) with MM with intent for autologous stem cell transplant (ASCT) has resulted in higher overall and deep response rates.

Aims: In this MRD-guided treatment design, we are investigating the impact of the addition of Elo to KRd on complete response (CR) and/or MRD-negative rates in newly diagnosed MM regardless of transplant eligibility.

Methods: Enrollment was completed from four MM Research Consortium sites into this phase 2 study. All patients receive 12 cycles of Elo-KRd in 28-day cycles: Elo per standard dosing, K 20/56/70 mg/m^2 days 1, 8 and 15, R 25 mg days 1-21, and dexamethasone 40 mg days 1, 8, 15, 22. ASCT eligible candidates can undergo stem cell collection after cycle 4 and then resume treatment; pts who elect to proceed to ASCT are censored for response at that time. Pts MRD(-) (<10^{-5}) by NGS after cycles 8 (C8) and 12 (C12) proceed to Elo-Rd until progression. Patients who convert from MRD(+) to MRD(-) between C8 and C12 receive an additional 6 cycles of Elo-KRd (total 18 cycles) followed by Elo-Rd, and pts MRD(+) after C12 receive an additional 12 cycles of Elo-KRd (total 24) followed by Elo-Rd. The primary endpoint of the study is sCR and/or MRD(-) rate after C8 E-KRd. MRD status was determined by ClonoSEQ next generation sequencing (NGS, <10^{-5}) [Adaptive Biotechnologies]. An improvement in the sCR and/or MRD(-) rate by NGS from a historical 30% to 50% at the end of C8 will be considered promising. Liquid chromatography mass spectrometry (MS) was also performed (Bristol Myers Squibb) from peripheral blood samples on an experimental basis to help distinguish elotuzumab from IgG Kappa paraprotein seen on immunofixation (IFIX).

Results: 44 pts are enrolled, 39 of whom are evaluable for response (cutoff Jan 10 2021). 6 pts (14%) are Black, with 30 (68%) White pts and 8 (18%) with race unreported. Median age is 62 years (range 43-81, 23% age ≥70) and 23 (52%) have IMWG high-risk cytogenetic abnormalities (HRCA) including 13 (30%) with ≥2 high-risk abnormalities (6 pts unknown cytogenetics). 24 pts (55%) have a monoclonal IgG Kappa isotype at baseline. 34/39 (87%) have MRD trackable by clonoSEQ. The rate of sCR and/or MRD(-) by NGS at the end of C8 is 19/33 (58%), meeting the statistical threshold for efficacy (2 pts censored for elective ASCT before C8 and 4 pts on therapy but have not reached C8). For those reaching MRD(-), the median time to MRD(-) is 8 cycles (range 4-18). At the primary endpoint, there was 70% agreement between IFIX and MS amongst 20 paired samples with 6 discordant cases all MS(+)/IFIX(-). There was 65% agreement between MS and NGS across all timepoints, with 13/84 (15%) MS(+)/NGS(-) and 16/84 (19%) MS(-)/NGS(+). With a median follow-up of 24 months, estimated 2-year progression free survival is 87% (100% for standard risk, 79% for HRCA) and estimated 2-year overall survival is 89% (82% for HRCA). No pt who was MRD(-) by NGS after C8 has progressed, including 6 pts with HRCA. Serious adverse events occurred in 30 pts (68%). 89% experienced treatment emergent AEs, the most common (>10%) of which was pneumonia (14%). One pt had grade 5 myocardial infarction.



Summary/Conclusion: Elo-KRd demonstrates tolerability consistent with known toxicities of these agents and met the primary endpoint of sCR and/or MRD(-) of >50% after 8 cycles. MS and NGS are complementary in defining deep responses. With longer follow-up, the study may validate that an MRD-adaptive design for de-escalation of therapy in MM can generate deep responses while reducing treatment exposure.

EP1011 REAL-WORLD DATA ON PATIENT CHARACTERISTICS AND TREATMENT PATTERNS FOR 3000 PATIENTS WITH SYSTEMIC AL AMYLOIDOSIS IN EUROPE BETWEEN 2011 AND 2018: A RETROSPECTIVE STUDY BY THE EUROPEAN MYELOMA NETWORK

G. Palladini [1], S. Schönland [2], G. Merlini [1], P. Milani [1], A. Jaccard [3], F. Bridoux [4], M. A. Dimopoulos [5], S. Ravichandran [6], U. Hegenbart [2], W. Roeloffzen [7], M. T. Cibeira [8], H. Agis [9], M. C. Minnema [10], R. Bergantim [11], R. Hájek [12], C. João [13], P. Sonneveld [14], E. Kastritis [5,*], A. Wechalekar [6]

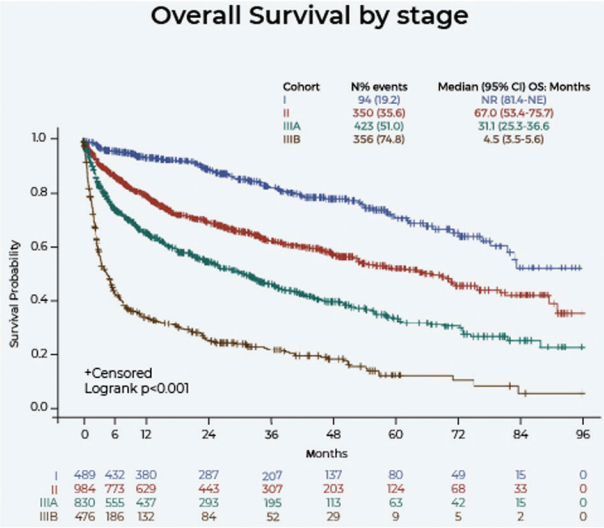
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Background: Systemic light chain (AL) amyloidosis is a serious plasma cell disorder where amyloid is deposited in various organs and tissues throughout the body, disrupting their function, and severely affecting the quality of life of the patients (pts). Therapeutic regimens have been used off-label until very recently, therefore leading to differences in treatment patterns across Europe.

Aims: The current analysis aims to describe differences in patient characteristics and treatment strategies among different European countries in the recent years.

Methods: EMN23 is an ongoing, retrospective, multicenter study aiming to enroll 5000 pts in 13 Sites from 10 European countries. Eligibility criteria include diagnosis of systemic AL amyloidosis, and first-line treatment initiation between 2004 and 2018. This report focuses on the most recent period and presents demographic and clinical characteristics as well as first- and second-line regimens for patients starting first line treatment between 2011 and 2018. Treatment information and efficacy outcomes for patients who participated in an interventional clinical trial have been excluded from the analysis.

Results: Overall, 3064 pts have been included from Austria (1.9%), Czech Republic (0.6%), France (5.8%), Germany (13.8%), Greece (5.8%), Italy (27.0%), the Netherlands (3.6%), Portugal (0.6%), Spain (2.9%), and UK (38.0%). The majority of pts were male (59%). Median age was 66 years, with 29% of the pts below 60 and 17% over 75 years. Heart (70%) and kidney (66%) were the organs most commonly involved and 17%, 35%, 28%, and 16% of the pts were at cardiac stage I, II, IIIA, and IIIB, respectively. Bortezomib-based (Bor-B) therapies were administered to 75% of pts at first line, without differences in age groups (74% in ages <65 years, 76% in ages ≥65), but they were more frequently used with more severe disease (65%, 73%, 81%, and 82% for pts of stage I, II, IIIA, and IIIB). Chemo-based regimens were administered to 9% of pts at first line, regardless of the cardiac stage but more frequently in older pts (5% vs 12%, for pts younger and older than 65, respectively). ASCT was used in 10% of those younger than 65, only in 2% those older than 65, and mostly to patients at earlier cardiac stage (14%, 4%, 3%, and 1% for stage I, II, IIIA, and IIIB). Overall, 984 pts received treatment at second line. Approximately half of the pts (48%) who received Bor-B therapy at first line received immunomodulatory-based (IMiD) at second line, 12% received chemo, 12% ASCT, and 14% were re-treated with Bor-B. About half of the pts (51%) who received chemo at first line continued with Bor-B at second line, 26% with IMiD, none received ASCT, and 3% proceeded with chemo again. Pts who received ASCT at first line continued with IMiD (40%), second ASCT (25%), Bor-B (8%), and chemo (4%). Median overall survival (OS) was 67, 31, and 4 months for pts of stages II, IIIA, and IIIB, and not reached for stage I pts (figure); for pts of revised stages (Mayo 2012) II, III, IV the median OS was 89.4, 29.6, and 14.3 months, and not reached for revised stage I pts.



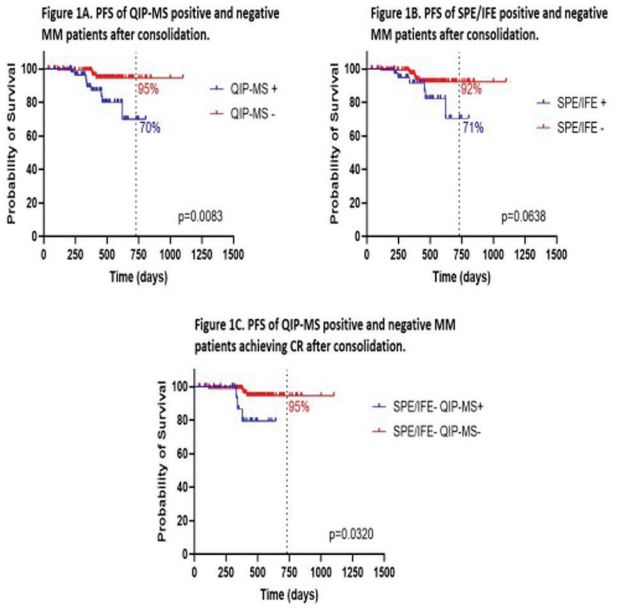
Summary/Conclusion: Bortezomib-based regimens are the most commonly used in the period 2011-2018, across all patients groups, irrespectively of age or cardiac stage. ASCT and chemotherapy-based are used only in a minority of patients in Europe and seldom in patients with advanced cardiac disease. The dismal prognosis of stage IIIB pts even in recent years shows that there is an urgent medical need for more efficacious treatments and new strategies for these patients.

EP1012 ASSESSMENT OF TREATMENT RESPONSE BY MASS SPECTROMETRY IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS FROM THE GEM2012MENOS65 CLINICAL TRIAL: COMPARISON WITH STANDARD SPEP/IFE

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Background: Various studies have demonstrated that Mass Spectrometry (MS) could be a more sensitive method than protein electrophoresis (SPEP) and immunofixation (IFE) for detecting the monoclonal component (MC) in serum in multiple myeloma (MM) patients.
Aims: To compare MS performance against conventional techniques (SPEP and IFE) for the detection of the MC in MM patients enrolled in the PETHEMA/GEM2012MENOS65 clinical trial.
Methods: Newly diagnosed MM patients enrolled in the PETHEMA/GEM2012MENOS65 received six induction cycles of bortezomib, lenalidomide, and dexamethasone (VRD), high-dose therapy (melphalan 200 or busulfan and melphalan) followed by autologous stem cell transplantation (ASCT) and two further cycles of consolidation with VRD. MC in serum was evaluated by conventional techniques (SPEP and IFE) and by Quantitative Immunoprecipitation Mass Spectrometry (QIP-MS) using IgG/A/M, kappa, lambda, free kappa and free lambda isotypic specific beads, both after induction (post-Ind), at day 100 after ASCT (post-ASCT), and after consolidation (post-Cons). The first 186 patients out of the 458 recruited were included in this study.
Results: QIP-MS identified the MC in 118/186 (63%) patients post-Ind, 80/173 (46%) post-ASCT and 61/168 (36%) post-Cons. By contrast, SPEP/IFE detected the MC in 97/186 (52%) post-Ind, 62/173 (36%) post-ASCT and 41/168 (24%) post-Cons. The percentage of discordant cases decreased from 18% post-Ind to 14% post-ASCT and 13% post-Cons. Most discordances were due to samples positive by QIP-MS and negative by SPEP/IFE (15% post-Ind, 12% post-ASCT and 13% post-Cons). In a minority of cases, the MC was exclusively detected by SPEP/IFE: 6/186 (3%) post-Ind, 3/173 (2%) post-ASCT, and 1/168 (1%) post-Cons. Most discrepancies occurred early during monitoring or after ASCT, and could represent false-positives due to gel interpretation issues and/or the presence of oligoclonal bands. Of note, none of these latter discrepant cases (QIP-MS neg/SPEP/IFE+) have relapsed so far.
Once confirmed the higher ability of MS to detect the MC as compared to standard methods, we decided to compare their respective clinical value in terms of progression free survival (PFS) at the completion of the treatment (post-Cons, Figure 1). The probability of PFS at 2 years post-Cons was 95% for QIP-MS- patients vs 70% for those QIP-MS+ (p=0.0083, HR=4.677; fig. 1A). By contrast, the differences in PFS at 2 years post-Cons between SPEP/IFE- vs SPEP/IFE+ cases did not reach statistical significance (92% vs 71%, p=0.0638; fig. 1B). Investigating the 127 patients achieving CR post-Cons, we found out that QIP-MS was able to identify the presence of a MC in 21 of them (16.5%); further, the identification of the MC by QIP-MS in this group of patients in standard CR (SPEP/IFE-) was associated with a significantly shorter PFS (p=0.0320; HR=10.07; fig. 1C).



Summary/Conclusion: As compared to standard methods to detect the MC in serum, in this study QIP-MS: 1) identified the presence of the paraprotein in a higher proportion of cases throughout monitoring; 2) was able to discriminate 2 groups of patients with different PFS at treatment completion and 3) identified residual disease in a cohort of patients in standard CR but at increased risk of progression.

EP1013 A META-ANALYSIS OF EFFICACY OF POMALIDOMIDE-BASED REGIMENS FOR THE TREATMENT OF RELAPSED OR REFRACTORY MULTIPLE MYELOMA AFTER LENALIDOMIDE EXPOSURE

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Background: Pomalidomide (POM)-based combination(s) are a standard therapy for patients with lenalidomide (LEN)-exposed relapsed or refractory multiple myeloma (RRMM). Multiple studies have assessed the efficacy and risk profile of POM-containing regimens, leading to the approval of regimens such as PVd, DPd, and EloPd.
Aims: To conduct a meta-analysis of progression-free survival (PFS) outcomes reported for POM-based combination regimens and generate a pooled efficacy estimate.
Methods: A targeted search was conducted to identify studies between 2016 and 2020 in patients previously treated with LEN. Trials had to include a POM-based combination with proteasome inhibitors (PVd, KPd), monoclonal antibodies (EloPd, DPd, IsaPd) or an alkylating agent (PCd). Kaplan-Meier curves reported in publications were digitized to reconstruct the individual patient data (IPD) through the Guyot algorithm. Reconstructed IPD were then used to generate survival analyses and obtain a detailed description of individual survival curves. Individual curves were pooled using a random-effects model and the DerSimonian and Laird method. The I2 statistic was used to test for heterogeneity between the studies, with 0% suggesting the lowest level of heterogeneity. Heterogeneity was observed between studies in terms of patient characteristics and number of prior lines of therapies. Three unadjusted analyses were performed: a meta-analysis to obtain a pooled median PFS based on all the studies, independent of the number of prior lines; a meta-analysis restricted to studies that included 2L patients (2L+); and a meta-analysis of PFS reported in 2L patients only. The 1- and 2-year PFS rates were then extracted.
Results: Five randomized controlled trials (RCTs) (OPTIMISMM—PVd vs Vd, APOLLO—DPd vs Pd, ELOQUENT-3—EloPd vs Pd, ICARIA-MM—IsaPd vs Pd, and NCT01432600—Cd vs Pd) and 6 single-arm trials (MM-014—DPd, MMRC—KPd, NCT02185820—KPd, NCT02176213—PCd, EMN1—KPd, and IFM2013—PCd) were identified. Eleven, 7, and 3 trials were included, with heterogeneity levels estimated at 15.3%, 13.2% and 0.0%, respectively. The overall population was found to have a median PFS of 14.1 months (**Table**). The unadjusted pooled median PFS in trials including 2L+ patients was 16.9 months. Finally, when considering only 2L patients, the pooled median PFS was 21.3 months. The PFS rates at 1 and 2 years were 57% and 30%, respectively, in the overall population, 62% and 39% for trials including 2L+ patients, and 74% and 42% when considering only 2L patients. Although unadjusted, the pooled estimated median PFS highlighted that POM-based combinations seem to have better efficacy when used in early treatment lines.

Table PFS rates at 1 and 2 years in the overall population, 2L+ patients, and only 2L patients

Analysis	Median PFS, mo	PFS rate at 1 year (95% CI), %	PFS rate at 2 years (95% CI), %
Overall population	14.1	57 (49–65)	30 (23–41)
Overall population (trials including 2L patients)	16.9	62 (52–73)	39 (30–50)
2L patients only	21.3	74 (66–83)	42 (31–56)

2L, second line; PFS, progression-free survival.

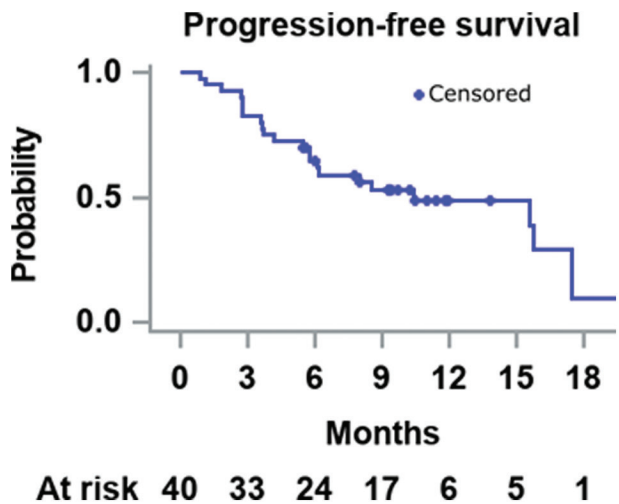
Summary/Conclusion: POM-based combinations have been an effective treatment strategy in RRMM post LEN. The efficacy associated with these combinations was found to be higher for patients treated in earlier lines (second line) compared with the overall population of previously treated patients. POM delivered consistent efficacy and synergy in combinations with protease inhibitors and monoclonal antibodies. These data suggest that class switch may not always be necessary when making treatment decisions.

EP1014 SAFETY AND EFFICACY OF DARATUMUMAB WITH IXAZOMIB AND DEXAMETHASONE IN PATIENTS WITH ONE PRIOR LENALIDOMIDE-BASED REGIMEN: THE DARIA STUDY

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Background: Second-line treatment of patients (pts) with multiple myeloma (MM), who are refractory to, or have relapsed after frontline lenalidomide-based therapy is challenging. Daratumumab (DARA), an anti-CD38 monoclonal antibody, has shown significant clinical activity and an acceptable safety profile in pts with relapsed/refractory multiple myeloma (RRMM) as monotherapy or in combination with other agents. Ixazomib, the first oral proteasome inhibitor, has also been shown to be efficacious and with a positive safety profile in newly diagnosed MM pts.
Aims: This study aims to evaluate the effectiveness of DARA in combination with ixazomib and dexamethasone (DId) as second-line therapy in pts with RRMM who have previously been treated with a lenalidomide-based regimen.
Methods: DARIA is an ongoing, prospective, open-label, multicenter, phase 2 study. Eligible adult pts with RRMM had measurable disease after 1 prior line with a lenalidomide-based regimen and a Karnofsky Performance Status (KPS) score of ≥70. Exclusion criteria included previous DARA or anti-CD38 or ixazomib treatment. Treatment with DId comprises an induction phase of 9 cycles (each of 28 days in duration) and a maintenance phase. In induction, pts received DARA 16mg/kg (weekly for cycles 1–2, every 2 weeks for cycles 3–6, and every 4 weeks thereafter) administered intravenously until November 2020 and subcutaneously at a fixed dose of 1800 mg thereafter; 4mg oral ixazomib (days 1, 8, and 15 of each cycle); and 40mg oral dexamethasone (weekly, each cycle). In maintenance, DARA and ixazomib are administered every 4 weeks until disease progression or unacceptable toxicity, with dexamethasone being discontinued. The primary endpoint is overall response rate (ORR). This report presents results for pts who received the first dose at least 6 months prior to the cut-off date (31/12/2020).
Results: This analysis includes 40 pts (median age: 69.0 years; male: 52.5%). At screening, 75.0% of pts had a KPS score of ≥90. 50.0%, 32.5%, and 17.5% had an International Staging System (ISS) stage of 1, 2, and 3, respectively; and 37.5%, 52.5%, and 7.5% had a revised ISS of 1, 2, and 3, respectively. 70.0% of pts were refractory to lenalidomide, and 37.5% of them had received prior autologous stem cell transplantation. The median time from diagnosis to first study dose was 2.1 years. Up to the cut-off date, pts received a median of 9 treatment cycles. ORR was 57.5% (complete response: 2.5%, VGPR: 30.0%, and PR: 25.0%). The median time from first DId dose until first response (PR or better) was 0.9 months. The median PFS was 10.4 months (figure), and 37.5% of the pts were still on treatment by the cut-off date. Of all pts, 62.5% discontinued treatment (40% due to progressive disease, 12.5% due to physician's decision, and 10% due to a safety event). Overall, 40% of the pts had ≥1 AE grade 3/4, the most common being thrombocytopenia (n=8, 20.0%), and 25.0% (n=10) had ≥1 serious adverse event, the most common being acute kidney injury (n=2, 5.0%) and pneumonia (n=2, 5.0%, one of which fatal). In total, there were 3 fatal SAE, the other 2 being infection and a lower respiratory tract infection.



Summary/Conclusion: Second-line treatment with DId in pts with RRMM who were previously treated with a lenalidomide-based regimen resulted in rapid (median time to PR or better was less than a month)

and deep responses (about a third of pts exhibited VGPR or better). The safety profile of DId was very good, and the majority of pts (60%) did not experience grade 3/4 AE, whereas 25% of them experienced a SAE.

EP1015 EARLY INTENSIVE CONSOLIDATION WITH AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN NEWLY DIAGNOSED HIGH-RISK MULTIPLE MYELOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

S. Gupta [1,*], R. Siddiqi [2], I. Riaz [3], M. Husnain [4], M. Aljama [5], F. Anwar [6], N. Asghar [7], R. Chakraborty [8]

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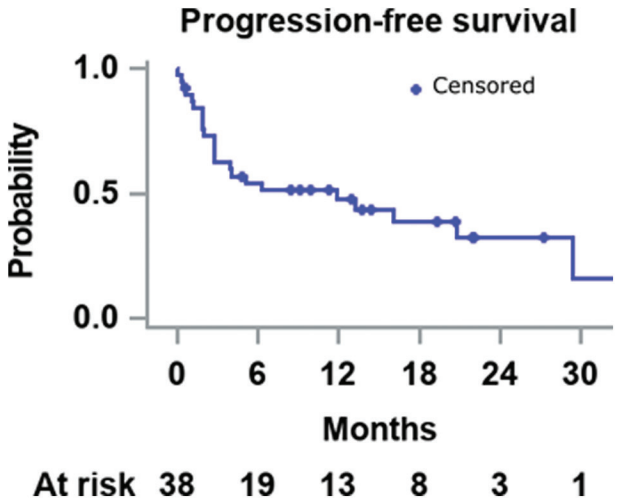
Background: In patients with newly diagnosed multiple myeloma, early intensive consolidation with high dose therapy-autologous hematopoietic cell transplantation (HDT-AHCT) leads to a superior progression-free survival (PFS) compared to standard dose therapy (SDT). However, whether patients with high-risk cytogenetics benefit from early HDT-AHCT remains unclear. To answer this question, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing consolidation with HDT-AHCT versus SDT in the era of proteasome inhibitor (PI) and/or immunomodulatory drug (IMiD)-based induction therapy.
Aims: The primary objective of this study was to evaluate the association of HDT-AHCT with PFS in newly diagnosed high-risk myeloma, with overall survival (OS) being the secondary objective.
Methods: Standard electronic databases were searched for citations of phase 3 RCTs comparing HDT-AHCT with SDT in newly diagnosed myeloma. High-risk myeloma was defined as subjects with adverse-risk cytogenetics, as specified by individual study protocol. Efficacy data was extracted using hazard ratios (HRs) for PFS and OS. We used DerSimonian-Laird random effects model to pool log HRs, and applied Hartung-Knapp adjustment as the total number of trials was small. Heterogeneity was assessed using the Cochran Q and the I^2 statistic.
Results: After screening all citations, a total of 17 RCTs were retrieved, of whom, 4 RCTs were deemed eligible for inclusion in the meta-analysis. An additional RCT was included after searching conference abstracts and grey literature. The included RCTs were as follows: IFM 2009 (Attal *et al*. NEJM. 2017), EMN02/HOVON 95 (Cavo *et al*. Lancet Haem. 2020 and Cavo *et al*. ASH 2020), RV-MM-EMN-441 (Gay *et al*. Lancet Oncol. 2015), RV-MM-PI-209 (Palumbo *et al*. NEJM. 2014), and FORTE (Gay *et al*. ASH. 2020). The induction regimens used were VRD (bortezomib-lenalidomide-dexamethasone; n=1), KRD (carfilzomib-lenalidomide-dexamethasone; n=1), VCD (bortezomib-cyclophosphamide-dexamethasone; n=1), and RD (lenalidomide-dexamethasone; n=2). Patients underwent a single HDT-AHCT in 2 trials, tandem in 2 trials and a combination of single or tandem in 1, with the conditioning regimen being melphalan 200 mg/m^2 in all RCTs. Three RCTs (IFM 2009, EMN02/HIVON95, and RV-MM-EMN-441) included post-transplant lenalidomide maintenance in all patients and 2 RCTs (RV-MM-PI-209 and FORTE) randomized patients to lenalidomide versus observation or carfilzomib-lenalidomide respectively. Early intensive consolidation with HDT-AHCT led to superior PFS compared to SDT, with the benefit consistent in both high-risk (Pooled HR, 0.50 [0.27-0.94]) and standard-risk (Pooled HR, 0.58 [0.46-0.73]) subrgoups (p-value for interaction=0.32). A subset of 3 RCTs (EMN02/HOVON95, RV-MM-EMN-441, and RV-MM-PI-209) reported OS in cytogenetic risk subgroups. Patients with high-risk cytogenetics had a greater OS benefit with early HDT-AHCT (Pooled HR, 0.59 [0.47-0.74]) compared to standard-risk (Pooled HR, 0.82 [0.63-1.07]) patients (p-value for interaction<0.01).
Summary/Conclusion: In patients with newly diagnosed myeloma undergoing induction therapy with PIs +/- IMiDs, early intensive consolidation with HDT-AHCT is associated with a superior PFS compared to SDT, with benefit being consistent in both high-risk and standard-risk subgroups. Furthermore, although HDT-AHCT leads to an OS benefit overall, high-risk patients derive greater benefit compared to standard-risk. HDT-AHCT should not be delayed in patients with high-risk myeloma outside of well designed clinical trials.

EP1016 RESULTS ON EFFICACY AND SAFETY OF DARATUMUMAB WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND SEVERE RENAL IMPAIRMENT: THE DARE STUDY

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Background: Severe renal impairment (RI) is a common myeloma (MM) complication. For patients with relapsed/refractory MM (RRMM) there is a need for effective therapies with low or minimal risk of renal toxicity. Daratumumab (DARA), an IgG1κ human monoclonal antibody that targets CD38, has shown durable responses and a favorable safety profile in heavily pretreated patients (pts) with RRMM. However, there is limited data on the safety and efficacy of DARA in pts with RRMM and severe RI.
Aims: DARE study aims to assess the safety and efficacy of DARA with dexamethasone in pts with RRMM and severe RI.
Methods: DARE is a prospective, open-label, multicenter, phase 2 study conducted in 7 sites in Greece and Italy, and has completed enrolment. Eligible adult pts had documented RRMM and severe RI (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2 or requiring dialysis), who had ≥2 previous treatments of both bortezomib- and lenalidomide-based regimens, had progressive disease after their last treatment and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Exclusion criteria included previous daratumumab or other anti-CD38 therapy. Pts received 28-day treatment cycles with 16 mg/kg intravenous daratumumab (weekly for cycles 1–2, every 2 weeks for cycles 3–6, and every 4 weeks thereafter) and oral dexamethasone (40 mg weekly). The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall response rate (ORR; partial response [PR] or better), renal response rate (RRR; best response of renal partial response or better), and safety. All responses were based on investigators' assessment as per IMWG criteria.
Results: In total, 38 pts (male: 76.3%; median age: 72 years; median time from diagnosis to study entry: 4.2 years) were included. The median number of prior therapies was 3, and 34.2% had undergone autologous stem cell transplantation. At study entry, 10.5% and 89.5% of pts had International Staging System (ISS) 2 and 3 disease, median eGFR was 13 mL/min/1.73 m^2, and 44.7% were on dialysis. The median follow-up is 10 months, and pts received a median of 8 cycles of DARA with dexamethasone. The 6-month and median PFS is 54% and 11.8 months respectively (Figure). The ORR was 47.4% (very good partial response: 34.2%, PR: 13.2%), and the ORR for pts on dialysis (n=17) was 47.1%. The median time from the first study treatment dose to first response (PR or better) was 0.9 months. The RRR was 15.8%. By the cut-off date (31/12/2020) 31.6% of pts were still receiving protocol therapy; 68.4% had discontinued treatment (progressive disease: 36.8%; lost to follow-up: 7.9%; patient choice 5.2%, and SAE: 18.4%). Overall, 50% of pts had ≥1 adverse event (AE) grade 3/4 (most common were anemia [15.8%] and hyperglycemia [13.2%]), and 26.3% (n=10) had ≥1 serious adverse event (SAE), mostly infectious complications: septic shock (n=3, all fatal), pneumonia, peritonitis (fatal), lower respiratory tract infection (fatal), ECOG PS worsened (fatal), cerebrovascular accident, myocardial infarction (fatal), acute kidney injury, and hyperkalemia (n=1 each).



Summary/Conclusion: DARA and dexamethasone is an effective treatment for RRMM with severe renal dysfunction or requiring dialysis, associated with rapid and high rates of hematologic and respectable rates of renal responses in this heavily pretreated population. Notably, responses were similar in pts regardless of being on dialysis or not. No new safety signals were observed but antibiotic prophylaxis may potentially reduce infection risk.

EP1017 SAFETY AND TOLERABILITY OF CAEL-101 IN COMBINATION WITH CYCLOPHOSPHAMIDE-BORTEZOMIB-DEXAMETHASONE AND DARATUMUMAB IN PATIENTS WITH AL AMYLOIDOISIS

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Background: Amyloid light-chain (AL) amyloidosis is a rare, potentially life-threatening disorder, caused by a plasma cell dyscrasia (PCD) that results in overproduction of immunoglobulin light chains, which misfold and aggregate to form amyloid fibrils. These deposit in tissues and/or organs, such as heart and kidneys, causing significant morbidity and mortality.

MedDRA Preferred Term	Part A CAEL-101 + CyBorD N=13	Part B CAEL-101 + CyBorD + daratumumab N=9	Overall (Part A+B) N=22
At least one TEAE	13 (100%)	5 (55.6%)	18 (81.8%)
At least one TEAE considered to be at least possibly related to study drug[1]	3 (23.1)	0	3 (13.6%)
At least one Grade 3 or higher TEAE	1 (7.7%)	3 (33.3%)	4 (18.2%)
At least one treatment-emergent SAE	2 (15.4%)	1 (11.1%)	3 (13.6%)
TEAEs leading to study discontinuation	0	0	0
TEAEs leading to death	0	1 (11.1%)	1 (4.5%)
Most Common TEAEs (≥9%)			
Nausea	4 (30.8%)	1 (11.1%)	5 (22.7%)
Constipation	2 (15.4%)	3 (33.3 %)	5 (22.7%)
Rash	2 (15.4%)	2 (22.2%)	4 (18.2%)
Fatigue	2 (15.4%)	2 (22.2%)	4 (18.2%)
Insomnia	2 (15.4%)	1 (11.1%)	3 (13.6%)
Diarrhea	3 (23.1%)	0	3 (13.6%)
Vomiting	1 (7.7%)	1 (11.1%)	2 (9.1%)
Anaemia	2 (15.4%)	0	2 (9.1%)
Hypokalaemia	0	2 (22.2%)	2 (9.1%)
Headache	2 (15.4%)	0	2 (9.1%)

Abbreviations: TEAE=treatment-emergent adverse event. A TEAE was defined as an adverse event occurring during or after study drug administration. SAE=Serious TEAE. DLT=Dose-limiting-toxicity.
[1] At least possibly related TEAEs were defined as TEAEs with relationship of possibly or related
Note: Patients experiencing more than 1 TEAE were only counted once under the greatest severity and causality.

Current treatments target the underlying PCD to arrest formation of additional misfolded light chains; there are no treatments currently available that target the removal of fibrils and amyloid deposited in organs. CAEL-101, a chimeric immunoglobulin that reacts specifically with light chain fibrils but not with the native form, is believed to inhibit fibril formation and improve outcomes by facilitating removal of amyloid deposited in tissues. Results of the dose selection part (Part A) of this Phase 2 study found that CAEL-101 in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD) was safe and well tolerated in doses up to 1000 mg/m^2 (Valent et al., ASH 2020).

Aims: To define the safety and tolerability through 4 weeks of treatment with CAEL-101+CyBorD (Part A) and CAEL-101+CyBorD+daratumumab (Part B) in patients with AL amyloidosis.

Methods: This ongoing multicenter, open-label, sequential cohort, dose-selection study of CAEL-101 in Mayo Stage I, Stage II and Stage IIIa AL amyloidosis patients was divided into two parts (NCT #NCT04304144). Staging was based on the European modification to the Mayo 2004 staging system (Wechalekar et al., 2013). Part A consisted of a 3 + 3 dose escalation design to determine the recommended dose for the Phase 3 study in combination with CyBorD. Part B studied 1000 mg/m^2 CAEL-101+CyBorD+daratumumab. The study included an initial 4-week dose limiting toxicity (DLT; Part A) and safety observation (Part B) period; patients are continuing to receive CAEL-101 until end of study or discontinuation. All patients in Parts A and B received CAEL-101 q1wk for the first 4 infusions, followed by CAEL-101 q2wk. Key inclusion criteria were adults ≥18 years old with a minimum life expectancy of 6 months and histopathological diagnosis of AL amyloidosis. Key exclusion criteria included any other amyloidosis, multiple myeloma, or supine systolic blood pressure <90 mmHg or symptomatic orthostatic hypotension. Outcomes for safety and tolerability are presented through the first 4 weeks of treatment.

Results: Of the 22 patients enrolled to date, 13 received 1000 mg/m^2 CAEL-101+CyBorD in Part A and 9 received 1000 mg/m^2 CAEL-101+CyBorD+daratumumab in Part B. Mean age was 65.1 years (range 47.6–79.6 years); the majority were male (72.7%) and white (90.9%), with Mayo stage I (9.1%), II (68.2%), and IIIa (22.7%). 72.7% had cardiac involvement and 68.2% had at least one prior PCD treatment. During the 4-week DLT/safety observation period, the most common TEAEs were nausea (22.7%), constipation (22.7%), rash (18.2%), and fatigue (18.2%). One death occurred in the setting of septic pneumonia during this study that was not considered related to study drug.

Summary/Conclusion: Safety data from this ongoing phase 2 study indicate that 1000mg/m^2 of CAEL-101 in combination with CyBorD alone or CyBorD+daratumumab is well tolerated in patients with AL amyloidosis during the first 4 weeks of treatment. Two Phase 3 trials, one enrolling Mayo Stage IIIa (NCT# 04512235) and Mayo Stage IIIb patients (NCT# 04504825), have been initiated to study the safety and efficacy of 1000 mg/m^2 CAEL-101.

EP1018 SAFETY AND TOLERABILITY OF CAEL-101 IN PATIENTS WITH AL AMYLOIDOSIS IN A PHASE 2 STUDY FOR A MEDIAN OF 38 WEEKS

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Background: AL amyloidosis is a rare, progressive disorder caused by misfolded immunoglobulin light chains that aggregate into amyloid fibrils which can deposit in tissues and organs, such as the heart, causing significant mortality and morbidity. Cardiomyopathy impacts prognosis, hence cardiac biomarkers are used in the Mayo staging system for AL amyloidosis (Dispenzieri et al., 2015). Median overall survival for patients with Mayo Stage II, IIIa, and IIIb is 54 months (m), 24 m, and 4 m, respectively (Dittrich et al., 2020).

Current treatment strategies do not directly target the amyloid deposited in organs. CAEL-101 is a chimeric immunoglobulin that binds specifically to misfolded light chain fibrils and is believed to facilitate removal

of amyloid deposited in tissues. Results from the dose limiting toxicity period of a phase 2 study with CAEL-101 in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD) demonstrated that CAEL-101 up to 1000 mg/m^2 was well tolerated and is the recommended dose for future studies (Valent et al., ASH 2020). Here we report results to date from this study.

Aims: To define the safety and tolerability of CAEL-101+CyBorD in patients with AL amyloidosis.

Methods: In this ongoing multicenter, open-label, sequential cohort, dose-selection study of CAEL-101 in AL amyloidosis patients (NCT #NCT04304144), a 3+3 dose escalation design was used to determine the recommended dose for Phase 3 studies. All patients received CAEL-101 q1wk for the first 4 infusions, after which patients receive CAEL-101 q2wk. Key inclusion criteria were adults ≥18 years old with a minimum life expectancy of 6 m, measurable hematological disease (dFLC > 5mg/dL or FLC >5mg/dL with abnormal ratio or SPEP M-spike >0.5 g/dL) and histopathological diagnosis of AL amyloidosis. Key exclusion criteria included any other amyloidosis, multiple myeloma, or supine systolic blood pressure <90 mmHg or symptomatic orthostatic hypotension. Assessments include clinical laboratory tests, echocardiograms, vital signs, physical exams and, treatment emergent adverse events (TEAEs).

Results: The 13 patients enrolled had a mean age of 65.2 years (range 47.6–79.6 years), were diagnosed with AL amyloidosis on average 29.4 m (range 2.7–163 m) prior to study enrollment, and were mostly male (76.9%) and white (84.6%). At baseline, 61.5% of patients had cardiac involvement with Mayo stage II (69.2%) and IIIa (23.1%). A majority (69.2%) had at least one prior PCD treatment; commonly reported prior treatments were bortezomib (61.5%), daratumumab (53.8%), cyclophosphamide (53.8%), melphalan (15.4%), carfilzomib (15.4%), lenalidomide (15.4%).

This study is ongoing with a current median treatment duration of 38 weeks (wk) (range 12 wk–48 wk), with most patients having had ≥20 infusions of CAEL-101. The most common TEAEs reported include diarrhea (46.2%), nausea (46.2%), rash (38.5%), and anaemia (38.5%). Using NT-proBNP and cTnT values to assess changes in Mayo staging, no patients have progressed from their baseline disease staging and none have died through a median of 38 wk of treatment.

MedDRA Preferred Term	CAEL-101 + CyBorD N=13
At least one TEAE	13 (100%)
At least one TEAE considered to be at least possibly related to study drug[1]	6 (46.2%)
At least one Grade 3 or higher TEAE	2 (15.4%)
At least one treatment-emergent SAE	2 (15.4%)
TEAEs leading to study discontinuation	0
TEAEs leading to death	0
Most Common TEAEs (≥15%)	
Diarrhea	6 (46.2%)
Nausea	6 (46.2%)
Rash	5 (38.5%)
Anaemia	5 (38.5%)
Constipation	4 (30.8%)
Fatigue	4 (30.8%)
Cough	4 (30.8%)
Insomnia	3 (23.1%)
Dyspnoea	3 (23.1%)
Hypertension	3 (23.1%)
Hyperkalaemia	2 (15.4%)
Vomiting	2 (15.4%)
Headache	2 (15.4%)
Pleural Effusion	2 (15.4%)
Arthralgia	2 (15.4%)

Abbreviations: TEAE=treatment-emergent adverse event. A TEAE was defined as an adverse event occurring during or after study drug administration. SAE=Serious TEAE. DLT=Dose-limiting-toxicity.
[1] At least possibly related TEAEs were defined as TEAEs with relationship of possibly or related.
Note: Patients experiencing more than 1 TEAE were only counted once under the greatest severity and causality.

Summary/Conclusion: These data suggest that treatment with CAEL-101+CyBorD through ~8.8 m is generally well tolerated, with possible stabilization of cardiac disease as assessed by Mayo staging. Additional data from this ongoing Phase 2 study, as well as from the two currently enrolling Phase 3 studies (NCT# 04512235 and 04504825) in patients with Mayo Stage IIIa and IIIb, will further evaluate the safety and efficacy of CAEL-101 in patients with AL amyloidosis.

EP1019 POMALIDOMIDE, DEXAMETHASONE, AND DARATUMUMAB IN RELAPSED REFRACTORY MULTIPLE MYELOMA (MM-014 PHASE 2 TRIAL): A SUBANALYSIS OF PATIENTS PREVIOUSLY TREATED WITH LENALIDOMIDE AND A PROTEASOME INHIBITOR

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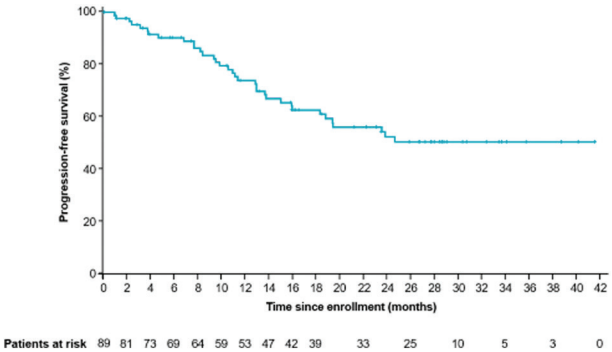
Background: Lenalidomide (LEN) with or without a proteasome inhibitor (PI) administered until disease progression is a standard treatment (Tx) approach for patients with newly diagnosed multiple myeloma (MM). However, recent clinical trials investigating triplet therapies did not have a large representation of patients whose disease has relapsed or become refractory to LEN after early-line Tx. The phase 2 MM-014 trial (NCT01946477) was designed to investigate the outcomes with sequencing pomalidomide (POM)-based therapy immediately after first- or second-line LEN-based Tx failure in patients with relapsed refractory MM (RRMM). In an earlier report of the intention-to-treat population (N = 112) from cohort B of this trial, POM + dexamethasone (DEX) + daratumumab (DARA) demonstrated promising efficacy and safety with an overall response rate (ORR) of 77.7%, and median progression-free survival (PFS) of 30.8 months (Siegel DS, et al. *Blood* 2020;136[suppl 1]: 16–17).

Aims: To report the efficacy and safety of POM + DEX + DARA immediately after LEN-based Tx failure in a subgroup of cohort B patients who received prior LEN + PI.

Methods: Patients with RRMM treated with 1-2 prior Tx lines, LEN-based Tx for ≥ 2 consecutive cycles as their most recent regimen, and progressive disease during or after their last line of Tx received POM + DEX + DARA. POM 4 mg/d was given orally on days 1-21; DEX 40 mg/d (20 mg/d in patients aged > 75 years) was given orally on days 1, 8, 15, and 22; and DARA 16 mg/kg was given intravenously on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 for cycles 3-6, and day 1 for cycles 7+. The primary endpoint was ORR; secondary endpoints included PFS and safety.

Results: In cohort B, 89 of 112 patients (79%; median age, 65.0 years) had received prior LEN + PI. Among this patient subgroup, 67 patients (75.3%) had LEN-refractory MM and 22 (24.7%) had MM that relapsed after LEN Tx; most patients (52 [58.4%]) received 1 vs 2 (37 [41.6%]) prior Tx lines. Median duration of treatment of POM, DEX, and DARA was 15.9. 14.0, and 16.1 months, respectively. At data cutoff (March 24, 2020), the ORR was 78.7% (≥ very good partial response [VGPR], 55.1%); median follow-up of 28.3 months. The ORR was 80.8% (≥ VGPR, 63.5%) and 75.7% (≥ VGPR, 43.2%) in patients with 1 vs 2 prior lines of treatment, respectively. Median duration of response and median PFS were not yet reached (Figure; 1-year PFS rate, 74.1%). Infusion-related reactions occurred in 28.1% of patients and were primarily low grade. Overall, 97.8% of patients had ≥ 1 grade 3/4 Tx-emergent adverse event. The most common grade 3/4 hematologic events were neutropenia (64.0%; febrile, 12.4%), anemia (19.1%), and thrombocytopenia (13.5%). Grade 3/4 infections occurred in 40.4% of patients, including 15.7% with grade 3/4 pneumonia.

Figure. Progression-free survival in the prior LEN + PI subgroup (n = 89)



Summary/Conclusion: In this subanalysis, POM + DEX + DARA administered immediately after LEN failure in a subgroup of patients previously treated with LEN + PI demonstrated a high response rate and a safety profile consistent with that in the overall cohort B population. The results support the use of POM-based therapy, integrating the monoclonal antibody DARA as early as second line in patients with RRMM, potentially immediately after LEN Tx failure. Furthermore, these data support subsequent Tx with the same immunomodulatory agent class in a patient population with LEN-relapsed or -refractory disease.

EP1020 EARLY MORTALITY AMONG PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA IN THE NETHERLANDS: A POPULATION-BASED STUDY

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Background: The introduction of novel agents and autologous stem cell transplantation improved the population-level survival of patients with multiple myeloma (MM). However, early mortality (EM) remains a major clinical issue. Identification of risk factors of EM may contribute to more rigorous supportive care measures or different therapeutic approaches in patients at risk for EM.
Aims: This population-based study aimed to assess trends in and risk factors of EM among MM patients diagnosed in the Netherlands during a 30-year period.
Methods: All MM patients diagnosed between 1989-2018 were identified in the Netherlands Cancer Registry, with survival follow-up through 2020. Data on primary therapy, i.e. no therapy and anti-neoplastic therapy were available for all patients. Patients were categorized into three calendar periods (1989-1998, 1999-2008, 2009-2018) and four age groups (≤65, 66-70, 71-80, >80 years). The impact of age, sex, period of diagnosis, hospital type at diagnosis, and prior malignancies, for EM was evaluated using uni- and multivariable Cox regression analyses. Moreover, for patients diagnosed in 2014-2018, detailed data on plasma cell percentage, cytogenetic risk, type of M-protein, levels of β2-microglobulin and albumin, as well as presence of thrombocytopenia, hypercalcemia, renal impairment, anemia, and bone lesions, type and number of novel agents (bortezomib, lenalidomide and/or thalidomide) was evaluated. EM was defined as the date from MM diagnosis to all-cause death ≤180 days.
Results: Our analytical cohort included 28,328 MM patients (median age 70 years; 55% males; 88% diagnosed in non-academic centers; 13% prior malignancies). EM for patients ≤65 was 11%, 11%, and 6% (P<0.001) in 1989-1998, 1999-2008, and 2009-2018, respectively. The corresponding proportions for patients aged 66-70 were 19%, 16%, and 8% (P<0.001), for patients 71-80, 25%, 22%, and 15% (P<0.001), and for patients >80, 40%, 41%, and 31% (P<0.001). EM was significantly lower among patients who received anti-neoplastic therapy as compared to patients who did not receive first-line therapy (13% vs. 29%; P<0.001) and EM decreased for both groups over time. When simultaneously adjusted for calendar period, sex, age, hospital type at diagnosis, prior malignancies, and treatment, patients diagnosed in 2009-2018 had a 42% lower risk of mortality as compared with patients diagnosed in 1989-1998 (hazard ratio, 0.58; P<0.001) with an adverse effect of older age, and prior malignancies.
In 2014-2018, 6,380 MM patients were diagnosed of whom 780 (12%) patients died ≤180 days post-diagnosis. For patients ≤70 years, EM was 6% for patients treated with bortezomib, 5% for lenalidomide, 3% for thalidomide as well as for treatment with two novel drugs (*P*=0.013). EM was similar for patients >70 years treated with bortezomib, lenalidomide, or thalidomide (12%, 15%, 14%, respectively; *P*=0.441). For patients >70 years treated with a combination of two novel drugs, none died ≤180 days. Albumin <35 g/L, β2-microglobulin ≥3.5 mg/L, thrombocytopenia, hypercalcemia, and poor renal function have an adverse effect on EM for patients ≤70 (Table). In addition, anemia and bone lesions have an adverse effect on EM for patients >70.

Table 1. Impact of various diagnostic parameters on risk of EM in 2014-2018 stratified by age.

	18-65 years				66-70 years				>70 years			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Male (vs. female)	1.22 (0.93-1.61)	0.390	-	-	1.55 (0.90-2.13)	0.126	-	-	0.90 (0.77-1.06)	0.218	-	-
Hospital type of diagnosis Non-academic (vs. academic)	1.44 (0.77-2.71)	0.248	-	-	0.98 (0.49-1.95)	0.957	-	-	1.22 (0.85-1.76)	0.265	-	-
Prior malignancy Yes (vs. no)	0.74 (0.34-1.59)	0.435	-	-	1.04 (0.62-1.74)	0.879	-	-	1.15 (0.97-1.38)	0.113	-	-
% plasma cells ≥60% (vs. <60%)	1.54 (1.00-2.36)	0.048	-	-	1.93 (1.29-2.88)	0.002	-	-	1.64 (1.34-2.00)	<0.001	-	-
Thrombocytopenia	3.81 (2.13-6.81)	<0.001	2.31 (1.31-4.09)	0.004	2.99 (1.55-5.81)	0.001	2.46 (1.29-4.70)	0.006	2.34 (1.73-3.18)	<0.001	1.48 (1.07-2.00)	0.013
Type of paraprotein IgA (vs. IgG) Free light chain (vs. IgG) Other (vs. IgG)	0.86 (0.49-1.51) 1.27 (0.78-2.12) 1.60 (0.69-3.73)	0.594 0.337 0.278	- - -	- - -	0.93 (0.52-1.63) 1.24 (0.73-2.12) 1.65 (0.75-3.66)	0.789 0.424 0.214	- - -	- - -	1.00 (0.81-1.24) 1.27 (1.01-1.60) 1.44 (1.01-2.07)	0.963 0.044 0.043	- - -	- - -
ß2-microglobulin ≥3.5 mg/L (vs. <3.5 mg/L)	4.50 (2.41-8.39)	<0.001	2.72 (1.40-5.25)	0.003	2.34 (1.31-4.15)	0.004	-	-	3.17 (2.30-4.37)	<0.001	1.83 (1.32-2.55)	<0.001
Albumin <35 g/L (vs. ≥35 g/L)	2.60 (1.72-3.93)	<0.001	1.71 (1.10-2.64)	0.018	2.75 (1.78-4.24)	<0.001	1.80 (1.13-2.85)	0.013	2.73 (2.29-3.27)	<0.001	1.86 (1.54-2.24)	<0.001
Hypercalcemia	3.05 (2.00-4.66)	<0.001	1.84 (1.16-2.91)	0.009	3.82 (2.50-5.83)	<0.001	2.10 (1.30-3.39)	0.002	2.71 (2.27-3.25)	<0.001	1.71 (1.44-2.07)	0.013
Poor renal function	3.98 (2.62-6.07)	<0.001	1.60 (1.01-2.54)	0.045	2.76 (1.79-4.24)	<0.001	1.92 (1.21-3.05)	0.006	2.20 (1.83-2.64)	<0.001	1.34 (1.11-1.63)	0.002
Anemia	1.83 (1.29-2.59)	0.002	-	-	1.96 (1.29-2.97)	0.001	-	-	2.42 (2.06-2.85)	<0.001	1.34 (1.30-1.83)	<0.001
Bone lesion	2.63 (0.93-7.39)	0.409	-	-	1.71 (1.04-2.79)	0.033	-	-	1.75 (1.45-2.13)	<0.001	1.51 (1.24-1.85)	<0.001
Cytogenetic risk High-risk (vs. standard-risk)	2.11 (1.26-3.54)	0.004	-	-	3.25 (1.97-5.38)	<0.001	-	-	1.16 (1.59-2.32)	<0.001	-	-

Abbreviations: HR, hazard ratio; CI, confidence interval. P-values in bold indicate statistical significance

Summary/Conclusion: In summary, EM among MM patients improved from 1999 onwards. Nevertheless, EM remains high, especially for patients aged >70 years. Patients at risk for EM may benefit from better supportive care or individualized anti-MM therapy.

EP1021 IMPACT OF T(11;14) ACCORDING TO INDUCTION REGIMEN IN NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS: LONG TERM FOLLOW-UP OF GEM05MENOS65 PETHEMA/GEM STUDY

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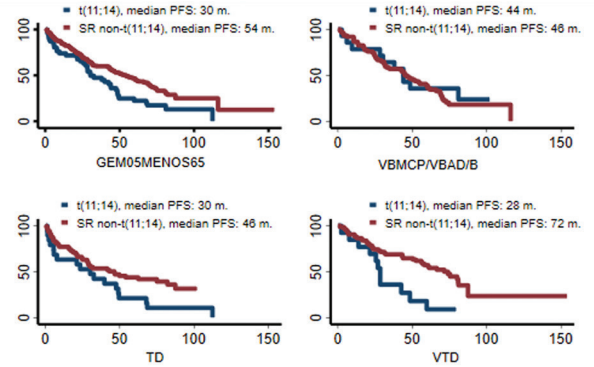


Figure 1. Progression free survival between patients with t(11;14) and SR non-t(11;14) in the GEM05MENOS65 global series and according to treatment arms.

Background: t(11;14) is the most frequently IgH rearrangement in multiple myeloma (MM) with a 15-20% prevalence and is considered a standard-risk cytogenetic abnormality (SR). However, t(11;14) is controversial since recent reports describe inferior outcomes in contrast to other SR patients.
Aims: To analyze the long-term outcome of t(11;14) compared with the remaining SR population in transplant-eligible (TE) patients included in the GEM05MENOS65 study.
Methods: From April 2006 to August 2009, 386 TE patients with newly diagnosed symptomatic MM were randomized to receive three induction regimens: six 4-week cycles of TD (thalidomide 200 mg daily; dexamethasone 40 mg on days 1-4 and 9-12) vs. six 4-week cycles of VTD (TD at identical doses plus iv bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11) vs. combination chemotherapy plus bortezomib (4 cycles of alternating VBMCP and VBAD chemotherapy followed by two cycles of iv bortezomib). All patients were planned to undergo autologous stem cell transplant (ASCT) with MEL-200 followed by maintenance therapy with thalidomide/bortezomib vs. thalidomide vs. alfa-2b-interferon for 3 years.
Results: A total of 53 (16%) patients were positive for t(11;14) but 7 patients harboring concomitant high-risk abnormalities were excluded. SR excluding t(11;14) were found in 215 (66%) patients. There were no differences in baseline characteristics among groups. In the overall series, there were no differences in overall response rate (ORR) after induction between patients with t(11;14) compared to SR (78 vs. 87%, p=0.1). However, the ≥VGPR and MRD negativity rates were lower in patients with t(11;14) (17 vs. 33%; p=0.03 and 6 vs. 33%; p=0.002). In the VBMCP/VBAD/B arm, there were no significant differences in ORR or CR rate after induction between patients with t(11;14) or SR. However, patients with t(11;14) treated with VTD had lower ORR and CR rates after induction than SR patients (ORR 85 vs. 97%, p=0.04; CR 15 vs. 38%, p=0.1). Patients with t(11;14) treated with TD had lower ORR and CR rates although the differences were not statistically significant (ORR 63 vs. 78%, p=0.2, CR 5 vs. 11%, p=0.4). In the overall series, on an intention-to-treat basis, the ORR after ASCT (65% vs 76%, p=0.1) as well as the CR and MRD negativity rates were lower for patients with t(11;14) (CR 28 vs. 45%; p=0.04, MRD negative 20 vs. 42%; p=0.01).
With a median follow-up of 63.4 months, median progression free survival (PFS) in the overall series was shorter for patients with t(11;14) (30 vs. 54 months; p=0.004). No differences in median PFS were observed in the VBMCP/VBAD/B arm (44 vs. 46 months; p=0.7). However, shorter PFS was observed in patients with t(11;14) in the TD (30 vs. 46 months; p=0.03) and VTD arms (28 vs. 72 months; p=0.003) (Figure 1). In the overall series, there were no differences in the overall survival (OS) between t(11;14) and SR patients. However, patients with t(11;14) treated in the VBMCP/VBAD/B arm showed shorter median OS than SR patients (66 months vs. not reached; p=0.03). In contrast, median OS was not reached in patients with t(11;14) or SR in both, TD and VTD arms.
Summary/Conclusion: In our study, bortezomib and thalidomide-based induction regimens (VTD/TD) are suboptimal in patients with t(11;14) concerning response rates and PFS than SR patients, although this does not impact on OS. Patients with t(11;14) receiving induction with chemotherapy have the same response and PFS than SR patients but display a shorter OS. These results should be confirmed in larger series.

EP1022 RISK OF MULTIPLE MYELOMA AND OTHER MALIGNANCIES AMONG FIRST- AND SECOND-DEGREE RELATIVES; A POPULATION BASED STUDY OF10035 PATIENTS IN NORWAY WITH MULTIPLE MYELOMA

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Background: The occurrence of two or more cases of multiple myeloma (MM) in the same family has been decribed in several countries whereas population-based studies on MM and other malignancies beyond first-degree relatives are scarce.
Aims: We wanted to investigate the risk of multiple myeloma (MM) and other malignancies in first- and second-degree relatives of MM patients based on information from the Cancer Registry of Norway (CRN).
Methods: All cases of MM diagnosed between January 1, 1982 and December 31, 2013 were retrieved. Population based control probands were retrieved in 4:1 and matched by year of birth, sex and county of residence. First-degree relatives for a given proband consisted of parents, siblings, and children. Second-degree relatives consisted of grand-parents, uncles and aunts, nephews and nieces, and grandchildren.
We used a Cox proportional hazards model to estimate the risk, denoted by the hazard ratio (HR), for MM and other malignancies in relatives of MM patients versus relatives of controls. An individual became at risk for a given cancer diagnosis after the date of birth or at the start of cancer registration (1953). Follow-up ended at the date of diagnosis of the cancer of interest, date of emigration, date of death, or end of study December 31, 2015. We adjusted for sex of the relatives, sex of the proband, and 15-y calendar period of birth in all analyses. The association between exposure and a diagnosis of MM was evaluated in all relatives. For MM, associations in subtypes of first- and second-degree were assessed. HR with 95% confidence intervals not including one were considered statistically significant.
Results: We included 7487 of 10035 MM patients diagnosed between January 1, 1982 and December 31, 2013 and 26 511 matched controls. The actual study population of relatives consisted 65 168 relatives of MM-patients and 223 643 relatives of matched controls.

Table 1.Hazard ratios for MM in relatives of MM patients vs. relatives of controls

	Cases‡	HR† (95% CI)
All relatives	101/182	1.89(1.40-2.57)*
All first-degree relatives	91/167	1.89(1.37-2.61)*
Offspring	31/49	1.90 (1.20-2.98)*
Siblings	17/27	2.29 (1.09-4.84)*
Parents	43/91	1.77 (1.23-2.55)*
All second-degree relatives	10/15	1.99(0.86-4.57)
Grandchildren	1/4	0.68 (0.07-6.20)
Grandparents	1/4	0.81 (0.09-7.31)
Uncles/aunts	3/4	2.25 (0.53-9.63)
Nieces/nephews	5/3	4.76 (1.19-18.9)*

* †Adusted for sex of the relatives, sex of the proband and 15y calendar period of birth,‡ Cases in 65 168 relatives of MM patients/cases in 223 643 relatives of controls,* 95% confidence interval not including one

First-degree relative of MM patients had approximately 2-fold increased risk for a MM diagnosis.
In second-degree relatives of MM-patients, no overall significant association with an MM diagnosis was observed. However, for nieces or nephews of MM patients, a significant association was found.
Summary/Conclusion: Overall, being a first-degree relative of MM patients was associated an approximately 2-fold increased risk for acquiring a MM diagnosis compared to relatives of controls. In second-degree relatives of MM-patients, no overall significant association with an MM diagnosis was observed. This was also true for subgroups, except for nieces or nephews of MM patients who had an icreased risk based on small numbers.

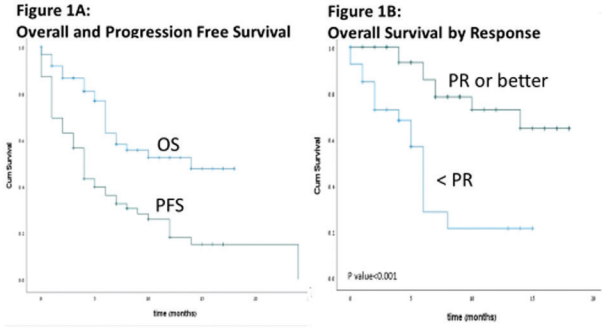
EP1023 BELANTAMAB MAFODOTIN TREATMENT FOR PATIENTS WITH RELAPSED/REFRACTORY MYELOMA VIA GSK EXPANDED ACCESS PROGRAM: REAL-WORLD DATA

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Background: Belantamab mafodotin (GSK2857916), an immuno-conjugate targeting B-cell maturation antigen, showed single-agent activity in the phase 1 and 2 studies in heavily pre-treated patients, and was recently approved for patients with relapsed/refractory multiple myeloma (RRMM) after 4 lines of therapy, including a proteosome inhibitor, immunomodulatory agent and an anti-CD38 monoclonal antibody. Real-world data and long-term follow-up are lacking.
Aims: To assess safety and efficacy of belantamb mafodotin therapy administered via the GSK expanded access compassionate care program for treatment of RRMM patients in a multi-site real-world setting.
Methods: All consecutive RRMM patients who received at least two doses of belantamab mafoditin under the expanded access compassionate care program in 9 Israeli centers were included. Data were extracted from medical charts focusing on demographics, disease characteristics, prior treatment, safety including ocular toxicity and disease responses. Primary endpoint was progression free survival (PFS), secondary endpoints included safety with focus on ocular toxicity, overall response rate (ORR), overall survival (OS), safety and tolerability.
Results: Sixty-seven RRMM patients, treated with belantamab mafodotin between July 2019 and February 2021 were included. Median follow-up was 16.1 (95% confidence interval [CI] 11.2-20.9) months. Median age was 70 (range 36-88) years. Forty-seven percent had a high-risk cytogenetic profile, including t(4;14), t(14;16), t(14;20), del17p and +1q). Patients were heavily pretreated with a median of 5 [IQR 4-7] prior therapy lines. Exposure rates to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab were 100%, 73%, 91%, 77% and 92%, respectively. Sixty-five percent and 23% were triple and penta- refractory, respectively. Median number of cycles was 4 (range 2-17) per patient. The maximal dose was 3.4 mg/kg and 2.5 mg/kg in 36% and in 56% of patients, respectively. Twenty-five percent (n=73) of the cycles beyond inital dose were delayed. Reasons for delays were mainly ocular toxicity (65%) followed by hematological (11%) toxicity and infections (5%). Ocular toxicity (keratopathy) occurred in 41 of 62 evaluable patients (66%). Worst ocular toxicity was grade 1, 2 and 3 in 10%, 23% and 32%, respectively. Resolution of grade ≥2 ocular toxicity to grade 1/0 was documented in 74% of the patients. Hematologic side effects included thrombocytopenia (39%, grade≥3: 31%), neutropenia (13%, grade≥3.9%) and anemia (9%, grade≥3.6%). Two grade 3 bleedings (epistaxis and upper gastrointestinal bleeding) were reported among patients with thrombocytopenia grade 3-4. Frequent non-hematologic adverse events included infection (10%, grade≥3: 6%) and elevation of liver enzymes (10%, grade≥3: 4%). Four patients (6%) discontinued therapy due to toxicity (ocular in all cases). ORR was 54%. Best response rates were: complete response, very good partial response, partial response, minor response, stable disease and progressive disease in 6%, 23%,25%,11%,14%, 20% of the patients, respectively. Median PFS was 4.4 (95% CI 3.3-5.5) months in the entire cohort and 8.8 (95% CI 6.2-11.3) months among responders (patients achieving PR or better, **figure 1A**). Median OS was 14 (95% CI NE) months. Among responders, median OS was not reached vs. 6 (95% CI 5.2-6.7) months in non-responders (p<0.001, **figure 1B**).



Summary/Conclusion: Belantamab mafodotin shows significant anti-myeloma activity in heavily pre-treated patients with RRMM in a real-world setting with a manageable safety profile.

EP1024 PHASE 3 STUDY OF DARATUMUMAB, BORTEZOMIB, MELPHALAN, AND PREDNISONE (D-VMP) VERSUS BORTEZOMIB, MELPHALAN, AND PREDNISONE (VMP) IN ASIAN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM): OCTANS

J. Hou [1,*], W. Fu [2], S.-M. Bang [3], H. Huang [1], K. Kim [4], W. Li [5], G. An [6], J.-J. Lee [7], Z. Cai [8], J. Jin [8], Y. Wang [9], C. S. Chim [10], M. Qi [11], J. Wang [12], X. Lu [13], Y. Song [13], B. Jia [14], X. Yang [14], W. Liu [13], Y. Li [13], R. Zhang [13], J. Wang [6]

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Background: Daratumumab (DARA), a human IgGκ monoclonal antibody that targets CD38, is approved for the treatment of NDMM in combination with standard-of-care regimens, including in combination with VMP based on results of the phase 3 ALCYONE trial. The phase 3 study OCTANS investigated the efficacy, safety, and pharmacokinetics (PK) of D-VMP in Asian NDMM patients.
Aims: To compare the efficacy, safety, and PK of D-VMP versus VMP in Asian and Chinese-only patients (NCT03217812).
Methods: Asian patients (from the following countries/regions: China, Hong Kong SAR, Taiwan, Korea, and Malaysia) with NDMM who were ineligible for autologous stem cell transplant were randomized (2:1) to D-VMP or VMP. Patients received 9 (42-day) cycles of bortezomib (1.3 mg/m^2 SC) twice weekly in Cycle 1 (Weeks 1, 2, 4, 5) then once weekly in Cycles 2-9 (Weeks 1, 2, 4, 5); melphalan (9 mg/m^2 PO) and prednisone (60 mg/m^2 PO) once daily on Days 1-4 of each cycle. Patients in the D-VMP arm received DARA (16 mg/kg IV) once weekly in Cycle 1, once every three weeks in Cycles 2-9, and once every four weeks thereafter until disease progression or unacceptable toxicity. The primary endpoint was the rate of very good partial response or better (≥VGPR). Key secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. DARA PK and minimal residual disease (MRD) negativity rates were exploratory endpoints.
Results: A total of 220 patients (Chinese patients, n=167) were randomized to D-VMP (n=146) or VMP (n=74). Baseline characteristics were well balanced between arms; median age was 69 (range, 57-84) years and 48 (21.9%) patients had high-risk cytogenetics. At the time of data analysis (clinical cutoff 02 Jul 2020), 51 patients (35.4%) in the D-VMP arm completed 9 treatment cycles and received DARA monotherapy; 20 (28.2%) patients in the VMP arm had completed all 9 cycles of treatment. After a median follow-up of 12.3 (range, 0.0-29.3) months, ≥VGPR rate was significantly improved with D-VMP versus VMP overall (74.0% vs 43.2%; odds ratio 3.57; 95% CI 1.99-6.43; *P*<0.0001) and among Chinese patients (74.6% vs 45.3%; odds ratio 3.51; 95% CI 1.76-7.00; *P*=0.0003). ORR was 88.4% with D-VMP and 78.4% with VMP. Median PFS was not reached in the D-VMP arm and was 18.2 months in the VMP arm (HR 0.43; 95% CI 0.24-0.77; *P*=0.0033); the estimated 12-month PFS rate was 84.2% in the D-VMP arm versus 64.6% in the VMP arm. PK results for DARA (overall population n=144; Chinese patients n=114) were comparable between the overall population and Chinese patients. The most frequent (≥10%) grade 3/4 TEAEs for the D-VMP/VMP arms were thrombocytopenia (46.5%/45.1%),

neutropenia (39.6%/50.7%), leukopenia (31.3%/36.6%), lymphopenia (30.6%/22.5%), pneumonia (29.2%/14.1%), anemia (24.3%/26.8%), and hypokalemia (13.2%/2.8%). TEAEs occurred at a similar rate in Chinese patients. Infusion-related reactions were observed in 44 patients (30.6%); the vast majority (n=41) were mild (grade 1 or 2). A total of 8 TEAE-related deaths (D-VMP, n=5; VMP, n=3) were reported. Additional data including the MRD negativity rate (10^{-5} threshold) will be presented.

Summary/Conclusion: The addition of DARA to VMP significantly improved efficacy outcomes for Asian patients with NDMM, consistent with results from the global ALCYONE trial. Safety profiles of D-VMP in an Asian population were also consistent with previously reported trials and no new safety concerns were identified. These data support the use of DARA plus VMP for the treatment of Asian and Chinese NDMM patients.

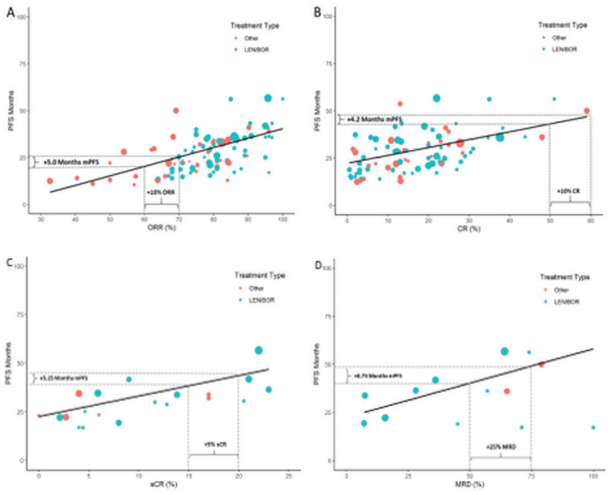
EP1025 OVERALL, COMPLETE, AND STRINGENT COMPLETE RESPONSE RATES AND MINIMAL RESIDUAL DISEASE AS POTENTIAL SURROGATES FOR PROGRESSION-FREE SURVIVAL IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background: The armamentarium of treatment for newly diagnosed multiple myeloma (NDMM) has recently expanded. Yet MM remains largely incurable and all patients inevitably relapse or fail treatment. Progression-free survival (PFS) is a common primary endpoint in NDMM trials; however, demonstrating improvements in PFS requires a larger sample size and longer follow-up compared with other endpoints.
Aims: Endpoints such as overall response rate (ORR), complete response (CR), stringent complete response (sCR), and minimal residual disease (MRD) may be clinically relevant surrogate endpoints; this study investigated their role as surrogates for PFS in NDMM.
Methods: Medline, Embase, and Cochrane databases were systematically searched for randomized controlled trials (RCT) studies published from 2010 to July 2020. Additionally, relevant congress abstracts from 2018 to 2020 were reviewed. Studies that reported ORR, CR, sCR, or MRD and median PFS were extracted. The correlations between PFS and ORR, CR, sCR, or MRD were estimated using Pearson's correlation weighted by sample size in each study arm. Surrogacy for PFS was evaluated using unadjusted and adjusted weighted linear regression models to estimate the gain in median PFS associated with each surrogate. Factors considered for adjustment included study year, age, sex, International Staging System risk stage, eligibility for transplant, and treatment type (lenalidomide/bortezomib [LEN/BOR] vs other). Optimal adjusted models were selected based on model fit statistics. Separately, a review of real-world evidence (RWE) studies was conducted following similar parameters to further investigate the association of MRD with survival.
Results: Seventy-five RCTs studies were identified with 101 study arms reporting median PFS. Final analysis datasets were developed that included study arms with valid pairs of median PFS with ORR (N=89), CR (N=87), sCR (N=20), and MRD (N=14). Moderate-to-strong significant correlations were observed for PFS with ORR (Pearson r=0.59), CR (r=0.48), sCR (r=0.68), and MRD (r=0.69). The unadjusted analysis models estimated an average increase of 0.50 (95% confidence interval [CI]: 0.36, 0.64), 0.42 (95% CI: 0.25, 0.58), 1.05 (95% CI: 0.58, 1.52), and 0.35 (95% CI: 0.12, 0.58) months of median PFS per percentage point increase in ORR, CR, sCR, and MRD, respectively (Figure 1). Following adjustment for age, and treatment type in the ORR model, and ISS risk stage in the CR model, the associations remained significant but were attenuated to 0.35 (95% CI: 0.21, 0.49) and 0.29 (95% CI: 0.16, 0.41) months of median PFS for each point of ORR and CR, respectively. Adjusted models could not be constructed for sCR or MRD models due to small sample size. The systematic review of RWE revealed 20 studies investigating the association between survival and MRD; 12 found significant ($p < 0.05$) survival benefit associated with MRD-negativity.

Figure 1. Scatterplots of ORR, CR, sCR, and MRD



Unadjusted linear model overlayed over raw data for A, ORR (%) vs PFS (months); B, CR (%) vs PFS (months); C, sCR (%) vs PFS (months); and D, MRD (%) vs PFS (months).
Note: Point size relates to the sample size of each study arm.
BOR: bortezomib; CR: complete response; LEN: lenalidomide; mPFS: median progression-free survival; MRD: minimal residual disease; ORR: overall response rate; sCR: stringent complete response

Summary/Conclusion: We demonstrated significant associations of PFS with ORR, CR, sCR, and MRD in NDMM, which may justify their use as surrogate endpoints to estimate PFS benefit in this population. Adjusted models estimate a 10% increase in ORR or CR is associated with 3.5 and 2.9-month increases in median PFS, respectively. The results of the exploratory MRD analyses of this study and RWE complement recent publications which have suggested that MRD-negativity is a viable surrogate endpoint for PFS in MM. The accumulation of evidence from multiple methodologies strengthens the argument that MRD is a suitable surrogate for PFS in NDMM.

EP1026 CHARACTERIZATION OF OCULAR ADVERSE EVENTS IN PATIENTS RECEIVING BELANTAMAB MAFADOTIN FOR ≥12 MONTHS: POST-HOC ANALYSIS OF DREAMM-2 STUDY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background: The B-cell maturation antigen–targeting antibody–drug conjugate belantamab mafodotin (belamaf; GSK2857916) is approved for the treatment of patients with heavily pretreated relapsed or refractory multiple myeloma (RRMM). Ocular symptoms (eg, dry eye, blurred vision, etc) and eye examination findings including keratopathy (superficial punctate keratopathy and/or microcyst-like epithelial changes) and changes in visual acuity are common with belamaf. These may be managed with dose modification (reduction and/or delay) or treatment discontinuation. Durable responses have been observed despite dose modifications. The safety profile of belamaf and longer-term management of ocular events need to be characterized more fully to optimize clinical care.

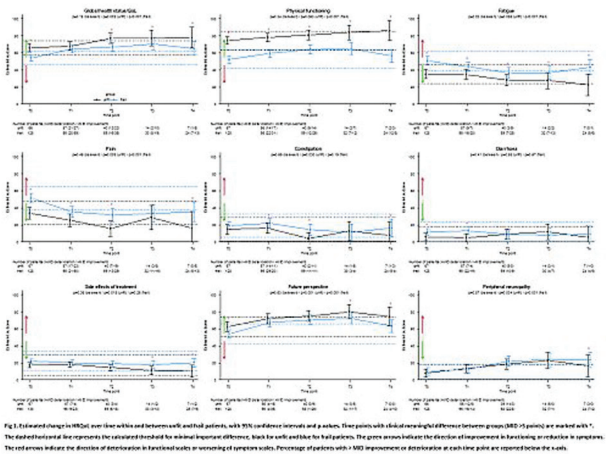
Aims: To characterize the safety profile of belamaf in patients treated for ≥12 months, in a *post-hoc* analysis of the 2.5 mg/kg Q3W arm of the open-label, Phase 2 DREAMM-2 study at 13-month follow-up.
Methods: Patients with RRMM who had ≥3 prior therapies and were refractory to an immunomodulatory agent and proteasome inhibitor and refractory and/or intolerant to an anti-CD38 monoclonal antibody received single-agent belamaf. Eye exams, including a corneal exam and assessment of best corrected visual acuity (BCVA) change, were conducted at baseline and prior to each dose. Dose modifications (delays/reductions) were made based on the most severe Keratopathy and Visual Acuity scale grading, which considers corneal exam findings and BCVA changes from baseline. Recovery was defined as Grade 1 exam findings/no exam findings, and ≤1-line decline in BCVA vs baseline. Patient-reported ocular symptoms were graded per CTCAE version 4.03.
Results: Of 97 patients randomized to the belamaf 2.5 mg/kg cohort, the clinical benefit rate (minimal response or better) was 36% at the 13-month cut-off. A total of 14 patients (15%) had received ≥12 months of treatment with 2.5 mg/kg Q3W belamaf at data cut-off. All 14 patients had experienced ≥1 ocular event (maximum grade of 2 [14%], 3 [79%], or 4 [7%]), and required ≥2 dose delays, with dose reduction (to 1.92 mg/kg) in 12 patients (86%). Dose delay or reduction permitted recovery of ocular events so that treatment could be restarted in all 14 patients. Patients underwent a mean of 3.6 dose delays over the ≥12 months of belamaf treatment (median: 3.5, range: 2–6). Median duration of dose delays was 41 days (range: 4–212). Ten patients (71%) required dose delays of >63 days. In general in this subset of 14 patients, long delays did not appear to negatively impact clinical response to belamaf: 12 (86%) had a clinical response (partial response or better; 11 [79%] for ≥6 months). In the subset of 14 patients analyzed here, all 14 had keratopathy. Ocular symptoms occurred in 13 patients (93%), most commonly blurred vision (57%), dry eye (36%), visual acuity reduced (21%), and photophobia (21%). No patients had permanent complete vision loss.
Summary/Conclusion: In this subset of patients receiving belamaf treatment for ≥12 months, dose modification was effective in managing ocular symptoms and decreasing findings at eye examination, and allowed patients the clinical benefit gained from continuing treatment with belamaf. The safety profile of belamaf will be further characterized in ongoing analyses and studies.
Funding: GlaxoSmithKline (Study 205678, NCT03525678). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

EP1027 HEALTH-RELATED QUALITY OF LIFE IN UNFIT AND FRAIL NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS TREATED WITH DOSE-ADJUSTED MELPHALAN-PREDNISONE-BORTEZOMIB

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Background: Frailty in non-transplant eligible (NTE) newly diagnosed multiple myeloma (NDMM) patients is associated with non-hematological toxicity which can negatively affect physical functioning (PF). Older patients increasingly prefer quality of life (QoL) and physical independence over length of life, highlighting the importance of health-related (HR)QoL assessment to take into account for treatment guidance. We here present the HRQoL results of the HOVON 123 trial. In addition to previous reports on HRQOL with MPV, we here present results by frailty level and also after completion of treatment for the first time.
Aims: To evaluate 2 year HRQoL in unfit and frail patients treated with MPV in the HOVON123 trial.
Methods: In this prospective phase 2 trial patients ≥75 years were treated with 9 dose-adjusted cycles MPV. Two HRQoL instruments (EORTC QLQ-C30 and MY20) were obtained at baseline (T0), after 3 (T1) and 9 (T2) cycles and after 6 (T3) and 12 (T4) months of follow-up for patients on protocol. Nine (3 functional; 6 symptom) subscales were presented as concepts relevant to patients: global QoL (GHS), PF, future perspective; fatigue, pain, constipation, diarrhoea, treatment side effects, and neuropathy (PNP, based on "tingling hands/feet" Q13 MY20). Baseline differences were analysed with independent t-tests, changes over time with linear mixed models. Minimal important difference (MID) from T0 within groups was defined as a score change of ≥1 SEM for multi-item scales or ≥0.5xSD for single-item scales. Cross-sectional clinically relevant superiority of one group was defined as MID≥5 between groups. HRQOL changes/differences were reported only when both statistically significant and clinically relevant (>MID). Analyses were based on only unfit and frail patients (based on IMWG-frailty index (Palumbo et al, 2015)).
Results: Of 238 included patients, 71 (30%) were unfit and 130 (55%) frail. Of those, 67 (94%) and 130 (100%) completed a baseline questionnaire. Compliance during T1-T4 was comparable between unfit and frail, ranging from 59-92%. At baseline, HRQoL was generally superior in unfit vs frail patients, which remained over time (Fig 1). In contrast, there was no difference in constipation, side effects and PNP between unfit and frail (Fig 1). When looking at unfit and frail patients separately, we observed that GHS, future perspective and pain improved, whereas PNP deteriorated in both groups. In addition, in frail patients also PF and fatigue improved, and in unfit patients constipation improved. Improvement in GHS, future perspective, pain, PF and fatigue was reached earlier in frail as compared to unfit patients (Fig 1). Importantly, these improvements were sustained after treatment completion. However, in frail patients a decrease in PF, fatigue and future perspective as compared to earlier time points was observed at T4 but still superior compared to baseline. With respect to PNP, a clinically relevant worsening was observed in both unfit and frail patients from T2 onwards.



Summary/Conclusion: In this first study reporting HRQoL in NDMM patients by frailty level, we show that unfit had a superior HRQoL as

compared to frail, both at baseline and follow-up. A HRQoL improvement over time was not only observed in unfit (4/9 scales) but importantly, also in the frail (5/9 scales) patients, who even showed an improvement at earlier time points. Only PNP worsened over time in both groups, as expected because of bortezomib treatment, however not negatively affecting physical functioning in those patients who completed 9 MPV-cycles.

EP1028 BRIDGE (OP-107): A PHASE 2 PHARMACOKINETIC STUDY OF MELFLUFEN PLUS DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND IMPAIRED RENAL FUNCTION

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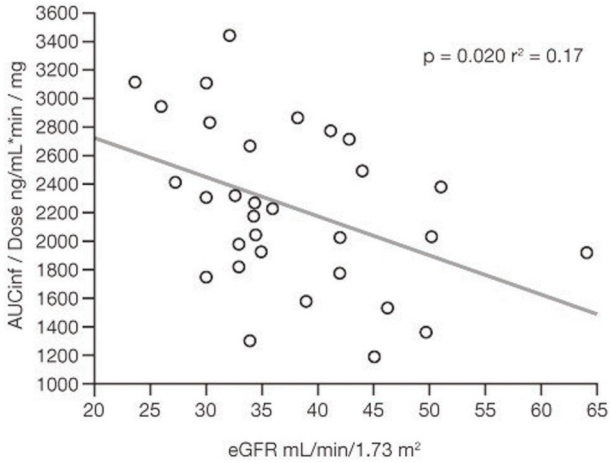
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Background: Melphalan flufenamide (melflufen) is an investigational first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and thereby rapidly delivers and releases alkylating agents inside tumor cells. It has shown promising clinical activity in relapsed/refractory multiple myeloma (RRMM). In cells, melflufen is rapidly metabolised to produce additional alkylating agents, including melphalan. Since melphalan, in contrast to melflufen, is partially cleared by renal elimination, it is important to assess the impact of renal impairment on melphalan pharmacokinetics (PK), particularly because impaired renal function is a common complication of RRMM.

Aims: The BRIDGE study aims to assess the relationship between renal function and the PK of melphalan in patients (pts) receiving melflufen for RRMM (NCT03639610).

Methods: BRIDGE is a phase 2, multicentre, open-label, single-arm study of pts with RRMM (following 2–4 lines of prior therapy). Informed written consent was obtained from pts with an estimated glomerular filtration rate (eGFR) of ≥30 to <45 ml/min/1.73m^2, who received 30 or 40 mg melflufen intravenously on Day 1, and 40 mg oral dexamethasone (20 mg for pts ≥75 yrs) on Days 1, 8, 15, and 22 of each 28-day cycle. PK sampling was performed 3 times in the first 2 cycles: 5–10 mins, 2–3 hrs, and 5–7 hrs after each melflufen infusion. Primary outcome measures were maximum observed concentration (C_{max}), area under the concentration versus time curve from 0 hrs to infinity (AUC_{inf}), and elimination phase half-life ($t_{½}$) of melphalan assessed using non-compartmental methods, and safety. Efficacy and renal function over time were also assessed.

Results: At data cut off (Nov 17, 2020), 31 pts had received melflufen (median age 71 yrs [range 52–85]; 52% male; median eGFR 35 mL/min/1.73m^2). Eighteen pts were evaluable for PK analysis. Dose-adjusted AUC_{inf} negatively correlated with eGFR ($p = 0.020$, $r^2 = 0.17$; Figure) and body surface area (BSA; $p = 0.006$, $r^2 = 0.23$; combined $r^2 = 0.44$). Dose-adjusted C_{max} negatively correlated with BSA ($p = 0.0009$, $r^2 = 0.32$) and $t_{½}$ negatively correlated with eGFR. 77% of pts had ≥1 Grade 3/4 treatment-emergent adverse event (TEAE), most commonly thrombocytopenia (58%), neutropenia (42%), and anemia (35%). Seven (23%) pts had ≥1 melflufen-related serious TEAE and 7 (23%) pts had TEAEs leading to melflufen discontinuation. Overall response rate was 48% and clinical benefit rate was 58%. Renal function remained stable; median pre-dose eGFR at Cycle 2 was 42 mL/min/1.73m^2.



Summary/Conclusion: For pts receiving melflufen in BRIDGE, exposure to melphalan increased with reduced eGFR, similar to what is observed during treatment with melphalan. The overall toxicity profile was as expected for melflufen and dexamethasone and no new safety signals were observed, supporting the use of melflufen in pts with moderate renal impairment. The optimal melflufen dose for pts with impaired renal function will be determined following recruitment of a second cohort of pts with severe renal impairment.

EP1029 PROGNOSTIC FACTORS AND OUTCOMES OF MULTIPLE MYELOMA PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 5 OR UNDER DIALYSIS

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Background: About one-third of the multiple myeloma (MM) patient are recognized to have renal impairment (RI) at initial diagnosis of MM and up to 10% of the patients present with RI severe enough to require dialysis. The prognosis of MM with RI has improved significantly over the past decade owing to the availability of new agents (including proteasome inhibitors and immunomodulatory drugs) and improvement of the supportive care measures. A recent data revealed an upward movement of survival curves after the introduction of bortezomib into the MM treatment. However, conventional staging systems are insufficient to prognosticate MM patient with RI.

Aims: This study aimed to investigate the prognostic factors and treatment outcomes in multiple myeloma patients with chronic kidney disease (CKD) 5 or patients under dialysis.

Methods: Patients who were confirmed multiple myeloma between January, 2001 to December, 2016 and had an estimated glomerular

filtration rate (eGFR) of less than 15 ml/min/1.73m^2 at the time of multiple myeloma diagnosis or receiving hemo- or peritoneal dialysis at the time of multiple myeloma diagnosis were included into the study. A total of 248 patients from 17 centers participating Korean multiple myeloma working party were analyzed. Renal reversibility was defined by international myeloma working group recommendation: renal complete response (CRrenal) as best eGFR of ≥ 60 ml/min/1.73m^2, renal partial response (PRrenal) of 30-59 ml/min/1.73m^2, and renal minor response of 15-29 ml/min/1.73m^2. Overall survival (OS) was defined by the date of MM diagnosis to the date of death by any cause or follow-up loss.

Results: Median age was 63.5 years (range, 32-91 years) and median eGFR was 8.9 ml/min/1.73m^2 (1.0- 40.0 ml/min/1.73m^2). 126 (50.8%) of the analyzed patients were under dialysis or were dialysated just after the diagnosis of MM. 79.4% of the patients received bortezomib and/or thalidomide (new agents group) as an induction regimen and 35.1% of the analyzed cohort underwent autologous stem cell transplantation (auto-SCT group). Dialysis stop rates were higher in the new agents group compared with no new agent group (49.5% versus 27.8%, P=0.088) and in the auto-SCT group compared with no auto-SCT group (77.6% versus 40.4%, P=0.000). With a median follow-up duration of 24.42 months (range, 0.20-134.93 months), the median OS in the total cohort was 46.83 months (95% confidence interval, CI, 29.39-64.27 months). OS was not different between the groups with or without new agents incorporated into the induction chemotherapy, but auto-SCT group showed a significantly prolonged OS compared with no auto-SCT group: 67.63 (95% CI, 36.07-99.19) vs. 40.60 months (28.94 - 52.26 months) (P=0.001). By the conventional international staging system (ISS) or revised international staging system (R-ISS), OS was not different between the groups. However, age (65 years or more), Eastern cooperative group performance status (2 or more), high risk cytogenetics by fluorescent in situ hybridization (FISH), and C-reactive protein (CRP) 1.0 mg/dL or more significantly affected OS by both univariate and multivariate analysis (Table 1).

Table 1. Univariate and multivariate analysis of factors affecting overall survival

	Univariate analysis		Multivariate analysis	
	HR	P-value	HR	P-value
Age				
< 65 years				
≥ 65 years	1.603 (1.093-2.350)	0.016	2.236 (1.250-4.002)	0.007
ECOG PS				
0 or 1				
≥ 2	2.117 (1.460-3.069)	0.000	2.201 (1.289-3.759)	0.004
Charson comorbidity index (renal disease excluded)				
0 or 1				
≥2	0.861 (0.584-1.269)	0.448		
BMI				
≥ 20 kg/m^2				
< 20 kg/m^2	1.735 (1.092-2.757)	0.020	0.997 (0.518-1.919)	0.993
serum albumin				
≥ 3.5 mg/dL				
< 3.5 mg/dL	1.835 (0.582-5.782)	0.300		
serum b2 microglobulin				
< 5.5 mg/L				
≥ 5.5 mg/L	1.835 (0.582-5.782)	0.300		
LDH				
≤ normal				
> normal	1.909 (1.289-2.828)	0.001	1.236 (0.736-2.077)	0.423
Cytogenetic risk by FISH				
Standard risk				
High risk	2.341 (1.423-3.850)	0.001	2.916 (1.620-5.250)	0.000
ISS				
I and II				
III	1.657 (0.529-5.222)	0.388		
R-ISS				
I and II				
III	1.601 (0.572-2.639)	0.065		
CRP				
< 1.0 mg/dL				
≥ 1.0 mg/dL	1.684 (1.099-2.580)	0.017	1.838 (1.020-1.313)	0.043

Abbreviation: ECOG PS, Eastern Cooperative Group performance status; BMI, body mass index; LDH, lactate dehydrogenase; FISH, fluorescent in situ hybridization; ISS, international staging system; R-ISS, revised international staging system; CRP, C-reactive protein

Summary/Conclusion: Autologous stem cell transplantation in MM patients with CKD5 or under dialysis is able to effectively reverse renal function and prolong overall survival. Conventional ISS or R-ISS was insufficient to predict survival outcome in this cohort. Other prognostic markers incorporating age, performance status, cytogenetics by FISH, and CRP should be considered for patients with poor renal function.

EP1030 A PHASE IA STUDY OF BISTHIANOSTAT, A NOVEL PAN-HDAC INHIBITOR IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): UPDATED RESULTS OF CH-020PI STUDY

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Background: Bisthianostat is a novel Histone deacetylase inhibitor (HDACi), derived by systematic optimizations on the basis of the thiazole-thiazoline core structure in natural HDACi Largazole (Nan et al., ACS Med Chem Lett. 2014). It displayed potent anti-MM activity as single agents and good synergistic effect with bortezomib both in vitro and in vivo. Herein, we presented our updated in-patient findings from CH-020PI study, an ongoing dose-escalating phase 1a study of bisthianostat in patients(pts) with RRMM(NCT03618602).

Aims: To investigate the safety, tolerability, pharmacokinetics, and efficacy of single-agent bisthianostat in pts with RRMM.

Methods: Adult pts with RRMM who had received ≥2 prior regimens were enrolled. Bisthianostat was administered orally on a twice-weekly schedule, in 4-week cycles, until progressive disease or unacceptable toxicities. The criteria of dose escalation were based on a modified Fibonacci method with dose increased by 100mg, 200mg, 400mg, and 600mg, respectively.

Results: As of Dec 29, 2020, 15 pts were enrolled at 4 dose levels from 100 to 600mg. The median age at enrollment was 60 years (range, 49-70 years). The median number of previous lines of therapy was 3 (range, 2-9) and included treatment with bortezomib (100%), ixazomib (13.3%), immunomodulatory drugs (lenalidomide/thalidomide, 93.3%). Among all treated pts (N=15), 93.3% of pts had treatment-emergent adverse events (TEAEs), which were mostly grade 1-2 (66.7%). Most common TEAEs (any grade, ≥20%) were: neutropenia (66.7%), urinary tract infection (33.3%), fever (20%), ECG QTc interval prolonged (20%) and diarrhea (20%). Grade 3/4 TEAEs were neutropenia (20%), anemia (6.7%) and pneumonitis (6.7%). Only one TEAE led to permanent treatment discontinuation in patient 009 (400mg cohort), who experienced QTc prolongation and was assessed as dose-limiting toxicity (DLT) per protocol. Later investigation indicated that this patient had QTc prolongation within 6 months prior enrollment. No further case of DLT or MTD was observed in cohort of 400mg and 600mg.

In the pharmacokinetic evaluation, for all of the 15 pts tested at day 1, the peak concentration of bisthianostat was reached within 0.5-2.25 h; half life time were 4.28-9.48 h; the mean C_{max} was 0.599, 1.11, 1.16, and 0.996 mg/mL at dose levels of 100, 200, 400 and 600 mg, respectively, and the mean $AUC_{0-\infty}$ was 2.07, 3.76, 5.53, and 4.68 h·mg /mL, respectively. The $AUC_{0-\infty}$ and C_{max} exhibited dose proportionality over the range of 100-200 mg, but they increased lower than dose-proportional manner from 200 to 400 mg. The exposure of bisthianostat at 600 mg was comparable to that at 400 mg. Similar results were found following multiple doses administration. Bisthianostat was not accumulated following a twice-weekly treatment.

The single-agent efficacy was modest. Of the 14 efficacy evaluable pts, seven pts (50%) experienced stable disease as their best response. One patient (004, 200mg cohort) remained stable for up to 6.5 months.

Summary/Conclusion: Bisthianostat proved to be well absorbed and tolerated. It exhibited modest anti-tumor efficacy in our cohort of RRMM pts. According to pharmacokinetic evaluation data, dose escalation will not proceed and a triple-weekly oral administration schedule is currently ongoing, Future trials in the combination with established MM therapy will be investigated in phase 1b study to enhance its efficacy via synergistic effect.

EP1031 TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH POMALIDOMIDE AND DEXAMETHASONE WITH OR WITHOUT SUBCUTANEOUS DARATUMUMAB: PATIENT-REPORTED OUTCOMES FROM APOLLO

D. M. Dimopoulos [1,*], E. Terpos [1], M. Boccadoro [2], S. Delimpasi [3], M. Beksac [4], E. Katodritou [5], P. Moreau [6], L. Baldini [7], A. Symeonidis [8], J. Bila [9], A. Oriol [10], M.-V. Mateos [11], H. Einsele [12], I. Orfanidis [13], K. S. Gries [14], J. Fastenau [14], T. Kampfenkel [15], Y. Qiu [16], H. Amin [14], P. Sonneveld [17]

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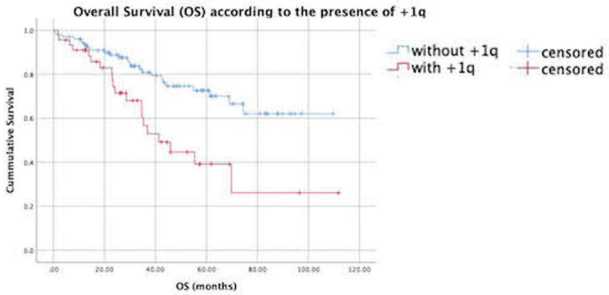
Background: Patients with relapsed/refractory multiple myeloma (RRMM) have a reduced health-related quality of life (HRQoL) compared with age- and sex-matched populations. In the phase 3 APOLLO study (NCT03180736), patients with RRMM who had received ≥1 prior line of therapy, including lenalidomide with a proteasome inhibitor, were treated with pomalidomide and dexamethasone (Pd) with or without subcutaneous daratumumab (D-Pd; 1800 mg, co-formulated with recombinant human hyaluronidase PH20 in 15 mL). The rate of progression or death was significantly lower with D-Pd (by 37%) vs Pd (median follow up, 16.9 months).
Aims: To present patient-reported outcomes (PROs) from the APOLLO study.
Methods: Patients were randomly assigned 1:1 to receive D-Pd or Pd in 28-day cycles until disease progression or unacceptable toxicity. Written informed consent was obtained from all patients. Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 item (EORTC QLQ-C30), EORTC QLQ Multiple Myeloma Module 20 item (MY20), and EQ 5D, PROs were assessed on Day 1 of each cycle. Intent-to-treat population with baseline and ≥1 postbaseline assessment were evaluated. Time to worsening was estimated using the Kaplan-Meier method, and treatment effect was evaluated using a mixed effects model with repeated measures.
Results: Overall, 304 patients (D-Pd: n=151, pd: n=153) were eligible. The median duration of treatment was 11.5 and 6.6 months in the D-Pd and Pd groups, respectively. At Cycle 16, 63 patients in the D-Pd group and 40 patients in the Pd group continued to be on treatment. The PRO compliance rates were similarly high in both groups. As measured with the EORTC QLQ-C30, pain reduced in D-Pd-treated patients (maximum improvement: 6.8 points at Cycle 12), and no mean change was observed in disease symptoms or treatment side effect subscales of the EORTC QLQ-MY20. Group mean physical and emotional functioning worsened from baseline in the Pd group (maximum worsening: 6.4 points at Cycle 4 and 9.1 points at Cycle 14) but was unaltered in the D-Pd group. A greater proportion of patients had a meaningful improvement from baseline with D-Pd vs Pd for disease symptoms (55.0% vs 49.0%), physical functioning (43.0% vs 35.3%), and emotional functioning (41.7% vs 31.4%). The median time to worsening was approximately 4 months, except for disease symptoms subscale, where the median time to worsening was approximately 10 months. No differences were observed between groups.
Summary/Conclusion: Combining daratumumab with Pd for the treatment of RRMM did not lead to any decrements in HRQoL. Some patients benefited from the combination through reduction in pain and clinically meaningful improvements in symptoms and emotional/physical function. These findings complement the clinical benefits of D-Pd in patients with RRMM and further support its use in this population

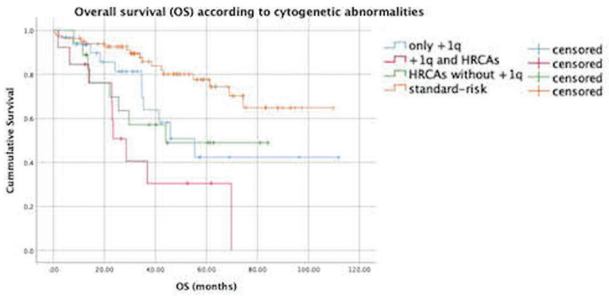
EP1032 GAIN IN CHROMOSOME 1 SIGNIFICANTLY IMPACTS SURVIVAL IN TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS

I. Paulos Mesquita [1,*], J. Vieira [1], S. Durão [1], E. Espada [1], H. Martins [1], I. Franco [2], C. Duarte [2], J. Raposo [1], G. Esteves [1]

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Background: Gain in chromosome 1q (+1q) is one of the most common recurrent cytogenetic abnormalities in multiple myeloma (MM). Previous studies indicate an association with inferior outcomes, but there is uncertainty about the prognostic impact of this abnormality relative to other high risk cytogenetic abnormalities (HRCAs).
Aims: To evaluate clinical characteristics, response to treatment and survival outcomes in newly diagnosed transplant-eligible MM patients (pts) with +1q
Methods: Single centre retrospective study including newly diagnosed transplant-eligible MM pts treated between January 2012 and December 2020, who had cytogenetic analysis by fluorescence in situ hybridization (FISH) performed at diagnosis. FISH abnormalities included +1q, del17p, t(11;14), t(4;14), t(14;16) and hyperdiploidy. +1q was defined by ≥3 copies of CKS1B locus (1q21), with a threshold of 3-5%. Clinical data were obtained by review of electronic medical records. Response evaluation was according to the International Myeloma Working Group (IMWG) criteria. HRCAs as defined by the Revised-International Staging System (R-ISS): del17p, t(4;14) and/or t(14;16).
Results: This cohort included 150 pts, with a median age of 60 years (range 35-72); 53.3% were male. 30.6% of the pts had documented +1q and 20.8% expressed HRCAs. All patients received bortezomib-based induction regimens, 42.0% in association with an immunomodulatory drug (IMiD) (thalidomide in 25.3% of the pts, lenalidomide in 16.7%), 52.0% with an alkylating agent and 4.0% with an anthracycline, followed by single autologous stem-cell transplantation (ASCT) in 74.0% and tandem ASCT in 16.0%. Median follow-up (FU) was 34.6 months (mo). Baseline clinical characteristics were similar in pts with +1q (gr 1) and without +1q (gr 2). There were also no differences in overall response rates to induction therapy between gr 1 and 2 (93.3% vs 89.9%; p=0.37). Overall survival (OS) and progression free survival (PFS) were compared between gr 1 and 2, and four other subgroups: standard risk cytogenetics (gr 3), presence of +1q alone (gr 4), presence of ≥1 HRCAs (gr 5) and presence of +1q and ≥1 HRCAs (gr 6). At median FU, OS was significantly lower in gr 1 compared with gr 2 (60.5% vs. 82.3%; p= 0.001), as was PFS (24.6% vs. 56.8%; p<0.001). OS was also lower in gr 4, 5 and 6, when compared with gr 3 [69.8% (vs 87.7%; p=0.019), 57.1% (vs. 87.7%; p<0.01) and 40.6% (vs. 87.7%; p=0.02), respectively], as well as PFS [23.0% (vs 67.0% p<0.001), 23.4% (vs. 67.0%; p=0.011) and 34.4% (vs. 67.0% p=0.032), respectively]. When comparing gr 1 and 2 according to induction regimen (IMiD vs non-IMiD), there was lower OS in gr 1 (56.0% vs. 80.9%; p=0.003) with non-IMiD-based regimens, but no difference with IMiD-based regimens (76.7% vs. 83.4%; p=0.288). In multivariate Cox-regression analyses including age, presence of HRCAs, presence of +1q, and IMiD-based induction regimens, +1q remained a significant and independent adverse factor for OS [HR 2.46 (95% CI 1.34-4.52); p=0.004] and PFS [2.13 (95% CI 1.34-3.38); p=0.001], whereas HRCAs only significantly impacted OS [3.03 (95% CI 1.61-5.72); p=0.001].





Summary/Conclusion: Our results corroborate the high prevalence of +1q in MM, although we found no association with any specific clinical characteristics at diagnosis. +1q had a significant negative impact in OS and PFS. IMiD-based regimens may have a beneficial effect in terms of survival in this subgroup of patients.

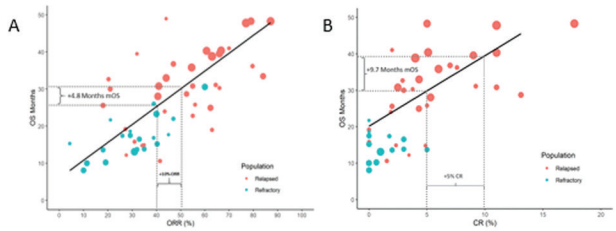
EP1033 OVERALL AND COMPLETE RESPONSE RATES AS POTENTIAL SURROGATES FOR OVERALL SURVIVAL IN RELAPSED REFRACTORY MULTIPLE MYELOMA

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Background: Several recent clinical trials in relapsed refractory multiple myeloma (RRMM) have demonstrated significant improvements in overall response rates (ORR), complete response (CR), and progression-free survival (PFS); however, few have reported improvement in overall survival (OS). As the "gold standard" for measuring the clinical benefits of a cancer drug, OS requires larger patient cohorts and longer follow-ups compared with other clinical trial endpoints.
Aims: The surrogacy of PFS for OS has been previously reported in RRMM; however, these analyses did not include most recent studies. This analysis aimed to investigate ORR and CR as potential surrogate endpoints for OS.
Methods: A systematic literature review of randomized controlled trials (RCTs) and single-arm studies in RRMM was conducted to identify studies that reported ORR or CR in addition to median OS. Medline, Embase, and Cochrane databases were systematically searched for randomized controlled trials published from 2010 to Jul 2020. Relevant congress abstracts from 2018 to 2020 were also reviewed. Correlations of OS with ORR and with CR were evaluated using Pearson's product–moment correlation weighted by study sample size. Unadjusted and adjusted weighted linear regression models were constructed to estimate the gain in median OS associated with each surrogate endpoint. Optimal adjusted models considered age, sex, study year, MM type, International Staging System risk stage, prior stem cell transplant, prior lines of therapy, and treatment type.
Results: Sixty-five studies were identified, including 55 treatment arms from 33 RCTs. Moderate-to-strong significant correlations were observed for median OS with ORR (Pearson r=0.79) and CR (r=0.57). The unadjusted absolute analysis models estimated an increase of 0.48 (95% CI: 0.39, 0.57) and 1.94 (95% CI: 1.36, 2.51) months of median OS on average for every additional percentage point of ORR and CR, respectively (Figure 1). Following adjustment for age, relapsed vs refractory MM, and study year, the association was essentially unchanged at 0.46 (95% CI: 0.34, 0.58) and attenuated to 1.17 (95% CI: 0.65, 1.69) months of median OS for each additional point of ORR and CR, respectively.

Figure 1. Scatterplots of ORR and CR with Unadjusted Linear Model



Unadjusted linear model overlayed over raw data for A, ORR (%) vs OS (months; and B, CR (%) vs OS (months).
Note: Point size relates to the sample size of each study arm.
CR: complete response; ORR: overall response rate; OS: overall survival; mOS: median overall survival

Summary/Conclusion: We demonstrated significant associations of median OS with ORR and CR, supporting the use of ORR and CR as surrogate endpoints for OS benefit in RRMM. Because MM is considered incurable, increasing survival is a key endpoint from both a clinical standpoint and a humanistic standpoint. Being able to predict survival outcomes through endpoints available earlier in a trial may help expedite the approval of novel therapeutics to address this unmet need. In addition, based on unadjusted analysis, there is a clear trend towards higher ORR and CR rates and longer survival among patients with relapsed disease compared with patients with refractory disease. Adjusted models estimated that a 10% increase in ORR predicts a 4.6 month increase in median OS, and a 5% increase in CR predicts a 5.85 month increase in median OS. Often, early phase trials provide initial evidence of treatment benefit, but the follow-up is not long enough to calculate OS. These results suggest that ORR results in initial trials can be used to project survival outcomes, thus potentially informing the design of subsequent trials and accelerating patient care and treatment.

EP1034 BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN HEAVILY PRETREATED MULTIPLE MYELOMA: OLD/NEW IN NOVEL AGENTS' ERA

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Background: Bendamustine is an old bi-functional alkylating agent which has proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM).
Aims: Thus, aiming to provide further insights in this field, also in novel agents'era, we present here a retrospective, real-life analysis of patients with relapsed/refractory MM (rrMM), who had received salvage therapy with bendamustine in combination with bortezomib and dexamethasone (BVD)
Methods: 81 patients (44 M/37 F), with rrMM, median age at diagnosis 59.4 years (r. 36-82), median age at start of treatment 63.6 years (r.37-86) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (B 90 mg/sqm days 1,2; V 1.3 mg/sqm days 1,4,8,11, D 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. All patients had previously received bortezomib-based and IMIDs-based treatments, and 32% (26/81) had also received radiotherapy. 69% (56/81) had undergone single or double autologous and three (2%) allogeneic stem cell transplant. All patients were relapsed and refractory to last therapies received before BVD.
Results: Bendamustine was well tolerated, with grade 3-4 transfusion-dependent anemia in 56% (46/81) of patients, and 43% (35/81) grade 3-4 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, ORR was 63% (51/81: 7 CR, 18 VGPR, 15 PR, 11 MR) with 11 PD and 19 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least

a PR, a bridge to second auSCT, and for two patients a bridge to allo-SCT. Eight patients have surprisingly achieved a notable PR after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide). Median time to response was 1.3 months (r.1-3), median OS from diagnosis was 67.3 months (r.6-151), median OS from start of Bendamustine was 9.6 months (r.2-36).

Summary/Conclusion: The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT, also after failure of novel agents.

EP1035 RAPID IMPLEMENTATION NATIONWIDE OF NEW TREATMENTS IN MULTIPLE MYELOMA, EXPERIENCE FROM MORE THAN 10.000 PATIENTS IN THE DANISH AND SWEDISH NATIONAL REGISTRIES.

C. Hveding Blimark [1,*], A. Juul Vangsted [2], T. W. Klausen [3], H. Gregersen [4], A. Gyula Szabo [5], E. Hermansen [6], G. Wålinder [7], D. Knut-Bojanowska [8], C. Zang [9], I. Turesson [10]

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Background: National registers including all multiple myeloma (MM) patients can give fast information on the implementation and effect of new treatment strategies. In Denmark ans Sweden MM patients have been registered at diagnosis of MM since 2005 and 2008, respectively. Data in characteristics, treatment and outcome is collected and the coverage is close to 100% coverage.

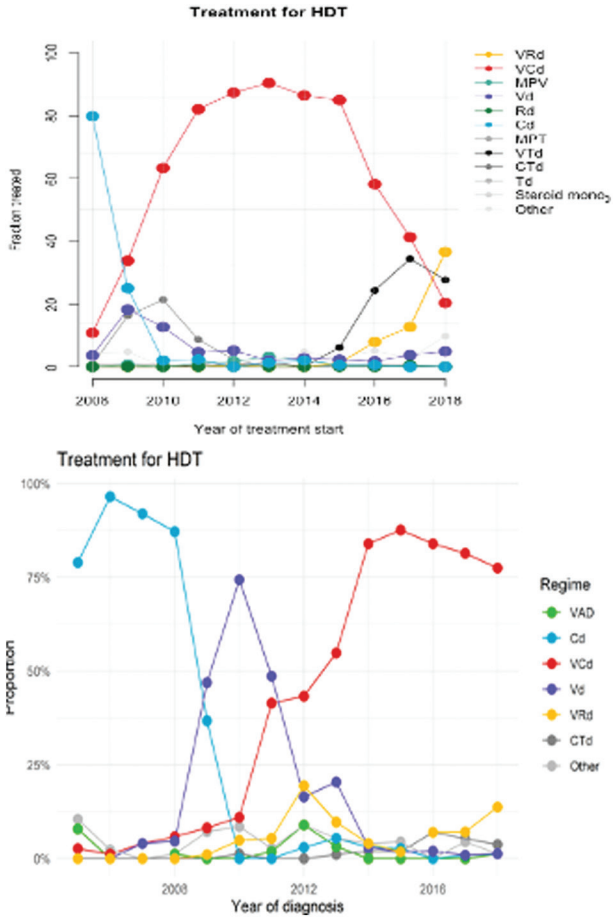
Aims: By merging the national databases in Sweden and Denmark where drug access and treatment guidelines are comparable and MM care universal, we study the implementation of guidelines and the effect of treatments in the real world.

Methods: We present treatment data from 10.062 patients annotated in the Danish Multiple Myeloma Registry (DMMR; n=4177) in the calendar period 2005 to 2018 and the Swedish Myeloma registry (SMR; n=5885) in the calendar period 2008-2018. Induction treatments for patients undergoing high-dose melphalan and autologous stem cell transplant, and first line treatment for patients with non-HDM/ASCT is presented.

Results: In both countries, 30% of newly diagnosed patients received HDM/ASCT upfront. Figure 1 A (above) and B (below) illustrate the use of induction treatment preceding HDT/ASCT for 1791 in Sweden, and 1281 patients in Denmark, respectively. Before 2010, induction treatment consisted of two-drug combinations of either cyclophosphamide/dexamethasone (Cydex) or bortezomib/dexamethasone (Vd) in both countries. Later, the 3-drug combination bortezomib/cyclophosphamide/dexamethasone (VCD) soon became a commonly used induction treatment. From 2015 an increasing proportion received 3-drug combinations containing an immunomodulatory drug (IMiD), a proteasome inhibitor (PI) and dexamethasone. In 2017-2018, the proportion of patients receiving induction treatment with VCD, thalidomide combinations and VRD was 79.8 %, 4.7% and 9.8 % in Denmark and VCD, VTd and VRD 32%, 32%, and 22% in Sweden, respectively.

In elderly patients, the use of 2-drug alkylator-based regimens melphalan/prednisone (MP) in Sweden and MP or CyDex in Denmark gradually shifted towards 2- or 3-drug combinations with an IMiD or a PI. In Sweden the use of MP decreased from 50 % in 2008 to 5 % in 2017-2018 and was replaced first by the combination of melphalan/thalidomide/prednisone (MPT) and later by melphalan/bortezomib/prednisone (MPV). In Denmark, a similar decrease in the use of MP was observed with a shift from MP to MPT followed by MPV. After 2015 an increasing proportion in both countries were treated with the combinations Vd and VCD while the use of lenalidomide-based combinations differed, with more patients treated with VRd in Denmark. In 2017-2018 the proportion of elderly patients treated with VD, VCD, Rd or VRD in 1st line were 13.1%, 20.7%, 8.7%, 15.0% in Denmark and 21%, 11%, 10%, and 7% in Sweden, respectively.

In the DMMR we show an increase in 5-year OS in patients ≤65 year from 59.8% in the calendar period 2008-2013 to 73.4% in the calendar period 2014-2019. In the same calendar periods an increase in 5-years OS was also noted for patients > 65 years from 27.5% (2008-2013) to 39.8% (2014-2019)(www.myeloma.dk). Similarly, in the SMR, in all patients diagnosed 2008-2019, the 5-year OS is now reaching 70% in patients ≤65 and 35% in patients >65 years (www.cancercentrum.se/Årsrapport2020).



Summary/Conclusion: National registries that include all MM patients are an important source of knowledge on treatment and outcome. Our data show that new treatment strategies are rapidly implemented in both countries in parallel with increased OS for all patient groups.

EP1036 DARATUMUMAB MONOTHERAPY IN NEWLY DIAGNOSED PATIENTS WITH STAGE 3B LIGHT CHAIN (AL) AMYLOIDOSIS: A PHASE II MULTICENTER STUDY BY THE EUROPEAN MYELOMA NETWORK

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Background: Light chain (AL) amyloidosis is a plasma cell disorder where amyloid deposition occurs in various tissues and organs. Heart is affected in most patients and cardiac dysfunction is the leading cause of death. Cardiobiomarker-based staging identifies patients with extremely

poor outcomes. These patients with stage 3B disease have a dismal prognosis of just a few months which despite recent advances has not been improved, mainly due to delays in hematologic responses and treatment-related toxicities. Daratumumab (DARA), a human IgG1κ monoclonal antibody which targets CD38, has shown rapid, deep, and high rates of response in patients with AL amyloidosis, and with a favorable safety profile.
Aims: The present analysis aims to evaluate the safety profile of DARA monotherapy in this high-risk population.
Methods: EMN22 is an open-label, multicenter, Phase 2 study aiming to enroll approximately 40 pts from 4 countries (Greece, the Netherlands, Italy, and France) with newly diagnosed stage 3B AL amyloidosis (i.e., with both a high sensitivity Troponin T (hsTnT) >54 pg/ml and NTproBNP ≥8500 pg/ml) who will receive primary therapy with DARA monotherapy. Pts initially received intravenous DARA, but from 2/2020 receive subcutaneous DARA at a fixed dose of 1800 mg, weekly for Cycles 1–2, every 2 weeks for Cycles 3–6, and every 4 weeks thereafter. Treatment continues until disease progression according to Major Organ Deterioration Progression-Free Survival (MOD-PFS) criteria, initiation of subsequent therapy, or a maximum of 2 years. Pts who do not achieve at least a hematologic VGPR, or hematologic PR with cardiac or renal response, may receive at Investigator's discretion additional treatment with Bortezomib (weekly for a maximum of 6 months) and low dose dexamethasone from Cycle 4. The current analysis includes pts who received the first dose of treatment at least 6 months prior to the cut-off date (31/01/2021).
Results: Overall, 7 pts were included. Median age was 65 years, and the majority were male (6 pts). Median baseline NT-proBNP and hsTnT levels were 33,442 and 166 pg/mL, respectively. ECOG Performance Status was 1 for 4 pts, 2 for 2 pts and 3 for 1 pt. Pts have received a median of 13 cycles, and until the cut-off date 4 pts are still on treatment; 3 pts died due to complications of the disease; no patient died due to treatment-related cardiac complications. In total, 6 pts had ≥1 adverse event (AE) grade 3 or 4, and 5 pts experienced ≥1 serious adverse event (SAE). No IRRs were reported. Most common grade 3/4 AEs were dyspnea (3 pts), atrial fibrillation (2 pts), and peripheral edema (2 pts). There were 10 SAEs reported: congestive heart failure (n=2, one of them fatal), dyspnea (n=2), atrial fibrillation, intracranial hemorrhage, muscle hemorrhage, sepsis (fatal), septic shock, and sudden death (1 pt each). Overall, 4 pts achieved a hematologic response (median time to first response <1 month), with 1 pt reaching PR, 2 pts VGPR, and 1 pt CR (also MRD negative). From the deceased pts, one died while in unconfirmed hematologic response while 2 pts had already discontinued treatment due to hematologic progression and major organ deterioration. The 6-month OS rate was 57.1%.
Summary/Conclusion: This early analysis shows that DARA monotherapy is safe with no treatment-related safety events or any signal of cardiac toxicity in patients with stage 3B disease. The enrollment in the study continues and more data will be available on safety and efficacy with the inclusion of additional patients in the updated analysis.

EP1037 PREDICTIVE FACTORS RELATED TO DISEASE PROGRESSION IN PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE IN A SINGLE CENTER DURING 9 YEARS

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Background: MGUS is the asymptomatic state of multiple myeloma and other plasma cell diseases.
Aims: To explore the disease progression rate and related factors in patients with monoclonal gammopathy of undetermined significance (MGUS).
Methods: NLP natural language processing technology and RegEx regular expression technology were used to mine clinical data from the medical hospital information system (HIS) of Peking Union Medical College Hospital and manage unstructured data. MGUS patients diagnosed from January 1, 2012 to January 31, 2021 were included, and demographic information, clinical data and follow-up results were recorded. A Cox regression model was established to evaluate the hazard ratio (HR) of various factors to the progression of multiple myeloma and other plasma cell diseases. According to the screened risk factors, a risk-stratification model was established to calculate the risk of disease progression (PD) under different risk strata.
Results: 1. A total of 1288 patients with MGUS were enrolled with a median age of 65 years (21-100), majority over 50 years old (86.3%). During a median follow-up of 41 months (3-127), 74 cases developed into plasma cell diseases such as multiple myeloma, Waldenström macroglobulinemia, POEMS syndrome and amyloidosis, with an average annual progression rate of 0.54%.
2. Univariate analysis of Cox regression model showed that a history of cancer (HR 5.260, P< 0.001), Fanconi syndrome (HR 5.268, P=0.021) and abnormal ratio of serum free light chain (sFLC) (HR 1.347, P=0.013) were risk factors for the disease progression of MGUS. Multivariate analysis suggested that serum M protein ≥15g/L (HR=2.778,95%CI 1.464-5.271, p=0.00176) and IgG M protein (HR=1.847,95%CI 1.006-3.391, p=0.04778) were risk factors for PD.
3. The Cox model was used to establish a risk stratification model. If two risk factors (M protein ≥15g/L, IgG type) were included, compared with the low-risk group (M protein <15g/L, non-IgG type), the relative risk (RR) of PD in the intermediate-risk group (1 risk factor) and high-risk group (2 risk factors) were 1.51 and 4.15, respectively. If three risk factors (a history of cancer was added) were included, compared with the low-risk group (none), the relative risk (RR) of progression in low-intermediate-risk, intermediate-high-risk and high-risk groups (1,2 and 3 risk factors, respectively) were 1.43,3.80 and 11.40, respectively.
Summary/Conclusion: During past 9 years, the disease progression rate of MGUS in our center is 0.54% per year. Serum level of M protein ≥15g/L, IgG M protein, a history of cancer are the predictive factors of disease progression. The annual disease progression rate of Asian MGUS is lower than that of European and American data.

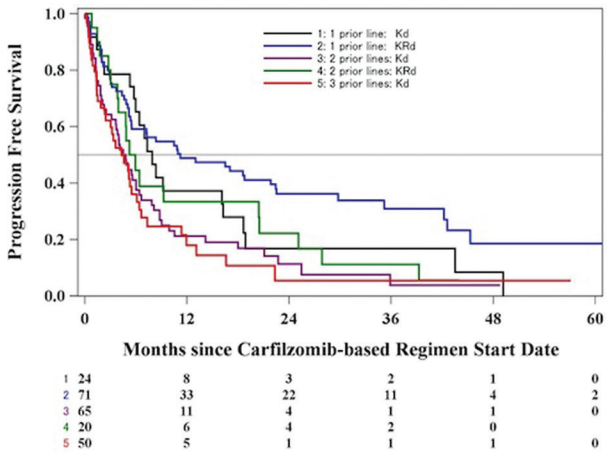
EP1038 CARFILZOMIB-CONTAINING REGIMENS FOR RELAPSED MULTIPLE MYELOMA IN A REAL-WORLD SETTING: A MULTI-INSTITUTIONAL REPORT FROM THE CANADIAN MYELOMA RESEARCH GROUP (CMRG)

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Background: Carfilzomib is approved for relapsed multiple myeloma (RRMM) based on 2 randomized controlled trials (RCTs). The ASPIRE trial of KRd after 1-3 prior lines (PLs) of therapy showed a progression-free survival (PFS) of 26.3 and overall survival (OS) of 48.3 mo,[1] while the ENDEAVOR trial of Kd reported a PFS of 18.7 and OS of 47.6 mo.[2] A recent analysis showed that >75% of patients (pts) with RRMM in routine practice would have been ineligible for pivotal RCTs.[3] Therefore, evaluation of the real-world (RW) efficacy of these regimens is needed.[4]
Aims: To evaluate the efficacy of carfilzomib-based regimens in a RW data set of pts with RRMM and 1-3 PLs of therapy.
Methods: We performed a retrospective study using the Canadian Myeloma Research Group Database (CMRG-DB), which includes >7500 MM pts from 15 Canadian sites and legacy data from 2007. All RRMM pts treated with approved carfilzomib-based therapies after 1-3 PLs analyzed up to 31/10/2020 were included. Primary outcome was PFS with each therapy; overall response rate (ORR), ≥very good partial response rate (VGPR), and OS were secondary outcomes. Survival was estimated using Kaplan-Meier methods.
Results: A total of 235 pts were identified: 139 treated with Kd and 96 with KRd. In the Kd group, 131 (94.2%) had prior PI and 93 (66.9%) had prior IMiD. For the KRd group, 93 (96.9%) had prior PI, and 19 (19.8%) had prior IMiD. In the Kd cohort, 24 (17.3%) of pts had 1 PL, 65 (46.8%) had two PLs, and 50 (36.0%) had three PLs of therapy. In

the KRd group, 71 (74%), 20 (20.8%) and 5 (5.2%) had one, two, or three PLs, respectively.
The ORR of the entire Kd cohort was 49.6%, with ≥VGPR in 27.0%. Median PFS was 5.2 mo and OS was 16.7 mo. By PL of treatment in the Kd cohort: ORR was 69.6%, ≥VGPR was 30.4%, median PFS was 7.92 mo and OS was 34.0 mo for pts with 1 PL; ORR was 48.1%, ≥VGPR was 28.9%, median PFS was 4.80 mo and OS was 19.69 mo for pts with two PLs; and ORR was 38.9%, ≥ VGPR was 22.2%, median PFS was 4.31 mo, and OS was 12.39 mo for pts with three PLs.
The ORR of the entire KRd cohort was 67.1%, with 53.2% of pts achieving ≥VGPR. The median PFS was 10.49 mo and OS was 42.84 mo. For 1PL, ORR was 66.1%, ≥VGPR was 50%, PFS was 11.21 mo, and OS was 42.84 mo; for 2PLs, ORR was 54.6%, ≥VGPR was 27.3%, median PFS was 5.61 mo, and OS was 15.52 mo. The 5 pts with three PLs were too few to evaluate separately.



Summary/Conclusion: In this real-world observational study, the responses and efficacy were less than that demonstrated in prospective RCTs. However, our findings are consistent with those reported by Chari et al in 208 patients with relapsed MM treated with KRd after a median of 2 PLs who experienced a median TTNT of 9.5 months[5] and in other real-world observational studies of carfilzomib-based regimens.[6,7] An improved understanding of the reasons underlying the difference in effectiveness, such as recent availability of more potent initial treatments, may lead to improved clinical decision-making and translate into better real-world outcomes.
1. Stewart et al, NEJM 2015 2. Dimopoulos et al, Lancet Oncol 2017 3. Chari et al, Clin Lymph Myel Leuk 2020 4. Richardson et al, Blood Cancer J 2018 5. Chari et al, Expert Rev Hematol 2020 6. Durie et al, Haematologica 2017 7. Danhof et al, Clin Lymph Myel Leuk 2015

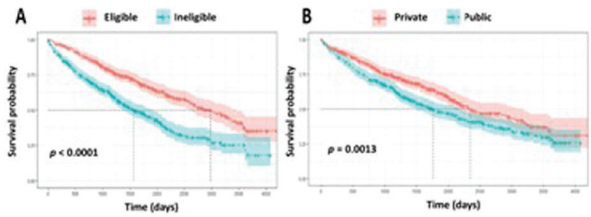
EP1039 MULTIPLE MYELOMA TREATMENT PATTERNS AND OUTCOMES IN THE PUBLIC AND PRIVATE HEALTHCARE SYSTEMS IN BRAZIL: ONE COUNTRY, TWO WORLDS - MMYBRAVE STUDY

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Background: Over the past two decades, the approval of several novel drugs has broadened therapeutic options for multiple myeloma (MM) patients, but has also raised concerns about increasing drug expenses and healthcare costs in general. Access to these treatments in public and private settings in Brazil differs significantly and it is unknown if shortcomings in treatment availability affect patient outcomes.
Aims: To understand the patient characteristics, treatment patterns and MM patient outcomes in private and public settings in Brazil.
Methods: MMyBrave is an observational, retrospective study with no control group. Eligible patients were diagnosed with active MM between January 1, 2008 and December 31, 2016 (cut-off date), at 17 public and private medical centers in Brazil. The MM diagnosis was performed at the discretion of the investigator. The data collection started on June 2018, after ethical approval, and progressed until August 2019. Sites with patients from both private and public sectors were considered hybrid centers.
Results: A total of 943 patients were included. Private, public and hybrid centers accounted for 49.3, 43.7 and 7.0% of patients, respectively. The mean age and male percentage at private, public and hybrid centers were 68.6, 68.5 and 66.0 years and 56.3, 51.2 and 50.0%, respectively. The International Staging System stages I, II and III and unknown stages were: 24.7, 24.1, 26.7 and 24.5 at private centers; 14.3, 18.4, 24.3 and 43.0 at public centers, and; 12.1, 19.7, 40.9 and 27.3% at hybrid centers. A total of 47.9% (41.8% public, 50.4% private and 7.7% hybrid) were eligible for stem cell transplantation (SCT). Proteasome inhibitor (PI) regimens (mainly regimens with bortezomib) were used by 50% at private centers (56% in SCT eligible (TE); and 44% in SCT ineligible (TI)), 11% at public centers (46% TE and 54% TI) and 8% at hybrid centers (80% TE and 20% TI). Regarding immunomodulator regimens (mainly thalidomide and rarely lenalidomide), 39% at private centers (53% TE and 47% TI), 71% at public centers (53% TE and 47% TI) and 80% at hybrid centers (58% TE and 42% TI). PI-immunomodulator regimens were used by 4% at private centers (93% TE and 7% TI) and 2% at public centres (17% TE and 83% TI). During the second-line treatment, PI regimens accounted for 46% at private centers, 31% at public centers and 17% at hybrid centers; immunomodulator regimens accounted for 27% at private centers (96% thalidomide and 4% lenalidomide), 57% at public centers (99% thalidomide and 1% lenalidomide) and 61% at hybrid centers (100% thalidomide). PI-immunomodulator regimens accounted for 16% at private centers and 3.0% at public centers. Less than 1% of patients have been treated with carfilzomib, daratumumab, ixazomib and pomalidomide. The median OS was 6.4 and 4.8 years ($p = 0.001$) for patients in the private and public systems; 8.2 and 4.3 years for TE (intention-to-treat population) and TI ($p < 0.0001$), respectively.

Figure 1: Kaplan-Meier overall survival curves for MM patients, eligible for SCT and ineligible (A) and private and public healthcare system (B).



Summary/Conclusion: Real-world MM patient outcomes at private and public institutions in Brazil were quite different. The superior OS among patients in the private healthcare system may be due, at least in part, to a wider availability of therapies enabling individualized management of MM patients.

EP1040 THE USE OF NON-CRYOPRESERVED AND CRYOPRESERVED HEMATOPOIETIC STEM CELLS FOR AUTOTRANSPLANTATION IN MULTIPLE MYELOMA.

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Background: Bone marrow (peripheral blood stem cells (PBSCs)) autologous transplantation is the standard care for transplant-eligible patients with multiple myeloma. This treatment option is somewhat limited due to the high consumption of economic resources and the access to

Cryobank. We performed a retrospective analysis of multiple myeloma patients who underwent autologous transplantation using non-cryopreserved and cryopreserved grafts at our institution from March 2016 to April 2020.
Aims: Compare the results of autologous transplantation using non-cryopreserved and cryopreserved hematopoietic stem cells (HSC).
Methods: 78 patients with MM were included in the study (male/female ratio 1.3:1).
All patients got the standard immunochemotherapy programs. They had remission (≥partial response) till the auto-HSCT. Patients were divided in two groups depending on the technique of HSC storage: non-CRYO (n=35) and CRYO (n=43). Cryopreservation is a standard method of storage of HSC suspension. In our work we used the native HSC suspension which was saved from +4 °C to +6 °C during 72 hours.
An effectivity and safety were evaluated in such parameters as the number of CD34+ and 7AAD- cells, colony-forming ability (CFA). All of these were made after apheresis and before reinfusion of HSC.
Additionally, the effectiveness of therapy was assessed according to the IMWG and MRD response criteria before SCT and on day +100.
Results: There were no differences in the total number of CD34 + cells x 10^6/kg, or in the level of 7AAD– cells, or in the total CFA. However, there was a significant difference in the percentage of loss of CD34+ cells from the moment of apheresis to the moment of reinfusion. We suppose it was caused adverse effects by temperature changes in CRYO group. In both groups, there were no severe infusion reactions on day 0. The adverse events were absent in the non-CRYO group. But 29/43 (67.4%) patients had such symptoms in the CRYO group on day 0 (nausea and vomiting – 7 patients (16,3%), tachycardia – 16 patients (37,2%), stenocardia – 3 patients (7,0%), arterial hypertension – 6 patients (13,9%), increased total bilirubin and indicator liver enzymes – 5 patients (11,6%)).
All patients had full recovery of hematopoiesis till discharge from the hospital. Neutrophil recovery was achieved at 11th day (range 9-14) and platelets at 12th day (range 8-19) in the non-CRYO group, and 10th day (range 8-14) and 12th day (range 8 -20) in the CRYO group, respectively.
The frequency of achieving a partial response before autoHSCT was 37% (13/35), a very good partial response - 40% (14/35), a complete response - 23% (8/35) in the non-CRYO group and 72% (31/43), 14% (6/43) and 14% (6/43) in the CRIO group, respectively. HSCT was improved the efficiency of treatment as well as the frequency of complete and MRD-negative responses in both groups. Partial response after autoHSCT was achieved in 23% (8/35) patients, very good partial response in 40% (14/35), complete response in 37% (13/35) in the non-CRYO group compared to the CRYO group (47% (20/43), 21% (9/43) and 32% (14/43), respectively).
The MRD status was assessed before and after autoHSCT in 48 patients. The frequency of MRD-negative response before autoHSCT was 37,5%, after transplantation – 54,5% in the non-CRYO group and 16% and 33% in the CRYO group, respectively.

Tab. 1. The results are presented in the comparison table of the evaluated parameters.

Parameters	Non-CRYO (n=35)	CRYO (n=43)	p
CD34 + (apheresis) x10^5 / kg	5,48±3,13	5,1±2,98	0,59
CD34 + (reinfusion) x10^5 / kg	2,71±1,36	2,49±1,17	0,44
7-AAD - (apheresis), %	98,65±1,64	99,11±1,35	**0,002**
7-AAD - (reinfusion), %	93,07±4,64	90,58±7,32	0,08
CFA, colonies 10^5/l (apheresis)	404,97±80,62	420,86±89,05	0,46
CFA, colonies 10^5/l (reinfusion)	306,71±138,66	257,55±126,46	0,14
Platelet transfusions, doses	4 (2-8)	4 (1-8)	0,35
Red blood cell transfusions, doses	1 (0-6)	1 (0-3)	0,18
Duration of hospital stay after HSCT, days	17 (13-26)	16 (11-24)	0,59
Febrile neutropenia, episodes	13 (37%)	21 (49%)	0,15
Enteropathy, cases	20 (57%)	13 (30%)	**0,02**
Mucositis, cases	15 (42%)	20 (46%)	0,37
Sepsis/bacteremia	0 (0%)	2 (5%)	
Pneumonia, cases	2 (6%)	2 (5%)	0,41
Mortality within 100 days after transplantation (%)	0 (0%)	0 (0%)	
No complications, number of patients (%)	6 (17%)	6 (14%)	0,35

Summary/Conclusion: The method of storage of PBSCs without cryopreserved is equal to traditional method controlled freezing with Dimethyl sulfoxide and can be used in hospitals which have no a Cryobank in their composition.

EP1041 MAINTAINING DELIVERY OF HIGH QUALITY SPECIALIZED CARE IN PATIENTS WITH MYELOMA DURING THE COVID-19 PANDEMIC: COMPARING 2019 TO 2020

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Background: The SARS-CoV-2 pandemic has caused innumerable social and economic consequences, has stressed health care systems, affecting the delivery of health care and raising concerns that many patients may have suffered delays in therapy and in the diagnosis of serious conditions, such as hematologic and other malignancies. This effect may be more pronounced in older patients, who are at higher risk for COVID-19 complications, but which may also be affected by social isolation and distancing, difficulties in reaching health care facilities and fear of acquiring the infection. Myeloma patients are a vulnerable, mostly elderly population who may have been affected in terms of diagnosis and treatment delivery during the pandemic. There is a concern that diagnosis may be delayed, potentially presenting with more advanced disease or more often with severe complications.
Aims: To provide evidence for the care of patients with myeloma, during the COVID-19 era, we compared the characteristics of newly diagnosed patients during 2020 and 2019 (i.e pre COVID-19 pandemic).
Methods: We compared baseline characteristics and short-term outcomes of newly diagnosed MM patients who were diagnosed and started therapy in a tertiary referral center (Department of Clinical Therapeutics, Athens) during two calendar periods, 2019 and 2020. Initial restrictive measures were first implemented in Greece in mid-February 2020 and national lockdown in mid-March. Data were collected through our prospectively maintained database that includes all patients with a diagnosis of myeloma in our center. Since the beginning of the pandemic in Greece, our department implemented preventive measures and operating procedures to ensure continuous delivery of care and reduce the risk of COVID-19 infection.
Results: In 2019, 125 MM patients with a new diagnosis of symptomatic disease started therapy vs 101 in 2020. The distribution of new cases per month was similar between the two years (p=0.542). Gender distribution was similar, but patients diagnosed in 2020 were slightly older (median 69 vs 66 years for 2019, p=0.084). There were no differences in baseline anemia, renal function, need for dialysis or ISS stage; however, slightly more patients had high risk cytogenetics in 2020 vs 2019 (37% vs 27%, p=0.129). The median time from the first test for the diagnosis to start of therapy was 15 days in 2019 vs 8 days in 2020. First line therapies were similar with the majority receiving a PI plus IMiD combination (mostly VRD: 70% in 2019 vs 76% in 2020). Radiotherapy due to MM-related complications was required in 2.4% vs 4% of patients in 2019 and 2020 respectively. Early mortality (death <3 months from start of therapy) was 2.4% in 2019 and 5% in 2020 (p=0.314). The number of autologous transplants was slightly smaller in 2020 vs 2019 (54 vs 61). Infection rates during induction, which may have been affected by the use of social distancing and protective measures, was similar (15% vs 16%); however, less patients required hospitalization for infection management in 2020 (in 8% vs 16% in 2019). Very few cases of COVID-19 occurred among our MM patients and in only one newly diagnosed MM patient.
Summary/Conclusion: Despite the pandemic, we did not observe significant delays or changes in the characteristics of patients that were diagnosed with myeloma between 2019 and 2020 in our center, neither in the short-term outcomes of our patients. Despite the pandemic it is possible to maintain delivery of high-quality specialized care in patients with myeloma.

EP1042 IXAZOMIB, LENALIDOMIDE AND DEXAMETHASONE IN ROUTINE PRACTICE: EXTENDED SUBGROUP ANALYSIS

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Background: Ixazomib, lenalidomide and dexamethasone (IRD) provide an efficient treatment for relapsed and/or refractory multiple myeloma (MM) based on the results of the TOURMALINE-MM1 study. Our recent analysis[1] showed that the IRD combination has a survival benefit over lenalidomide and dexamethasone alone (RD) in the routine practice.
In the registration trial, the subgroups with greater benefit included patients with 2 or 3 prior therapies, or 1 prior therapy without transplant. Our analysis showed better results in the first relapse with no adverse impact of previous autologous stem cell transplant (ASCT) on the outcome.
Aims: The aim of the present analysis was to determine which subgroups had adverse outcomes regardless of treatment used.
Methods: We assessed a group of 127 patients with relapsed and/or refractory MM treated with IRD and 217 patients with RD regimen. With known data on PFS (17,5 vs 11,5 months) and OS (36,6 vs 26,0 months) we looked for the subgroups who did not benefit from either therapy.
The analyzed parameters were: age (≤65, 66-75, >75 years), ISS stage, cytogenetics, presence of extramedullary disease (EM), line of treatment, maximal treatment response, pretreatment by proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) or ASCT, disease status (relapsed vs relapsed and refractory).
Results: We previously reported adverse impact of EM in both IRD and RD arms (PFS 6,5 and 10,5 months), decreasing PFS with number of prior lines (1 line 32.7 vs 14.8 months, 2 lines 23.1 vs 9.3 months, 3 lines 9.7 vs 9.0 months and ≥4 lines 5.0 vs 9.9 months), with increasing age (≤65 years: 23.0 vs 10.8 months, 66-75 years: 17.8 vs 11.5 months, >75 years: 11.1 vs 11.7 years), more advanced disease by ISS stage (ISS 1 32.7 vs 17.1 months, ISS 2 25.8 vs 9.7 months, ISS 3 9.9 vs 6.4 months), and that there was no adverse impact of previous ASCT – patients after ASCT did better in IRD than RD arm (PFS 23.0 vs 9.7 months).[1]
The subsequent subgroup analysis showed following results: There was only a limited number of patients with known high-risk cytogenetics (IRD 15, RD 19), still, with a trend to negative impact on PFS (7,3 and 9,9 months). Pretreatment with PIs did not significantly affect the outcomes. There was, however, negative impact of exposure to IMiDs in both IRD (PFS 11,3 months vs not reached) and RD arms (PFS 9,3 vs 18,0 months). Patients who were relapsed and refractory did worse to those who were relapsed only in both IRD (PFS 9,7 months vs not reached) and RD arms (PFS 6,0 vs 14,8 months).
Summary/Conclusion: Most of the subgroups that do not benefit with either treatment, correlate with either patient´s overall condition or the aggressiveness of the disease itself. Groups with worse outcomes were as follows: later relapse (≥4), higher age (≥75 years), the presence of high risk features – extramedullary disease, high-risk cytogenetics, higher stage (ISS 3) and refractory status in the previous line. We did not find an adverse impact of pretreatment by PIs or ASCT but patients with previous IMiDs had worse outcomes in both IRD and RD arms.
With support of AZV 17-29343A, NV18–03-00500, MH CZ – DRO (FNOl, 00098892), IGA-LF-2020-002.
1) Minarik J, Pika T, Radocha J. *et al.* Survival benefit of ixazomib, lenalidomide and dexamethasone (IRD) over lenalidomide and dexamethasone (Rd) in relapsed and refractory multiple myeloma patients in routine clinical practice. *BMC Cancer* 2021; **21:** https://doi.org/10.1186/s12885-020-07732-1

EP1043 RESPONSE-ADJUSTED ISS SCORE IN TRANSPLANT INELIGIBLE PATIENTS WITH MULTIPLE MYELOMA: DOES IT MATTER?

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Background: Achievement of the complete remission (CR) represents one of the most powerful prognostic indicators in patients (pts) with multiple myeloma, along with prognostic indices as International Staging System (ISS) and recently established Revised ISS score (R-ISS).
Aims: The aim of study was to analyze prognostic significance of Response-adjusted ISS (RaISS) in transplant ineligible MM pts.
Methods: The study included 257 newly diagnosed, transplant ineligible MM, diagnosed during period 2009-2020 (129 male; 128 female, mean age 66 yrs, range 35-85 yrs). The IgG myeloma was diagnosed in 155pts (60.3%), IgA in 50 (19.5%), BJ in 43 (16.7%), IgD in 3 (1.2%) and IgM in 1pt (0.4%). According to the clinical stage (CS, Durie-Salmon), patients were distributed as follows: III 207pts (80.5%); II 38pts (14.8%); and I CS 10pts (3.9%). Renal impairment was present in 82pts (31.9%) and elevated LDH in 58pts (22.6%). Regarding ISS score, the group included: ISS1 had 55pts (21.4%), ISS2 65pts (25.3%) and 137pts (53.3%) had ISS3. According to the Revised ISS (R-ISS) score, R-ISS1 was found in 40pts (15.6%), R-ISS2 in 164pts (63.8%), while R-ISS3 was present in 53pts (20.6%). Treatment with triple thalidomide (Thal) based chemotherapy (HT) was applied in 129pts (50.2%) with standard risk features (R-ISS1), while bortezomib (Bz) based triplets were applied in 95pts (37%) with high risk features (R-ISS2 and R-ISS3). Standard HT was applied in 33pts (12.9%).
Results: Considering RaISS score, the group of pts treated with Thal-based HT, consisted of: 15pts (11.6%) with low risk (RaISS 0-1); 65pts (50.4%) with intermediate risk (RaISS 2-3); and 49pts (40.3%) with high risk (RaISS 4). There was significant difference in PFS (Log Rank 7.197; p=0.027), and, even more pronounced, in OS (log Rank 22.192; p=0.000) between low risk pts (RaISS 0-1), and intermediate or high risk pts (RaISS 2-3; RaISS 4), treated with Thal-based HT. The distribution according the RaISS score in the pts group treated with Bz-based combos was as follows: low risk - 11pts (11.6%); intermediate - risk 36pts (37.9%); high risk- 48pts (50.5%). Although there was no difference in PFS (Log Rank 3.307; p=0.191), pts of low risk, with RaISS score 0-1, had significantly longer OS (Log Rank 13.894; p=0.001) in comparison to the pts of intermediate and high risk (RaISS ≥2), treated with Bz-based triplets. There was no difference in PFS (Log Rank 0.008; p=0.930) or OS (Log Rank 0.502; p=0.479) between pts with RaISS 4, and pts with R-ISS 3 (Log Rank 0.008; p=0.930) treated with Thal-based HT. Likewise, no difference was found considering PFS (Log Rank 0.168; p=0.682) and OS (Log Rank 0.923; p=0.337) in patients treated with Bz-based triplets with RaISS 4 in comparison to the pts with R-ISS3.
Summary/Conclusion: RaISS score represents simple and powerful prognostic tool. Compared to R-ISS scoryng system, it seems that tailored treatment approach according to the R-ISS, overcomes high-risk features in patients with multiple myeloma.

EP1044 CHARACTERISTICS AND OUTCOME OF TRANSPLANT INELIGIBLE MYELOMA PATIENTS ACHIEVING SUSTAINED PARTIAL RESPONSE VS. THOSE EXHIBITING COMPLETE REMISSION AFTER 1ST LINE THERAPY: SINGLE CENTER REAL-WORLD DATA

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Background: Complete remission (CR) is an important prognostic factor for overall survival (OS) in Multiple Myeloma (MM). The prognostic significance of sustained partial response (sPR) defined as PR >24

months, however, may be a sufficient goal in MM patients, ineligible for transplant (NTE). The characteristics of NTE MM patients who achieve sPR and its prognostic role has not been sufficiently explored.
Aims: Herein, we investigated the characteristics, the prognostic impact and OS rates of NTE patients achieving sPR, compared with those who achieve CR after induction therapy.
Methods: We studied 255 patients (M/F: 130/125, median age: 68, range: 43-83, IgG: 151. IgA: 64, light chain: 31, non-secretory: 9), who were considered eligible for analysis among 487 consecutive NTE MM diagnosed and treated in our department between 2001-2019; 62 fulfilled the criteria of sPR whereas the rest (n=193) achieved CR after induction treatment. Importantly, patients in CR were considered as eligible for analysis if OS exceeded 24 months. The 2 groups were compared for standard prognostic factors such as age, International Staging System (ISS) and revised ISS (RISS), β2 microglobulin (β2M), lactate dehydrogenase (LDH), hemoglobin (Hb) and estimated glomerular filtration rate (eGFR). Comparisons were performed with Pearson's x^2 test, Mann-Whitney-*U*-test and One-Way ANOVA. Prognostic factors for the type of response (sPR vs. CR) were evaluated with binary logistic regression analysis; OS was plotted with Kaplan-Meier; $p<0.05$ was considered as statistically significant boundary.
Results: Median age at diagnosis was higher in the sPR group. Patients with sPR had better performance status, higher eGFR and less often anemia, abnormal LDH, and advanced stage (ISS3/RISS3) at diagnosis ($p<0.05$). With regard to molecular cytogenetics overall, high-risk features were less common in the sPR group ($p<0.05$); in particular, t(4;14) was not detected in any patient with sPR vs. 10% in the CR group, whereas del17p was found in 2% of patients with sPR vs. 14% in the CR group ($p<0.05$); the rate of t(14;16) or 1q+ did not differ between groups ($p>0.05$); 71% of patients with sPR was treated upfront with novel agents compared with 24% of those in the CR group ($p<0.05$). Overall, 65% of the studied population received 2nd line therapy (sPR vs. CR group: 51% vs. 69%; $p<0.05$). Age >65, RISS1/2 and absence of anemia (Hb<10g/dL) were independent predictors for achieving sPR vs. CR ($p<0.05$). In the univariate analysis for OS, established markers such as ISS, RISS and LDH confirmed their prognostic value for the whole study population ($p<0.05$). In addition, type of response (sPR vs. CR) was an independent prognostic factor for OS after adjustment for the type of initial therapy (HR: 0.59; p=0.009). Patients who achieved sPR exhibited significantly longer OS compared with those achieving CR (84 months vs. 59 months; p=0.008). In the multivariate analysis, RISS was the strongest prognostic factor for OS (HR: 0.32; p=0.002).
Summary/Conclusion: Patients who achieve sPR represent a unique group of NTE MM patients with higher age and favorable prognostic characteristics. Achievement of sPR was a positive prognostic factor for OS, which led to 41% reduction of the risk of death; this latter finding supports that probably in a subgroup of NTE MM patients with favorable features, therapeutic strategy should not always aim for CR, at the expense of safety and quality of life.

EP1045 EFFICACY AND SAFETY OF DARATUMUMAB FOR THE TREATMENT OF MULTIPLE MYELOMA: A SERIES OF COCHRANE REVIEWS

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Background: Daratumumab has approved indications for the treatment of patients with newly diagnosed multiple myeloma (NDMM) both eligible and ineligible for transplant and treatment of relapsed or refractory multiple myeloma (RRMM).
Aims: To evaluate the efficacy and safety of daratumumab for transplant-ineligible NDMM patients (PICO 1), transplant eligible NDMM patients (PICO 2), and for RRMM patients (PICO 3).
Methods: For each PICO we conduct one Cochrane review according to the standard methodology as outlined in the Cochrane Handbook for Systematic Reviews of Interventions, and assess the certainty in the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Our prioritised outcomes were overall survival, adverse events (CTCAE grade ≥3), serious adverse events, and quality of life.
Results:
Transplant-ineligible NDMM (PICO 1): We identified two RCTs (MAIA, ALCYONE) reporting on 1443 patients. Treatment with daratumumab probably increases overall survival (HR 0.67, 95% CI 0.5 to 0.85, I^2 39%, moderate-certainty evidence), results in a slight increase of adverse events (grade ≥3) (RR 1.05, 95% CI 1.0 to 1.11, I^2 26%, high-certainty evidence) and may increase serious adverse events (RR 1.14, 95% CI 0.86 to 1.51, I^2 85%, very low-certainty evidence) compared to treatment without daratumumab. More people receiving daratumumab probably gain at least 10 points of global health status after start of treatment when compared to people receiving no daratumumab (RR 1.13, 95% CI 1.13 to 1.23, I^2 0%, moderate-certainty evidence).
Transplant-ineligible NDMM (PICO 2): We identified two RCTs (CASSIOPEIA, GRIFFIN) reporting on 1292 patients. GRIFFIN included 207 patients, but did not report any of our crucial outcomes. Treatment with daratumumab may increase overall survival (HR 0.52, 95% CI 0.33 to 0.82, low-certainty evidence), results in a slight increase of adverse events (grade ≥3) (RR 1.06, 95% CI 1.0 to 1.13, high-certainty evidence) and people may experience less serious adverse events (RR 0.91, 95% CI 0.73 to 1.14, I^2 52%, low-certainty evidence) when compared to treatment without daratumumab. More people receiving daratumumab may gain at least 10 points of global health status after start of treatment compared to people receiving no daratumumab (RR 1.07, 95% CI 0.91 to 1.24, low-certainty evidence) at 9.0 months after start of treatment.
RRMM (PICO 3): We identified four RCTs (CANDOR, CASTOR, LEPUS, POLLUX) reporting on 1717 patients. Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab (HR 0.62, 95% CI 0.49 to 0.79, I^2 7%, moderate-certainty evidence). Two studies reported safety outcomes for 1044 patients. Treatment with daratumumab probably results in a slight increase of adverse events (grade ≥3) (RR 1.17, 95% CI 1.04 to 1.31, I^2 64%, moderate-certainty evidence) and probably increases serious adverse events when compared to treatment without daratumumab (RR 1.21, 95% CI 1.09 to 1.35, I^2 0%, moderate-certainty evidence). More people receiving daratumumab may gain at least 10 points of global health status after start of treatment compared to people receiving no daratumumab (RR 1.07, 95% CI 1.07 to 1.22, I^2 0%, low-certainty evidence) at 9 months after start of treatment.
Summary/Conclusion: Treatment with daratumumab is likely to retrieve gain in survival, but increases the risk of grade ≥3 and serious adverse events and may contribute to a clinically important improvement of quality of life compared to treatment without daratumumab.

EP1046 ASSESSING TIME TO DETERIORATION IN HRQOL IN PATIENTS WITH MULTIPLE MYELOMA USING VENETOCLAX IN COMBINATION WITH BORTEZOMIB AND DEXAMETHASONE COMPARED WITH PATIENTS USING BORTEZOMIB AND DEXAMETHASONE

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Background: Patients with MM experience treatment and disease-related symptoms that impact their daily living and health-related quality of life. Among patients with MM the commonly reported disease symptoms that impact patient daily life include pain, and fatigue (Gonzalez-McQuire, MDM Policy Pract. 2019). BELLINI (M14-031, NCT01794520) phase

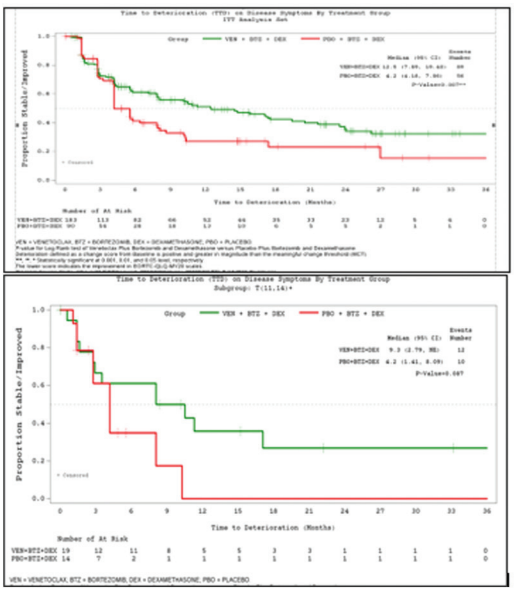
3 double-blind randomized clinical trial compared venetoclax (ven) in combination with bortezomib (bort) and dexamethasone (dex) compared with placebo (pbo), bort and dex. The primary study results readout in 2019 reported that the primary endpoint of PFS (HR 0.63, 95% CI=0.44-0.89) was achieved but higher risk of death (HR 2.027, 95% CI=1.04-3.95) was observed in the treatment (trt) arm compared with pbo arm (survival data not yet mature; Kumar, S et al. EHA Library. Jun 16 2019;273254:LB2601).

Aims: The current analysis compared time to deterioration (TTD) in patient-reported outcomes (PROs) as measured by the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires (PROs assessed at Cycles 1, 3, 5, 7 and every other cycle starting cycle 9) between the M14-031 study groups

Methods: BELLINI enrolled adult patients with RR MM with exposure to 1-3 prior lines of therapy. For current analysis, meaningful change thresholds (MCTs) for the EORTC-QLQ-C30 (Osoba et al 1998), and EORTC-QLQ-MY20 (Sully et. al 2019) measures were defined using published literature. For each PRO domain, meaningful deterioration was defined as a change of at least one unit of the scale specific MCT at any time point after the baseline observation. Kaplan-Meier (KM) curves and corresponding nominal log-rank P-value were used to assess differences between trt arms (reported for the overall and t(11;14) positive sub-group).

Results: The intention-to-treat (ITT) dataset included 194 pts (≥65 years: 56%; 2-3 prior lines: 46.1%) in the trt group and 97 pts (≥65 years: 54%; 2-3 prior lines: 51.5%) in the pbo group. The t(11;14) positive sub-group included 35 patients of which 20 were in the ven arm and 15 in the pbo arm. For the ITT population, delay in TTD was observed for the EORTC QLQ-MY20 disease symptom domain (e.g., bone aches or pain, back pain, hip pain) in the trt group compared with the pbo group (12.5 vs. 4.2 Months; P = 0.042; Figure 1). TTD in EORTC QLQ-MY20 disease symptom domain was longer but not statistically significantly in the trt group compared with the pbo group in the t(11;14) MM sub-group (Figure 1). KM analysis for the EORTC QLQ-C30 domains indicated delay in cognitive functioning deterioration for the trt group versus the pbo group (4.6 vs. 4.2 months; P = 0.042). No statistically significant differences were observed in TTD between the two study groups for the EORTC QLQ-C30 emotional (P = 0.437), physical (P = 0.754), role (P = 0.623) functioning domains, fatigue (P = 0.829) and global health status/quality of life (P = 0.623) domains.. In multivariate Cox proportional hazard model, reduction in the risk of deterioration in EORTC QLQ-MY20 disease symptoms domain was estimated at 38% (hazard ratio;95% CI: 0.62; 0.44 - 0.88) in the trt group compared with the pbo group.

Figure 1: Time to Deterioration on Disease Symptoms Measures Using EORTC QLC-MY20, Overall and t(11;14) Sub-Group



Summary/Conclusion: In this analysis of the M14-031 PRO data, delays in TTD were observed in in the ven-based trt arm compared with the pbo group for the myeloma-specific disease symptom domain. This finding was consistent in the overall ITT population and positive trend in the t(11;14) sub-group. Smaller sample size for the t(11;14) positive sub-group likely limits drawing meaningful inferences.

EP1047 DISCREPANCIES IN ETHNIC DIVERSITY OF PATIENTS ENROLLED INTO UK MULTIPLE MYELOMA CLINICAL TRIALS

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Background: The incidence of multiple myeloma (MM) varies with ethnicity with black patients (pts) approximately twice as likely to develop MM to white pts or Asians (males, black: white 2.9; females, black: white: 2.2 (median, source: CRUK)). Despite this, a lower proportion of black pts have been reported to be enrolled into clinical trials. In some countries, survival may be inferior and appear to be linked to access to treatments and other socio-economic factors. If these are corrected, survival appears to be similar to white pts. However, it is unknown if these discrepancies exist in a state funded health care system with intended equitable access to treatments.

Aims: The primary aim was to assess the proportions of ethnic groups enrolled into clinical trials in the UK National Health Service (NHS). Secondary aims were to determine differences in patients enrolled into early phase vs late phase trials by ethnicity, sex and age; to assess the ethnic diversity of MM pts attending MM clinics and compare if the same diversity was observed in clinical trial enrolment, to assess the overall survival (OS) of patients enrolled into clinical trials by ethnic group.

Methods: Cross-sectional population-based analysis was assessed in participants enrolled into MM clinical trials from 2014 to 2021 in a large specialist MM centre receiving referrals from across the UK. Age, sex and ethnicity was determined by electronic health records. Ethnicity was divided by White, Black, Asian and Mixed/Other. Statistical analysis was performed by one-way ANOVA, Fisher's exact test and Chi-squared (GraphPad Prism version 9).

Results: 182 pts (Phase I/II: 57; Phase II/III: 125) from 25 clinical trials were assessed. The ethnicity was: white 143 (79%), black 23 (13%), Asian 8 (4%), mixed/ other 7 (4%). The black: white ratio was 0.16 . This discrepancy was more marked for Phase I/II trials: white 49 (86%), black 5 (9%), Asian 2 (4%), mixed/other 0 (0%); black: white 0.10 than Phase II/III trials: white 94 (75%), black 18 (14%), asian 6 (5%), mixed/ other 7 (6%); black: white 0.19. Male: female ratio was 1.38 in keeping with incidence of MM by sex. The median age of patients enrolled was 65 years (range 38-85) which is lower than expected for the population. Within the MM clinics (n=192 over a 4 week period), ethnicity was again skewed to white pts but less so than trial enrolment: white 124 (65%), black 32 (17%), Asian 15 (8%), mixed/ other 19 (10%); black: white 0.25. Comparing ethnicity within clinics and clinical trial enrolment, there was a lower proportion of non-white pts enrolled into trials, p=0.0038 and this was particularly observed for Phase I/II trials, p=0.0014. However, there was no significant difference in white: non-white pts between clinic and Phase II/III trial enrolment, p=0.0804. There was also a lower proportion of mixed/ other pts enrolled into clinical trials, p= 0.0247.

Despite these differences, the OS for those pts enrolled into clinical trials by ethnicity was not significantly different (p=0.4352). OS (years): white: 10.9, black: 11.8, Asian 15.1, mixed/ other 13.5.

Summary/Conclusion: The proportion of ethnic minorities enrolled into MM clinical trials was lower than expected compared to the incidence of MM in the UK. This was particularly apparent in Phase I/II clinical trials where patients are referred from a wider geographical area. Further research is required to understand and improve ethnic diversity into MM trials in state funded health care systems.

EP1048 DETECTION OF CIRCULATING TUMOR CELLS IN MULTIPLE MIELOMA BY FLOW CYTOMETRY AND CLINICAL SIGNIFICANCE

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Background: The improvement and practical application of high-sensitive molecular biological assays to detect of tumor cells has made it possible not only to determine the circulating tumor cells (CTCs) in the peripheral blood and to measure them quantitatively, but also to analyze their morphological and immunophenotypic characteristics. The use of multi-color flow cytometry makes it possible to characterize the biological features of tumor myeloma cells not only in the bone marrow, but also to identify the population of such cells in the peripheral blood.
Aims: The aim of the study was to investigate the immunophenotypic features of bone marrow tumor plasma cells (BM PLCs) and circulating tumor plasma cells in multiple myeloma (CTC MM) in comparison with the clinical features of the disease.
Methods:: A parallel immunophenotypic study of bone marrow (BM) and peripheral blood (PB) samples was performed in 34 patients with a newly diagnosed MM by 4-color flow cytometry (FACSCalibur (Becton Dickinson, USA). Bone and extramedullary plasmocytomas were detected in 10 MM patients with stage III disease, and chronic renal failure (CRF) was detected in 24 patients. The isolation of tumor PLCs was carried out from a gate of CD38-positive (bright) plasma cells against a lateral light scattering (SSC) signal, and at least 500,000 events were included in the analysis. The expression of CD138, CD45, CD56, CD19, CD20, CD79b, CD11c, CD33, CD28, CD117 was determined. Quantitative assessment of PLCs was carried out by the content of CD38+(bright) cells in terms of all nucleated cells of BM and/or PB.
Results: In all patients with newly diagnosed MM, CTCs MM was characterized by significantly lower expression of CD138, CD56, CD28, and CD79b compared to BM PLCs.
The immunophenotypic profile of CTCs compared to BM PLCs in patients with plasmocytomas was characterized by a significant decrease (p=0.0003) in the expression of syndecan-1 (CD138), and a significant (p=0.0004) increase in the content of CD138-negative and CD19-positive PLCs in the population. In patients with MM, not complicated by plasmocytomas, a significant (p=0.03) decrease in the expression of CD138 and CD28 (p=0.02) in the CTCs compartment was revealed. CD79b expression on CTCs MM was significantly more frequently detected in extramedullary plasmocytomas. When comparing BM PLCs in MM patients with or without kidney lesions, no significant differences in the frequency of antigens were obtained. The high content of PLCs positive for CD138, CD56, CD11c, CD28, CD79b was noted. CTCs MM in patients with renal lesions were characterized by the same phenotype as BM PLCs, as well as significantly more frequent positive expression of CD56. CTCs MM in patients with MM without impaired renal function were characterized by reduced expression of CD138, CD28. Thus, in the case of kidney damage in patients with MM, a large number of cells positive for CD138, CD56, CD28 enter the circulation, which is not observed in the absence of this complication.
Summary/Conclusion: Our study has shown that in MM with a complicated course, the identified CTCs subclone has a unique immunophenotypic protein expression profile, characterized by a less "mature" phenotype and variable expression of adhesive molecules (CD138, CD56), which increases their ability to enter the peripheral blood from the bone marrow and cause extramedullary lesions. The data obtained are consistent with the literature data on the significant role of CD138-negative cells in MM, less "mature" phenotype, and resistance to chemotherapy.

EP1049 CILTACABTAGENE AUTOLEUCEL VERSUS SELINEXOR + DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) TREATED WITH ≥3 LINES OF PRIOR THERAPY: A MATCHING ADJUSTED INDIRECT COMPARISON

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Background: Multiple myeloma (MM) remains incurable and relapses are common despite new treatment options. Most patients eventually progress despite an increasing armamentarium of anti-myeloma drugs such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies. Recycling of previous treatment regimens is often the only alternative available for these patients, which highlights the need for new drug targets and treatment options. The chimeric antigen receptor (CAR) T-cell therapy ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) has two BCMA–targeting single-domain antibodies designed to confer avidity. Initial results from the phase 1b/2 CARTITUDE-1 study (NCT03548207) have shown that a single infusion of cilta-cel yielded early, deep, and durable responses with a manageable safety profile in patients with heavily pretreated RRMM. To date, cilta-cel has not been directly compared with other therapies in development for RRMM in clinical trials. A systematic literature review using PRISMA guidelines identified selinexor + dexamethasone as a potential non-BCMA-targeting comparator in the triple-class exposed RRMM patient population.
Aims: To compare efficacy outcomes in patients who received cilta-cel in CARTITUDE-1 to those who received selinexor + dexamethasone in the STORM trial (Part 2; NCT02336815).
Methods: CARTITUDE-1 included triple-class exposed patients who received ≥3 prior lines of therapy or were double refractory to an IMiD and PI, had ECOG score of ≤1, and disease progression ≤12 months after the last line of therapy. Unanchored matching-adjusted indirect treatment (MAIC) comparisons were performed based on individual patient-level data from 97 infused patients in CARTITUDE-1 and published aggregate-level data from STORM Part 2 (N=122). Patients from CARTITUDE-1 (N=73) who matched the eligibility criteria for STORM Part 2 (penta-drug exposed, ≥ triple-class refractory, and refractory to daratumumab and last line of treatment) were included in the analysis. Individual patient data for time-to-event outcomes from STORM Part 2 were simulated based on the published Kaplan-Meier curves. CARTITUDE-1 patients were matched to the modified intent-to-treat population from STORM Part 2 on available prognostic factors identified from the literature and based on clinical expertise using propensity score weighting methods. Outcomes included overall response rate (ORR), complete response or better (≥CR), progression-free survival (PFS), and overall survival (OS). For ORR and ≥CR, the relative effects of cilta-cel versus selinexor + dexamethasone were quantified using odds ratios (OR) and 95% confidence intervals (CI) derived from a weighted logistic regression analysis, while time to event endpoints were analyzed using a weighted Cox proportional hazards model. A similar comparative analysis was performed which included all enrolled patients in CARTITUDE-1.
Results: Cilta-cel was associated with statistically significant improvements in ORR, ≥CR, PFS, and OS versus selinexor + dexamethasone in a population matched to STORM Part 2 (Table). Similarly, cilta-cel was associated with higher efficacy in the comparative analysis which included all patients enrolled in CARTITUDE-1.

Outcome*	Cilta-cel vs. selinexor + dexamethasone mITT
ORR, OR (95% CI)	121.17 (34.16, 429.83)†
≥CR, OR (95% CI)	111.13 (24.09, 512.60)†
PFS, HR (95% CI)	0.16 (0.09, 0.31)†
OS, HR (95% CI)	0.24 (0.12, 0.49)†

*Patient populations from CARTITUDE-1 (N=73; penta-drug exposed, ≥ triple-class refractory, and refractory to daratumumab and last line of treatment) and STORM Part 2 (N=122) were matched on refractory status, cytogenetic risk, and R-ISS; †P<0.0001.
CR, complete response; CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; OR, odds ratio; OS, overall survival; PFS, progression-free survival; R-ISS, revised international staging system.

Summary/Conclusion: These analyses demonstrated improved efficacy with cilta-cel versus selinexor + dexamethasone for ORR, ≥CR, PFS, and OS, highlighting its potential in patients with heavily pretreated RRMM.

EP1050 IXAZOMIB VERSUS LENALIDOMIDE OR IXAZOMIB AND LENALIDOMIDE COMBINATION AS MAINTENANCE REGIMEN FOR PATIENTS WITH MULTIPLE MYELOMA: INTERIM ANALYSIS OF A MULTI-CENTER PROSPECTIVE STUDY IN CHINA

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Background: Maintenance therapy deepens response and prolongs progression free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) after frontline regimens. Ixazomib, a 2nd generation oral proteasome inhibitor (PI), has been approved for maintenance therapy because of the convenience and tolerability.
Aims: We conducted this prospective multi-center study to compare the efficacy and safety of Ixazomib (I-MT) or Ixazomib plus Lenalidomide (IL-MT) to Lenalidomide (L-MT) as maintenance regimen in NDMM patients.
Methods: This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and registered (NCT04217967). NDMM patients were enrolled from 7 centers of North China MM Registry, since September 2019. After 4 cycles of front-line induction therapy, patients reached partial response (PR) or above would receive autologous stem cell transplantation (ASCT) if eligible, or another up to 5 cycles of same regimens if ineligible, then started maintenance. Patients who did not achieve PR within 4 cycles would switch to second-line induction for 2-5 cycles and start maintenance once PR or above was achieved. For maintenance therapy, Ixazomib was given 4mg on day 1,8,15, and 25mg every other day for Lenalidomide on days 1–21 of 28day cycles. Patients in dual drug group were administrated with both Ixazomib and Lenalidomide. The primary endpoint was PFS from maintenance.
Results: A total of 85 patients were enrolled, including 37 in I-MT, 28 in L-MT and 20 in IL-MT. The demographic and clinical characteristics were comparable among three groups at baseline, including gender ratio, age, paraprotein isotype, ISS, R-ISS, and response evaluation before MT (Figure 1). Though patients on IL-MT were slightly younger. The proportions of patients with high-risk cytogenetic abnormalities (HRCAs), defined as amplification 1q21 (1q21+), deletion 17p (17p-), t(4,14) and t(14,16), were also comparable, as well as the ratios of each CA. However, L-MT cohort had a lower percentage of patients with double hit CA. The ratio of ASCT in L-MT cohort was also greater the others.
The median follow-up duration since maintenance was 4.0, 8.5 and 4.6 months in I-MT, L-MT and IL-MT groups, respectively. Disease progression was recorded in 2 patients (5.4%) on I-MT, 3 (10.7%) on L-MT and 2 (7.1%) on IL-MT. The median PFS was not reached (NR) in all groups. Meanwhile, 6 patients (16.2%) on I, 2 (7.1%) on L and 6 (30%) on IL had improved response after maintenance. No mortality was recorded in all patients.
Peripheral neuropathy with grade 1 was observed in 4 patients (10.8%) on I-MT, 7 (35%) on IL-MT and 0 on L-MT. Gastrointestinal events occurred in 5 patients (13.5%) on I-MT, 5 (25%) on IL-MT and 0 on L-MT. The prevalence of hematologic toxicities was 2.7%, 10% and 7.1%, respectively. Whereas infection rate was 8.1%, 5% and 3.6%. The incidence of skin rashes was 2.7%, 5% and 10.7%, respectively. No patients have discontinued maintenance due to adverse events.

		Ixazomib N= 37	Lenalidomide N= 28	Combination N=20	p-value
Gender (male%)		22 (59.5%)	17 (60.7%)	12 (60%)	0.99
Age (ave±sd/yr)		62.0±9.3	63±2.8	57.5±9.1	0.07
Paraprotein isotype (%)	IgG	21 (56.8%)	12 (42.9%)	11 (55.0%)	0.72
	IgA	5 (13.5%)	7 (25.0%)	1 (5.0%)	
	IgD	0 (0)	0 (0)	2 (10.0%)	
	Light Chain	10 (27.0%)	8 (28.6%)	5 (25.0%)	
	Other or NA	1 (2.7%)	1 (3.5%)	1 (5.0%)	
ISS	I	7 (18.9%)	5 (17.9%)	2 (10.0%)	0.88
	II	11 (29.7%)	7 (25.0%)	9 (45.0%)	
	III	17 (45.9%)	14 (50.0%)	8 (40.0%)	
	Missing	2 (5.4%)	2 (7.1%)	1 (5.0%)	
R-ISS	I	4 (10.8%)	3 (10.7%)	1 (5.0%)	0.79
	II	22 (59.5%)	19 (67.9%)	16 (80.0%)	
	III	9 (24.3%)	4 (14.3%)	2 (10.0%)	
	Missing	2 (5.4%)	2 (7.1%)	1 (5.0%)	
HRCAs		18/31 (58.1%)	14/21 (66.7%)	9/14 (64.3%)	0.81
Cytogenetic abnormalities	Gain(1q21)	13/34 (38.2%)	12/23 (52.2%)	9/19 (47.4%)	0.57
	Del(17p)	2/26 (7.7%)	1/22 (4.5%)	1/13 (7.7%)	0.89
	t(4,14)	4/30 (13.3%)	1/23 (4.3%)	2/16 (12.5%)	0.53
	t(14,16)	5/28 (17.9%)	3/22 (13.6%)	3/15 (20%)	0.87
	Double Hit	6/31 (19.4%)	2/21 (9.5%)	4/14 (28.6%)	*0.049
Response prior to maintenance	sCR+CR	13 (35.1%)	16 (57.1%)	7 (35.0%)	0.30
	VGPR	13 (35.1%)	5 (17.9%)	6 (30.0%)	
	PR	11 (29.8%)	7 (25.0%)	7 (35.0%)	
ASCT before MT		2 (5.4%)	10 (35.7%)	3 (15.0%)	*0.006

ISS: international staging system; R-ISS: revised-ISS; HRCAs: high risk cytogenetic abnormalities. sCR: stringent complete response. CR: complete response. VGPR: very good partial response. PR: partial response.

Summary/Conclusion: Due to inadequate access to melphalan and low rate of ASCT in China, there is still a gap of PFS in NDMM patients with those in western countries. We herein design this multi-centered prospective study to evaluate if dual drug maintenance will further strengthen response and make up the gap. Though the primary endpoint--PFS has not been reached in all treatment groups, dual drug maintenance is quite tolerable. Clinicians prefer to administrate Ixazomib in patients with complex cytogenetic abnormalities in the real-world practice.

EP1051 ASSESSMENT OF CLINICAL USE PARAMETERS ASSOCIATED WITH A SWITCH FROM INTRAVENOUS TO SUBCUTANEOUS DARATUMUMAB ADMINISTRATION IN PATIENTS WITH MULTIPLE MYELOMA AT MAYO CLINIC

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Background: Subcutaneous daratumumab (DARA SC), which is approved for the treatment of multiple myeloma (MM), has efficacy comparable to intravenous (IV) DARA, but it takes only 3-5 min to administer vs 3-7 h for DARA IV and is associated with reduced rates of administration-related reactions (ARRs) in clinical studies. However, DARA IV to SC switch has not been studied, and ARR rates and patient management data (eg, time in/through clinic) associated with the switch are not well characterized.
Aims: To assess real-world evidence on chair time, post-administration observation time, and ARR rates in patients with MM switching from DARA IV to SC
Methods: Patients aged ≥18 years with an ICD-9/10 diagnosis code of MM and a first DARA treatment between April 1, 2017 and December 31, 2020 were identified in Mayo Clinic's Electronic Health Records database. A scheduling and pharmacy software that tracked patient movement through appointments at a Mayo Clinic infusion center was used for data extraction. Data from patients initiating DARA by a single administration route (IV or SC) and patients who received DARA IV for ≥2 doses before switching to SC within 6-60 days were evaluated. The primary objective of the study was to describe the characteristics of DARA administration. The incidence of ARRs was determined in patients who switched from DARA IV to SC using ARR-associated events, including treatment, ICD codes, or admission to emergency department (ED).
Results: Overall, 737 patients initiated DARA treatment for MM (IV, n=640; SC, n=97); 74 patients who initiated DARA IV switched to SC. The median total chair time for DARA SC was 2.4 to 3.4 h shorter compared with DARA IV across all doses (Table). The median observation time decreased from Dose 1 to Dose 3 by 3.0 h (70%) in the SC group and by 2.8 h (82%) in the IV to SC switch group. Among patients who switched from IV to SC, the ARR rate was 1.4% for Dose 1 and 0% for both Doses 2 and 3, with no ARRs leading to ED visits for any dose. The analysis was limited in terms of data completeness, past treatments, and other temporal confounding factors.

	Dose 1			Dose 2			Dose 3			Dose 4+		
	IV	SC	IV to SC+	IV	SC	IV to SC+	IV	SC	IV to SC+	IV	SC	IV to SC+
Evaluable patients, n[†]	424	97	72	419	93	64	402	91	57	455	83	46
Total chair time (incl. observation time), median (hr)[‡]	8.8	5.6	4.5	5.9	2.5	1.7	4.9	2.5	1.3	3.6	1.2	1.1
Observation time, median (hr)[§]	0.3	4.3[‖]	3.4[¶]	0.3	1.4	1.0	0.3	1.3	0.6	0.3	0.4	0.3
ARRs, n (%)[#]	-	-	1 (1.4)	-	-	0	-	-	0	-	-	2 (2.7)
ARRs leading to ED visits, n (%)	-	-	0	-	-	0	-	-	0	-	-	0

*Dose number reflects dose after switching to DARA SC. [†]Available data. [‡]Later of check out time/end of admin – infusion room entry time. [§]Mayo mandated observation time at Dose 1 was [‖]4 hr or [¶]3 hr. [#]ARR data collected only for IV to SC patients (n = 74).

Summary/Conclusion: A shorter median total chair time and low ARR rates were observed across all SC doses in this real-world study, based on which modification of the observation time after Dose 1 are being considered. This may lead to improved practice efficiency and support initiating DARA therapy with SC administration or switching from DARA IV to SC.

EP1052 QUANTIFYING THE BURDEN OF ILLNESS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA, AND THEIR CAREGIVERS, IN THE FIRST YEAR AFTER DIAGNOSIS

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Background: Newly Diagnosed Multiple Myeloma (NDMM) is recognised as a source of significant morbidity and mortality. Though current therapies have been associated with substantial improvements in patient outcomes for both transplant eligible (TE) and non-transplant eligible (NTE) individuals, the magnitude of the burden of illness (BoI) among NDMM patients, and their caregivers, in the first year after diagnosis has yet to be defined.
Aims: To quantify the BoI in TE and NTE NDMM patients, and their caregivers at 3 timepoints: pre-treatment (TP0), at 3 months (TP3) and at 12 months post-treatment (TP12).
Methods: A prospective, longitudinal, observational NDMM study was conducted amongst TE and NTE patients, and their caregivers, from France, Germany, Italy, and Spain between January 2019 and January 2021. Participants were recruited through their haematologist/haemato-oncologist. A structured, online questionnaire incorporating standardised assessment tools for measuring disease burden, including direct costs, indirect costs, and health-related quality of life (HRQoL) was used. Where possible, respondents completed all timepoints; however, some additional recruits were included at TP3 and TP12 to account for drop-outs. Descriptive statistics were performed and informed consent was obtained.
Results: Across the 3 timepoints, 160-190 NDMM patients [majority older than 65 years of age; multimorbid; self-described as relatively healthy; not working; living with the caregiver] answered the questionnaire. Throughout the 12 months, patients progressively lost independence to perform daily activities [IADL scores]. Median 3-month direct medical costs peaked at 3 months, being significantly higher amongst TE patients than NTE patients, due to increased testing and overnight hospital stays. Specialist consultations and hospital admissions were the greatest cost component amongst TE and NTE patients, respectively. In addition, home adaptations raised out-of-pocket expenditures amongst some NTE patients. Although always a minority, the share of working patients declined across the 12 months; those still describing themselves as working spent a median zero hours in the office at all timepoints, with associated costs for the employer. After a partial recovery at TP3, the numeric rating of pain intensity (mean) raised, more significantly among NTE patients. Accordingly, opioid utilisation increased from TP0 to TP12, particularly for NTE patients. Despite this, overall health status and HRQoL [EORTC QLQ-C30] remained stable with average scores over time. Across timepoints, 122-131 caregivers [patient's partner or adult child; self-rated good health; not employed; caring for the patient more than 4 days a week] answered the questionnaire. Mean self-rated burden score rose over the 12 months. By TP12, half of caregivers developed stress, anxiety or depression related to the patient's NDMM. Though most employed caregivers continue to be able to work, productivity was low at TP0 with a trend to recovering at TP12. Caregivers of NDMM NTE patients reported greater time burden compared to TE individuals. As seen with the patients, caregivers' HRQoL remained stable over time [CarerQoL 7D score].
Summary/Conclusion: NDMM is highly burdensome for patients and caregivers in the first year after treatment initiation. NTE patients experience greater pain and are more dependent on caregivers than TE patients. Despite the economic, physical, and emotional burden, HRQoL remains stable possibly indicating resilience and illness adjustment amongst patients and caregivers.

EP1053 EVERY CLOUD HAS A SILVER LINING: EVEN AN EARLY HEMATOLOGICAL PARTIAL RESPONSE COULD IDENTIFY LONG-TERM SURVIVORS IN HIGH-RISK AL AMYLOIDOSIS PATIENTS. A SINGLE CENTER EXPERIENCE.

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Background: Immunoglobulin light chain (AL) amyloidosis is a heterogeneous disease. The prognosis is highly related to the stage of the disease which, in turn, is dependent on the hearth involvement. At diagnosis, patients in Mayo stage III and IV represent the majority of AL amyloidosis, and are defined "high-risk" because their outcome is poor.
Aims: From 2003 to 2019, 111 patients were diagnosed with systemic AL amyloidosis in our Center; 52 patients were identified as "high risk". We retrospectively analyzed the impact of hematological responses (HeR) by day 30 on overall survival (OS). All patients underwent first line bortezomib-based chemotherapy (6 cycles, weekly administration).
Methods: Baseline characteristics are shown in Table 1. All patients had an initial dFLC >50 mg/L, and a NTproBNP value above the normal limit. Diagnosis of amyloidosis was biopsy-proven and amyloid typing was established by immunoelectron microscopy in all cases. Patients were considered to have cardiac amyloidosis based on the accepted criteria for the definition of organ involvement. Hematologic and organ responses (OR) were defined according to Palladini et al.
Results: By day 30 of treatment, 23 patients (44%) achieved a HeR (11 CR and 12 VGPR). Twenty-nine patients (56%) attained PR or NR (14 and 15 patients, respectively). At 6 months 21 out of 29 patients with an inadequate response at day 30 did not change their hematological status (7 and 14 of them were PR and NR respectively at day 30), and 8 out of these 21 patients experienced early (i.e., within 6 mo.) death. All these latter patients were NR at day 30. The remaining 8 patients (7 PR and 1 NR at day 30) achieved a VGPR with no treatment modification. Remarkably, 12 out of 14 PR patients at day 30 achieved an organ response at the end of treatment; 7 of them achieved a VGPR while in 5 the hematological status did not change. The median OS of patients achieving the HeR, PR and NR at day 30 were 43, 24, 11 months, respectively.
At univariate analysis, achieving a HeR and PR at day 30 significantly predicted survival, with respect to NR (respectively p=0.001 and p=0.007). These results were confirmed even in the final multivariate Cox model (HeR *vs* NR p=0.001 and PR *vs* NR p=0.04).
Summary/Conclusion: In this limited retrospective analysis, HeR (CR+VGPR) at day 30 confirmed its prognostic value. Nevertheless, patients who reached a suboptimal response (PR) at day 30 have reasonable chances of survival, and do not necessarily need a change in therapeutic strategy even in the face of permissive clinical conditions. Therefore we confirm that achieving a rapid HeR and, to a lesser extent, a PR to bortezomib at day 30 in patients in newly diagnosed high-risk AL amyloidosis, has a favorable prognostic value. On the other hand, an early identification of NR patients should prompt a shift in therapy trying to improve the well-known dismal prognosis of these patients.

EP1054 DARATUMUMAB (DARA), CYCLOPHOSPHAMIDE, THALIDOMIDE AND DEXAMETHASONE: A QUADRUPLET INTENSIFIED TREATMENT FOR TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA (TE NDMM) PATIENTS

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Background: Newly drugs access for MM treatment still a challenge in some countries. One of the most available inductions for TE NDMM

patients (pts) worldwide is cyclophosphamide (C), thalidomide (T) and dexamethasone (d)- (CTd). Dara the first anti- CD38, had been combined with VCd, VTd and VRd and markedly increased the depth and duration of the response. We hypothesized that the combination of Dara and CTd could be safe and allow deeper activity as an alternative protocol.
Aims: The primary endpoint was to evaluate the VGPR after two consolidation cycles post-autologous stem cell transplantation (ASCT). Secondary endpoints were the overall response rate during all treatment phases and minimal residual disease (MRD), based on the International Myeloma Working Group (IMWG) criteria that includes the next-generation flow (NGF) by the EuroFlow® and PET-CT and the safety profile.
Methods: This is a phase II, open-label single-center clinical trial. The main inclusion criteria were: TE NDMM, creatinine clearance ≥ 30 ml/min, normal cardiac, renal and liver function and the Easter Cooperative Oncology Group (ECOG) performance status = 0 - 2. The protocol was Dara-CTd for up to four 28-day induction cycles: C-500mg oral (PO) on days 1,8 and 15, T at 100-200mg PO on days 1 to 28, (d) at 40mg PO on days 1,8,15 and 22 and Dara at 16mg/Kg/dose intravenous (IV) on days 1,8,15 and 22 during cycles 1 - 2 and every other week in cycles 3 – 4, followed by ASCT. All pts received up to four 28-day consolidation cycles that was started at D+30 after ASCT: Dara at 16mg/Kg and (d) at 40mg every other week, associated with T at 100mg PO on days 1 - 28. Dara at 16mg/Kg was used monthly as maintenance until progression or limiting toxicity. G-CSF was used for stem cell (SC) mobilization and plerixafor had been allowed whenever the pts need. All pts received antiviral, anti-pneumocystis and anti-thrombotic prophylaxis.
Results: The first pts was enrolled in November 2018. A total of 21 pts were included, the median age being 56 (range 37 – 67 years), 19 (90%) were non-white, 3 (14%) had an R-ISS = 1, 12 (57%) had an R-ISS = 2 and 3 (14%), an R-ISS = 3. Five (24%) pts had high-risk chromosomal abnormalities [del17p, t(4;14) or t(14;16)]. To date, all pts have completed induction, 19 have received transplant and 17 have completed D+90 post-transplant assessment. No SC mobilization failure was observed, and five (26%) pts needed plerixafor use. In an intention to treatment analysis, after the end of induction (cycle 4), 19 (90%) of the pts obtained > PR and 8 (38%) obtained ≥VGPR, including three MRD negativity by NGF. 17 pts have completed two consolidation cycles after transplant and 94% obtained ≥ VGPR as best response, 12 (70%) obtained MRD negativity by NGF and nine (53%) had negative PET-CT. Seven (41%) pts had both flow and PET-CT negativity. Three pts died from infection, one before transplant because of Covid infection, on post-transplant, considered not related to the investigational agent, and another after consolidation, related to the investigational agent. The most common nonhematological adverse events (AEs) grades 3 and 4 before ASCT were neuropathy (n = 6), infusion reaction (n = 7), infection (n = 2), hypertension (n = 1) and rash (n = 1).
Summary/Conclusion: This is the first study that combined Dara with CTd as induction for TE NDMM pts. This present data has shown that the association of Dara-CTd achieved the primary end point once ≥ 90% of the pts achieved VGPR after two consolidations cycles, and safety profile was acceptable. Clinical trial information: NCT03792620.

EP1055 INTERMITTENT TREATMENT OF NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: RESULTS OF A PHASE II TRIAL EVADING AUTOLOUGOS STEM CELL TRANSPLANT (ASCT)

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Background: ASCT is still the standard of care for newly diagnosed patients with MM; however, it carries a high toxicity profile compared with chemotherapy or/and new agents such as thalidomide, lenalidomeide and anti-CD38.
Aims: the study aims to evaluate the treatment of newly diagnosed patients with MM using an intermittent therapy rather than autologous stem cell transplantation
Methods: The study was carried out at Al Bairouni University Cancer Center in Damascus, Syria between 2012 and 2017 and concluded 123 patients received three lines: (thalidomide+bortizomib+dexamethasone)/(lenalidomide+dexamethasone) and (bortizomib+dexamethasone), 44, 53 and 26 patients respectively. Evaluated evry 3 months and treatment was ceased in complete responders after 6 months of treatment and restarted upon documented relapse.
Results: Complete response was documented in 55 (44.7%) patients at the end of the 3rd month versus 102 (82.9%) at the end of 6th month. All patients relapsed or progressed at different times of treatment then they were retreated with the same induction or switched to another protocol. 112 patients were still alive at 5 years with an overall survival of 91%. In a univariate analysis, factors associated with poor survival are: patients with spinal cord compression at presentation with an odds ratio (OR) of 0.33 (95% CI, 0.11-0.83) and p value 0.04, extramedullary localization with an OR of 0.66 (95% CI, 0.15-0.95) and p value 0.09 and acute renal failure at presentation with an OR 4.5 (95% CI,0.9-9.7) and p value 0.004. The toxicity profile was acceptable.
Summary/Conclusion: Though all patients progressed or relapsed; however, 65 patients (52.8%) re-experienced the same complete response for at least four times using the same protocol, while the remaining 58 patients were responded at least 2 times then switched to other protocols in 3 occasions. Those with renal failure were correlated with poor survival taking into account the inability to deliver zoledronic acide. The toxicity profile was well tolerated and most patients continued their daily life with a good quality.
Results are comparable to those treated with ASCT taking into account the safe toxicity profile. Intermittent therapy is well tolerated, less aggressive and it had a better impact on the psychiatric status of the recruited cohort; however, a phase III head to head with ASCT is warranted in future.

EP1056 THE RETROSPECTIVE ANALYSIS OF MULTIPLE MYELOMA PATIENT SURVIVAL IN ARMENIA

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Background: It is well known that the increased incidence of hematological malignancies is mainly caused by the growth of non-Hodgkin's lymphoma and multiple myeloma (MM). MM is the second most commonly diagnosed hematological neoplasm over the world. The indicated annual increase of MM incidence in the world is 0.7%. MM primarily affects the elderly and is typically diagnosed between the ages of 65-74 years and characterized by severe bone, blood and renal complications, impacting therapy choices and quality of life.
Aims: The aim of the current study was a comprehensive analysis of MM, i.e., their prevalence, incidence and survival rates in Armenia for the period of 2006-2020.
Methods: The main data source for this study was outpatient and dispensary cards, hospitalization journals, as well as clinical data from the Register of Blood Diseases of the Hematology Center after. prof. R. Yeolyan. This information has been supplemented by the data from National Oncological Centre after V.A. Fanarjyan as well as from death registration service at Ministry of Justice RA. Demographic indicators were derived from the database of Statistical Committee of Armenia. Diagnosis of MM and the definition of the stage were carried out according to the criteria proposed by the International Myeloma Working Group. Survival (OS) was determined by the period between the date of diagnosis and the date of death. Direct method of adjustment was used for elimination of possible influence of changes in age structure of population through passage of fifteen years. The time series data was analyzed using least squares regression analysis.
Results: We analyzed the data of 589 (48.2% female and 51.8 male) patients with MM registered in Armenian Hematology Center of the Ministry of Health of the Republic of Armenia from 2006 to 2020. The median age was 60.6 years (range 31–89). Data analysis showed that during the reported time period the increase of the MM incidence was 1.23 per 100 000 population. In comparison to the results obtained for 1966-1971 and 1998-2004, a significant increase in incidence of MM (about 3.6 and 1.4) was found. The low five-year survival rates were beaten in groups of patients who initially refused therapy and / or were diagnosed already in higher ISS stage for this disease. Among patients receiving therapy, the best survival rates were beaten on MP, VAD protocols and VCD and transplantation. The median survival for ISS stage II disease was 26 months, stage III disease 7 months and stage I disease 20 months. The incidence rates for the MM increased during the analyzed period and male over 60 years old were particularly in the risk group.
Summary/Conclusion: In general, the results of treatment in the Armenian population with MM were comparable with the data of the total European cohort. The survival rate was lower in patients with higher ISS stage for this disease and untreated patients. Survival rate seems to be better among younger patients than in older ones even with lower ISS stage of this disease. The MM-related deaths prevailed in the first 5 year of MM therapy. The appropriate monitoring and therapy

interventions during the first year of MM treatment are apparently important for the long-term treatment results

Myeloproliferative neoplasms - Biology & Translational Research

EP1057 ANTI-TMPRSS6 RNAI THERAPY AS A NOVEL TREATMENT OPTION FOR POLYCYTHAEMIA VERA

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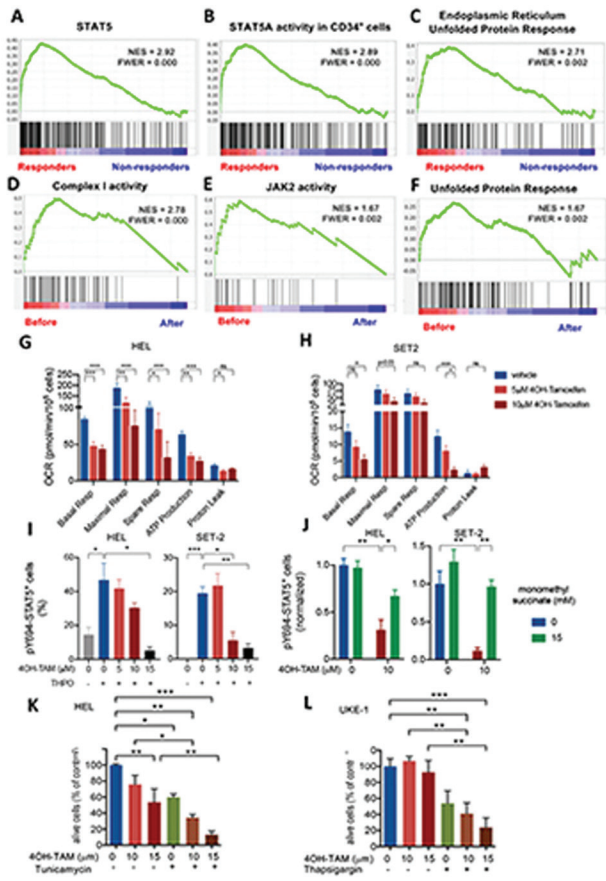
Background: Polycythaemia Vera (PV) is a myeloproliferative neoplasm (MPN) in which overproduction of mature red cells renders patients at increased risk of serious thrombotic events. First line therapy includes periodical venesection (blood withdrawal) to reduce haematocrit, and thus risk of thrombosis, and induces whole body iron deficiency, which suppresses further red cell production. However, resulting systemic iron deficiency and fluid shifts lead to unwanted side effects including vaso-vagal complications, fatigue and cognitive dysfunction. Therefore, venesection is often poorly tolerated.
Hepcidin, the liver-derived hormone that regulates systemic iron homeostasis, is normally suppressed in iron deficiency (via decreased BMP/SMAD signalling) or by increased erythropoiesis (via increased erythroferrone expression) but is increased by inflammation (via IL6- STAT3 signalling). Interestingly, hepcidin levels are not suppressed in PV despite sustained increased erythropoiesis and iron deficiency, suggesting relative upregulation in this disease context.
Aims: We hypothesised that further upregulation of hepcidin in PV limits iron available for erythropoiesis. This would prevent patients from obtaining the high red cell counts that are incompatible with life. We aimed to discover whether therapeutically increasing endogenous hepcidin expression in PV through knock-down of its regulator, *Tmprss6*, could act as a therapeutic phlebotomy and decrease disease severity.
Methods: We developed a novel bone marrow transplant model of PV driven by the mutant human JAK2V617F allele. PV and control mice were subcutaneously administered anti-Tmprss6 siRNA or a non-targeting control siRNA once every 3 weeks for 3 doses. Mice were humanely euthanised and organs collected for downstream analysis.
Results: PV mice had comparable levels of hepcidin mRNA and protein as control mice, recapitulating what has previously been observed in patients. Mice administered anti-Tmprss6 siRNA showed ablated *Tmprss6* gene expression which resulted in sustained increase of endogenous hepatic hepcidin mRNA and serum protein levels, compared to mice given non-targeting siRNA. Increased serum hepcidin significantly decreased serum iron levels but did not cause iron deficiency in peripheral organs, as determined by liver iron content. PV animals administered anti-Tmprss6 siRNA had significantly lower haematocrit (45.9 vs 61.2%; P<0.0001), haemoglobin levels (12.0 vs 17.7g/dL; P<0.0001) and mean cell volume (36.1 vs 48.4fL, P<0.0001) than PV animals treated with control siRNA.
Summary/Conclusion: These data provide pre-clinical evidence that increasing endogenous hepcidin expression via anti-Tmprss6 RNAi could be a viable therapeutic avenue for treatment of PV. This treatment approach does not affect fluid levels and may reduce risk of systemic iron deficiency, the two concerns with conventional first line therapy. A related siRNA compound targeting TMPRSS6, SLN124, is in clinical development for hepcidin deficient anaemias. The inherent long-lasting duration of action coupled with patient friendly route of administration could provide benefit by decreasing the requirement for venesection and increasing comfort for patients with PV.

EP1058 TAMOXIFEN CAN REDUCE MITOCHONDRIAL RESPIRATION, ONCOGENIC JAK-STAT SIGNALING AND MUTANT ALLELE BURDEN IN A SUBSET OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS – RESULTS OF THE TAMARIN PHASE II STUDY

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Background: Myeloproliferative neoplasms (MPN) most frequently originate from mutations in hematopoietic stem and progenitor cells (HSPCs) affecting JAK2 or CALR. Tamoxifen restores normal apoptosis in mutated HSPCs in preclinical studies. The results of the TAMARIN Phase II study assessing tamoxifen's safety and activity in reducing molecular markers of disease burden in MPN have been recently reported (Blood 2020;136(Supplement 1):33-35).
Aims: Here we have investigated tamoxifen's mechanism of action in human MPN.
Methods: CD34+ HSPCs were isolated from peripheral blood at baseline, 12w and 24w after tamoxifen treatment for RNA-Seq, also performed on JAK2V617F-mutated human cell lines 4h after 4-hydroxytamoxifen (4OH-TAM) treatment. ATP generation from Oxidative phosphorylation (OXPHOS) and glycolysis was measured by Seahorse. STAT5-Y694 phosphorylation and apoptosis were measured by flow cytometry in Ba/F3 cells expressing erythropoietin receptor (EpoR) and WT or mutant JAK2, HEL, SET2 and UKE1 cells treated with different drugs including unfolded protein response (UPR) stressors thapsigargin and tunicamycin.
Results: Weighted correlation network analysis (WGCNA) revealed two gene modules with increased expression in HSPCs from responders at baseline. Gene-set enrichment analysis (GSEA) highlighted in responder HSPCs genes related to STAT3, STAT5, inflammation, apoptosis, reactive oxygen species (ROS), starvation or ATF response to UPR and cellular stress, suggesting that differential UPR determines sensitivity to tamoxifen. Indeed, nutrient deprivation or UPR stressors sensitised JAK2^{V617F+} cells to 4OH-TAM-induced cell death. 4OH-TAM-induced cell death was



more pronounced in Ba/F3 cells carrying the mutant human JAK2^{V617F}, supporting an increased activity of tamoxifen in the mutant cells. The expression of OXPHOS-related genes was high at baseline and specifically reduced by tamoxifen in responder HSPCs. This was mimicked by 4OH-TAM-sensitive and resistant cell lines. OXPHOS-derived ATP was markedly reduced by 4OH-TAM in sensitive cells including permeabilised cells, suggesting a direct inhibition of mitochondrial complex I. Complex II activators (succinate prodrug) protected from 4OH-TAM-induced cell death by rescuing ATP generation. Since ATP binding to the pseudokinase domain of JAK2 is critical for pathogenic activation of JAK2^{V617F}, but is not required for WT JAK2 activity, we hypothesized that reduced ATP generation might compromise pathogenic JAK2^{V617F}-STAT5 activation and possibly explain the selective proapoptotic effect of tamoxifen in mutant cells. STAT5-Y694 phosphorylation after Epo or Tpo stimulation was dose-dependently inhibited by 4OH-TAM. However, restoration of the mitochondrial electron transport and ATP generation by succinate prodrugs or cell-permeable ATP rescued pathogenic JAK2^{V617F}-STAT5 activation in 4OH-TAM-treated cells.
Summary/Conclusion: Longitudinal transcriptomic analysis of HSPCs from TAMARIN study patients and JAK2^{V617F}-mutated cells lines showed high UPR activity and expression of OXPHOS genes, specifically reduced by tamoxifen in sensitive cells. 4OH-TAM inhibits mitochondrial complex I and ensuing ATP synthesis, causing decreased pathogenic (but not WT) JAK2 signalling. These studies advocate for future studies on the transcriptomic and metabolic effects of selective oestrogen receptor modulators to target metabolic vulnerabilities in MPN with careful consideration of thrombotic risk.

EP1059 INVESTIGATION OF FEASIBILITY AND EFFICACY OF AN ANTI-INFLAMMATORY ANTI-IL-6 TREATMENT IN THE JAK2-V617F MOUSE MODEL

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Background: The classic Philadelphia-chromosome negative chronic myeloproliferative neoplasms (CMN) are characterized by clonal proliferation of myeloid cells, increased thrombotic risk, inflammation and splenomegaly. Besides driver mutations (e.g. JAK2-V617F mutation), inflammation plays a key role in pathophysiology in CMN. Amongst other cytokines, IL-6 levels are elevated in CMN-patients. The pleiotropic cytokine IL-6 was described as a master cytokine due to its involvement in a wide range of physiological and pathological mechanisms. It was shown that IL-6 reduction by ruxolitinib correlates with improvement of symptom burden in CMN. Additionally, IL-6 and the downstream molecule STAT3 were described to link inflammation with malignant proliferation. Recently, pro-inflammatory cytokines are discussed as interesting anti-inflammatory targets in CMN treatment to inhibit inflammation driven transformation into myelofibrosis and/or acute leukemia.
Aims: This study aimed to investigate the impact of an anti-IL-6 treatment on disease specific parameters (e.g. cytokine levels in serum, hematocrit, and splenomegaly) in a polycythemia vera - like JAK2-V617F knock-in mouse model.
Methods: JAK2-V617F knock-in mice (11-13 weeks old) were treated (3x/week for three weeks) with anti-IL-6 antibody (clone MP5-20F3) and isotype IgG control, respectively. A wide panel of pro-inflammatory cytokines was measured in serum of treated mice by Eve Technologies Corporation (Mouse Cytokine Array/Chemokine Array 31-Plex; Calgary, AB, Canada). Blood parameters were analyzed by ADVIA®2120i Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). For histopathologic analysis, hematoxylin-eosin staining was performed on isolated spleens sections.
Results: Reduced inflammatory cytokine levels (factor 0.3 – 0.8) were measured in serum of anti-IL-6 treated JAK2-V617F mice for CXCL1, CCL11, CXCL2, G-CSF, CXCL10, CXCL5, IL-13, CCL4 and CCL5. Interestingly, high dose isotype IgG control antibody also reduced levels of a number of these cytokines in JAK2-V617F mice.
The reduced inflammatory environment upon anti-IL-6 treatment did not result in improvement of hematological parameters. For example, hematocrit (82.0 % vs 76.0 %) and erythrocyte blood cell (20.8 Tpt/L vs 21.5 Tpt/L) were still significant elevated at the end of anti-IL-6 treatment. Another characteristic parameter of JAK2-V617F mice is a splenomegaly. The reduced cytokine levels showed no impact on the elevated spleen weight and size. In addition, there was no apparent amelioration of spleen histopathology.
Summary/Conclusion: Anti-IL-6 treatment was shown to reduce a number of pro-inflammatory cytokine levels in serum of JAK2-V617F mice. However, this change had no apparent impact on hematologic disease parameters. Furthermore, anti-IL6 treatment had no impact on extramedullary hematopoiesis presenting as splenomegaly and on histopathology of the spleen. This suggests that inhibition of IL-6 in CMN may be compensated by IL6-independent inflammatory pathways *in vivo* and may not be useful as a therapeutic approach in patients.

EP1060 EXOSOMES IN POLYCYTHEMIA VERA: "MINI PLATELETS" WITH ONCOGENIC AND THROMBOGENIC POTENTIAL

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Background: Thrombotic complications across the vascular tree are frequent in patients with polycythemia vera (PV). These patients also have an increased risk of second primary malignancies. Although genetic predisposition may partially explain these links, whether and how the presence of PV-clonal cells induce pro-thrombotic and oncogenic environment is poorly understood. Secreted by all types of cells, exosomes are nano-scaled particles which carry a molecular cargo that reflects, *at least* partially the molecular makeup to their cell of origin. Exosomes travel in blood, may reach distant sites away from their cell of origin and affect various physiological and pathological processes. These features led us think that PV-derived exosomes (hereafter PV-exosomes) contribute to the thrombotic manifestations and oncogenic potential of our patients. Since mutated *JAK2* is present in virtually all patients with PV, we hypothesized that exosomes that are derived from a PV clone, carry the mutated *JAK2* oncogene and contribute to the increased incidence of thrombogenic complications and oncogenic risk.
Aims: 1) Determine whether PV-exosomes harbor mutated *JAK2* transcripts.
2) Determine whether PV-exosomes are pro-thrombotic.
3) Explore the oncogenic potential of PV-exosomes.
Methods: We isolated microparticles by serial ultracentrifugation, confirmed the presence of exosomes by NTA (Malvern) and imaged them by EM. We extracted RNA, generated cDNA (Invitrogen) and amplified a 465 bp long DNA segment within exon14 of JAK2 by PCR. Sanger sequencing was used to determine the JAK2 mutational status. We used thrombin generation assay to assess the thrombotic potential of PV-exosomes and Trans Epithelial Electric Resistance (TEER) assay to assess endothelial dysfunction. We measured exosomal uptake by HUVECS and keratinocytes by flow cytometry and assessed the oncogenic potential of these exosomes by the NIH/3T3 assay.
Results: To determine whether PV-exosomes carry mutated *JAK2* transcripts, we harvested exosomes from the peripheral blood of 21 patients with PV and 20 healthy individuals. Reverse-transcriptase PCR revealed the presence of mutated *JAK2* mRNA in all patients and the presence of wild type JAK2 in all healthy individuals. Because mutated *JAK2* induces endothelial dysfunction, we wondered whether JAK2^{mutated}-exosomes are taken up by endothelial cells and induce endothelial dysfunction. We stained PV-exosomes with the FM-1-43 dye and showed by flow cytometry that these exosomes are taken up by Human-Umbilical-Vein-derived-Endothelial-Cells (HUVECs) in a dose- and time- dependent manner, peaking at 24 hours. To assay the functional status of the endothelium, we measured the membranal resistance of HUVECS prior to and after exposure to PV-exomes for 24 hours. The resistance was dramatically decreased in the presence of PV-exosomes, indicating that the tight junction between adjacent cells was impaired implicating that PV-exosomes induce endothelial dysfunction. To assess the thrombogenic potential of PV-exomes, we measured the rate of thrombin generation in platelets poor plasma and recorded an increase in the peak thrombin concentration in the presence of PV-exosomes compared with exosomes from healthy individuals. Finally, using the NIH/3T3 platform we found that PV-exosome have the capacity to transform normal cells from various tissues.
Summary/Conclusion: Like their parental cells, PV-derived exosomes carry mutant JAK2 transcripts. These exosomes are pro thrombotic and have transforming potential both directly and indirectly through endothelial dysfunction.

EP1061 RUXOLITINIB DOWN-REGULATES SELECTIVELY-ACTIVATED CCL2/CCR2 SIGNALING AXIS IN PRIMARY MYELOFIBROSIS CELLS

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Background: Primary Myelofibrosis (PMF) represents the paradigm of onco-inflammatory disorders. In fact, although its pathogenesis is cell-intrinsic and triggered by acquired somatic mutations in specific myeloid genes, cell-extrinsic effects exerted by the malignant clone via inflammatory mediators result in systemic complications (Jutzi & Mullally, 2020). Moreover, chronic inflammation elicits clonal evolution, in a self-perpetrating vicious cycle (Hasselbalch, Mediators Inflamm 2015).

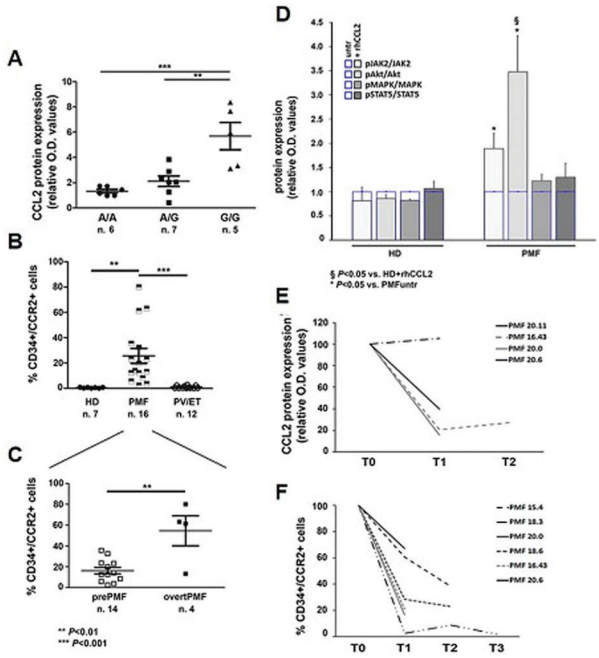
CCL2 (also known as Monocyte Chemoattractant Protein-1) is one of the most potent immune-modulatory cytokines known to be elevated in PMF and exerts its biological effects by preferentially engaging its cognate receptor CCR2, activating a downstream signaling which includes G-proteins, MAPK/ERK, PI3K/Akt and JAK/STAT pathways (Lim, Oncotarget 2016).

SNPs in the regulatory regions of *CCL2* gene account for the great inter-individual variability in CCL2 expression levels. Specifically, the rs1024611 (A>G) SNP of *CCL2* leads to higher chemokine production upon inflammatory noxa (Tam, PlosOne 2012). We recently demonstrated that homozygosity for the G allele variant of this SNP is associated to reduced survival in PMF (Masselli, ASH 2019 abs#1689).

Aims: Here we sought to prove the functional relevance of this finding by assessing expression and function of CCL2/CCR2 axis in PMF and its down-regulation induced by immunomodulatory therapy with ruxolitinib.

Methods: MNCs from therapy naïve PMF stratified according to the *CCL2* SNP (n. 25), and from PMF before (T0) and after Ruxolitinib start (T1→T3) (n. 6) were in part pelleted and in part cultured for 20h in 10% fetal bovine serum-enriched RPMI medium with 1.1 mg/ml of IL1-β as described (Rovin, BBRC 1999). Cells were then subjected to western blot for CCL2 expression. Immunomagnetically-isolated primary CD34+ cells from PMF and healthy donors (HD) were checked for CCR2 expression by flow cytometry and cultured for 24h in serum-free X-vivo medium with and without rhCCL2 (100 ng/mL). Cells were subjected to western blot to assess signaling pathways activation.

Results: The rs1024611 SNP is functionally relevant in PMF since the G allele exerts a dose-dependent effect on CCL2 expression, with G/G PMF significantly overexpressing CCL2 as compared to the other genotypes (panel A). We asked whether PMF hematopoietic progenitors could be a target of CCL2 and we found that PMF CD34+ cells uniquely display CCR2 (> 60 fold-higher expression as compared to HD and >26 fold-higher as compared to PV and ET, which share with PMF the same driver mutations) (panel B). Additionally, among PMF, overtPMF significantly overexpress CCR2 as compared to prePMF (panel C). When PMF CD34+ cells were stimulated with rhCCL2, a significant phosphorylation of JAK2 and Akt was detected. As control, CCR2-negative CD34+ cells were subject to the same treatment and do not display CCL2-mediated phosphorylation of JAK/STAT, Akt and MAP-kinase pathways (panel D). Finally, we proved that ruxolitinib is effective in turning-off CCL2/CCR2 signaling. In fact, MNCs from patients at 1, 3 and 6 months of therapy (T1→T3) display a significantly reduced capacity to produce CCL2 upon inflammatory stimulus as compared to T0 (before ruxo start). A significant and stable reduction of the chemokine receptor on PMF CD34+ was detected as well (panel E-F).



Summary/Conclusion: CCL2/CCR2 chemokine axis is selectively activated in PMF, boosting pro-survival signals induced by driver mutations. Ruxolitinib effectively counteracts CCL2 production and down-regulates CCR2 expression in PMF cells.

EP1062 FEDRATINIB DEMONSTRATES LIMITED SUPPRESSION OF T- AND NATURAL KILLER- (NK) CELL ACTIVITY EX VIVO COMPARED WITH RUXOLITINIB AT CLINICALLY RELEVANT DOSES

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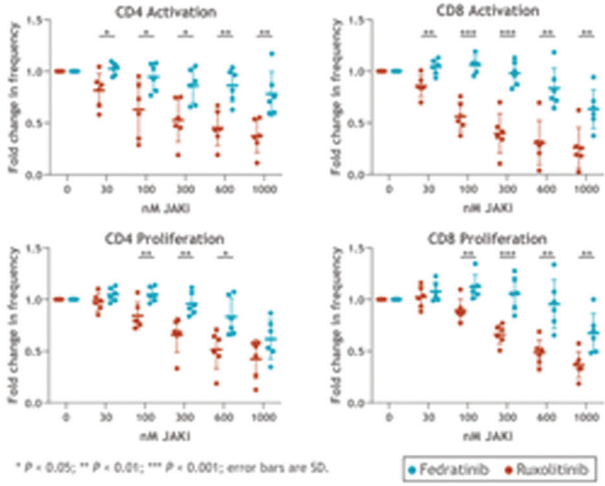
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Background: Myelofibrosis (MF) is a debilitating clonal myeloproliferative neoplasm characterized by anemia, splenomegaly, and constitutional symptoms, often presenting with activating Janus kinase 2 (*JAK2*) mutations. Two JAK inhibitors (JAKis), ruxolitinib (RUX) and fedratinib (FEDR), are approved for treatment (Tx) of intermediate- or high-risk MF, and others, such as momelotinib and pacritinib, are in late-stage clinical development. FEDR is an oral, selective inhibitor of wild-type and mutant JAK2 and fms related receptor tyrosine kinase 3 (FLT3) approved in the United States (US) and European Union (EU) for adult patients (pts) with intermediate-2 or high-risk primary or secondary MF. Ruxolitinib (RUX) is a multikinase inhibitor with broad activity against JAK family kinases including JAK1, JAK2, JAK3, and TYK2. RUX is approved in the US and EU for Tx of pts with intermediate or high-risk primary or secondary MF. Due to variations in JAK specificity, FEDR and RUX may have differential immunomodulation effects, which could have important clinical implications.

Aims: Determine the relative immunomodulatory activity of FEDR and RUX in human *ex vivo* culture model systems.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from heathy subjects (n = 6) with standard Ficoll gradient centrifugation. Primary cells (PBMCs and CD56+ NK cells) and cell lines (Raji and K562) were co-cultured in triplicate with FEDR, RUX, or vehicle control

at different effector:target (E:T) ratios and assayed by flow cytometry. Activation was assessed by ELISA for interferon γ (IFNγ) secretion after Tx with 50 ng/mL *Staphylococcus* enterotoxin B (SEB). Though the recommended clinical dose of FEDR, 400 mg/day, is ~10-fold higher than the recommended RUX dosages of 30–50 mg/day (15–25 mg BID), the observed peak plasma concentrations for both are ~1–2 µM. Thus, FEDR and RUX activity were compared by using equal concentrations of drug at 30, 100, 300, 600, 1000 nM, or vehicle control. A two-parameter, unpaired Student's t-test was used to compare Tx groups.
Results: PBMCs were cultured with equal concentrations of FEDR or RUX. Overall, Tx with FEDR showed significantly reduced CD4+ and CD8+ T-cell suppression at clinically relevant doses compared with RUX. Compared with vehicle control, activation and proliferation of CD4+ T cells were suppressed with RUX Tx by 48% and 35%, respectively, and by 14% and 4% with FEDR Tx (each at 300 nM). Similarly, CD8+ T-cell activation was reduced by 60% and proliferation by 34% with RUX vs. control, compared with 2% and no reduction, with FEDR vs. control ($P > 0.01$) at 300 nM (**Figure**). In a co-culture system (E:T ratio, 3:1 NK:Raji cells) using 2 µg/mL rituximab (or isotype control) to tag CD20+ Raji cells, the reduction in NK-mediated antibody-dependent cellular cytotoxicity (ADCC) was significantly greater with RUX than FEDR after 4 hr. In assays of HLA-dependent cytotoxicity (E:T ratio, 20:1 NK:K562 cells; no antibody), FEDR showed limited inhibition of NK cells compared with RUX after 6 hr in 4/5 NK cell donor samples.



Summary/Conclusion: Overall, Tx with FEDR resulted in significantly lower suppression of T- and NK-cell proliferation and activation *ex vivo* when compared with RUX. FEDR also displayed limited suppression of NK-cell–mediated ADCC and HLA-dependent cytotoxicity in *ex vivo* model systems. These findings elucidate some of the variable immunomodulatory effects of JAKis and may aid in development of clinical trials combining FEDR with immunotherapies for MF and other neoplasms.

EP1063 DISTINCT GENE EXPRESSION PROFILES AND MOLECULAR MARKERS IN CD34+ CELLS FROM PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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Background: Myeloproliferative neoplasms (MPN) are hematological disorders of the myeloid lineage characterized by hyperproliferation of mature blood cells. In classical Ph$^-$ MPN, comprising polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), mutations in the genes of *JAK2*, *CALR* and *MPL* are frequently observed. The most commonly detected mutation is *JAK2*V617F, a gain-of-function mutation, that results in expansion of stem and progenitor cells. Mutations in additional genes have been identified as potential high molecular risk factors for progression. The prediction of clinical course and progression remains incompletely understood and new molecular components whose targeting might result in further improvement of risk stratification and therapeutic strategies are of high interest. Several CD34$^+$ gene expression studies have been conducted to investigate deregulated gene sets in MPN. However, most studies do not include all MPN subtypes, impeding a comparison, especially with regard to disease progression. Thus, further studies are necessary.
Aims: We conducted a CD34$^+$ gene expression study to identify signatures and potential biomarkers in the different MPN subtypes with the aim to identify new therapeutic targets and predict the transition of a rather benign, chronic to a more malignant, aggressive state.
Methods: In this study, we performed gene expression analysis (GEA) of CD34$^+$ peripheral blood and bone marrow (BM) mononuclear cells from MPN patients and healthy controls. A total cohort of 36 samples (6 ET, 11 PV, 9 PMF, 4 secondary myelofibrosis (SMF; post PV or post ET) patients and 6 healthy donors) were objected to Affymetrix GeneChip HTA 2.0 analysis.
Results: GEA revealed a variety of differentially regulated genes in the different MPN subtypes compared to healthy controls, with PMF (200 genes) and SMF (272) resulting in stronger differences than ET (132) and PV (121). PROGENγ analysis revealed the significant induction of NF-κB and TNFα signaling (particularly in SMF) and a reduction of estrogen signaling (PMF and SMF). We performed gene ontology (GO) enrichment analysis and discovered the induction of inflammatory pathways, particularly in PMF and SMF. Biological processes associated with RNA splicing were downregulated in PMF. Several potential marker genes that might be utilized as diagnostic or prognostic markers were identified such as *AREG*, *CYBB*, *DNTT*, *TIMD4*, *VCAM1* and members of the S100 family (*S100A4/8/9/10/12)*. S100 proteins are pro-inflammatory alarmins that might contribute to the high risk of leukemic transformation. RT-qPCR analysis in full BM cells revealed that the deregulation was mainly restricted to the CD34$^+$ compartment. 98 genes were deregulated solely in SMF and may be used to predict the progression into myelofibrosis. The strongest deregulated genes in this group included *CLEC1B*, *CMTM5*, *CXCL8*, *DACH1* and *RADX* that potentially play a role in MPN pathogenesis due to their described functions.
Summary/Conclusion: Our study is the first to provide gene expression signatures in CD34$^+$ stem and progenitor cells of all classical Ph$^-$ MPN subtypes ET, PV, PMF and SMF supporting the paradigm of early and late stage MPN. We identified a strong activation of inflammatory pathways in PMF and especially SMF. GO analysis revealed that the downregulation of RNA splicing pathways was restricted to PMF patients. Furthermore, we identified a variety of deregulated genes and pathways that might serve as molecular markers for diagnosis or prediction of disease transition and may lead to the development of new therapeutic modalities.

EP1064 CLONAL HAEMATOPOIESIS PROMOTES ADVERSE OUTCOMES IN CHRONIC KIDNEY DISEASE

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Background: Age-related clonal haematopoiesis (CH) is a risk factor for atherosclerotic cardiovascular disease (CVD) and all-cause mortality. Chronic kidney disease (CKD) is a worldwide health problem associated with an elevated risk of CVD, but the relationship between CH and CKD is unknown.
Aims: To assess the relationship between CH and CKD in UK Biobank, a prospective, population-based cohort of UK subjects aged 40-69 years recruited between 2006-10.
Methods: We focused on subjects with both genomewide SNP array and WES data (n=200,361; median age = 58y, median follow up = 11y). Array allelic intensities were used to infer mosaic chromosome abnormalities (mCA), which were categorized as myeloid, lymphoid or other based on known cytogenetic associations. Likely somatic driver mutations were extracted from WES variant calls (DeepVariant) based on VAF, recurrency in COSMIC, CADD pathogenicity score and a binomial test against the mean VAF. Estimated Glomerular Filtration Rate (eGFR) was calculated using CKD-EPI formula using cystatin-C (eGFR.cys), creatinine (eGFR.creat), or both (eGFR.creat.cys). 10,144 participants were considered ineligible for analysis due to end stage kidney

disease (n=211), any eGFR score <15 (n=20) or missing biochemistry measures (n=9,913) at study entry. Linear and logistic regression models were used with kidney function defined as (i) a binary trait (CKD, eGFR <60; control, eGFR ≥60) or (ii) a continuous trait. A Cox proportional hazard model was used to assess the risk of developing adverse outcomes defined by death, myocardial infarction or stroke. All P values were corrected for false discovery rate

Results: CH, defined as the presence of any mCA and/or somatic mutation, was identified in 5,449 (2.9%) eligible subjects. CH was negatively associated with eGFR.cys (OR=0.44, P=5.9x10^{-5}), but not other eGFR scores, when tested as a continuous variable and was specifically associated with CKD defined by eGFR.cys <60 (n=5,449/185,038, OR=1.02, P=1.2x10^{-8}). Focusing on CH defined by mCA only (n=1,918), eGFR.cys was associated with myeloid mCA (n=176, OR=0.01, P=5.9x10^{-5}) and not lymphoid (n=229, P=0.13) or other mCA (n=1495, P=0.18). Similarly, for CH defined by somatic mutations (n=3,686), the association with eGFR.cys was due myeloid-malignancy related genes (n=3323, OR=0.26, P=1.2x10^{-7}), particularly *JAK2* V617F (n=139, OR=6.5x10^{-4}, P=1.6x10^{-9}) and *TET2* (n=788, OR=0.13, P=9.5x10^{-5}) but not *DNMT3A* or *ASXL1*. The link between myeloid malignancy and CKD is well established, and was replicated in our series, which included participants with a myeloid malignancy diagnosed prior to or within a year of study entry (n=320, OR= 3.9x10^{-3}, P=7.0x10^{-12}). Excluding these cases and also those with any prior history of CVD (n=8,459), we confirmed that myeloid CH was associated with adverse outcomes during follow up (RR=1.57, n=338/3,078, P=1.1x10^{-12}) compared to myeloid CH-free participants (n=9174/176,944). For subjects who had CKD, the risk of adverse outcomes was higher: RR=2, n=1,186/6,991 P=7.6x10^{-78} compared to CKD free participants (n=8326/173,031). Within the CKD group, the risk was further increased for subjects with myeloid CH (RR=1.63, n=59/226, P=1.5x10^{-3}) compared to those who were myeloid-CH free (n=1,127/6,765).

Summary/Conclusion: CH, and specifically myeloid CH, is associated with CKD defined by eGFR.cys. Myeloid CH promotes adverse outcomes in CKD, highlighting the importance of the interaction between intrinsic and extrinsic factors to define the health risk associated with CH.

EP1065 CDK4/CDK6-INHIBITION AS A POTENT APPROACH TO AUGMENT ANTI-NEOPLASTIC EFFECTS OF MIDOSTAURIN, AVAPRITINIB AND NINTEDANIB IN KIT D816V+ NEOPLASTIC MAST CELLS

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Background: Advanced systemic mastocytosis (AdvSM), including aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL) are rare, KIT-driven malignancies with a grave prognosis. Although KIT D816V inhibitors, such as midostaurin or avapritinib, are available, most patients do not achieve a durable complete remission upon treatment with such drugs. Drug combinations may be an approach to improve the outcome of these patients. Cyclin-dependent kinase-4 (CDK4) and CDK6 contribute to cell cycle initiation and growth of normal and neoplastic cells. However, CDK4/CDK6 have not been analyzed as targets in AdvSM so far.

Aims: We aimed at elucidating the role of CDK4/CDK6 as therapeutic targets in AdvSM and evaluated anti-proliferative effects of CDK4/CDK6-inhibitors, alone or in combination with KIT D816V-targeting drugs, on neoplastic mast cells (MC).

Methods: Primary neoplastic cells were isolated from bone marrow (BM) samples of 21 patients [indolent SM (ISM; n=5), ASM (n=2), MCL (n=3) and SM-AHN (n=11)] and used in proliferation studies. mRNA was obtained from 70 additional patients with SM [ISM (n=45), SSM (n=2), ASM (n=7), SM-AHND (n=11), MCL (n=5)]. The MCL-like cell lines HMC-1.1 (lacking *KIT* D816V), HMC-1.2 (*KIT* D816V+), ROSA$^{KIT\ WT}$, ROSA$^{KIT\ D816V}$ and MCPV-1 (expressing RAS G12V, hTert and Large T) were also tested. Expression of CDK4, CDK6 and cyclins D1 and D2 was analyzed by qRT-PCR. Phosphorylation of the retinoblastoma gene product (RB1) was analyzed by Western blotting. The functional role of CDKs was evaluated by shRNA-mediated knockdown of CDK4 and/or CDK6 in HMC-1.2 cells. Proliferation was determined by measuring ^{3}H-thymidine uptake. Apoptosis was quantified by flow cytometry.

Results: CDK4, CDK6 and cyclins D1 and D2 were found to be overexpressed in BM samples from patients with AdvSM compared to samples of ISM patients. shRNA-mediated knockdown of both CDK4 and CDK6 resulted in a growth-arrest in HMC-1.2 cells, suggesting a functional role of CDK4/CDK6 in MC expansion. The pharmacologic CDK4/CDK6-inhibitors palbociclib, ribociclib and abemaciclib were found to suppress proliferation of HMC-1 cells and ROSA cells expressing or lacking *KIT* D816V, with reasonable IC_{50} values (<0.5 µM). In MCPV-1 cells, abemaciclib also induced growth-inhibition (IC_{50}: 1–3 µM), whereas no substantial growth-inhibitory effects were seen with palbociclib and ribociclib (IC_{50} >10 µM). However, neoplastic cells in all primary samples tested were found to be sensitive to palbociclib, ribociclib and abemaciclib (IC_{50}: <0.5 µM), with no differences seen between sub-types of SM. In the MCL-like cell lines, growth-inhibition was accompanied by apoptosis, cell cycle arrest and inhibition of phospho-RB1, the main target of CDK4/CDK6. CDK4/CDK6 inhibitors were also found to induce apoptosis in CD34^{+}/CD38^{-} stem cells obtained from 3 patients with AdvSM. Finally, cooperative effects of drug combinations involving CDK4/CDK6-inhibitors and KIT D816V-targeting drugs were assessed. In these experiments, palbociclib, ribociclib and abemaciclib were found to synergize with the KIT-inhibitors midostaurin, avapritinib and nintedanib in inducing growth inhibition in all MCL-like cell lines, including MCPV-1 as well as in primary neoplastic MC.

Summary/Conclusion: CDK4/CDK6 inhibition is a potent approach to block growth and survival of neoplastic MC and to potentiate anti-proliferative effects of KIT-targeting drugs in AdvSM. Whether such concepts can improve clinical outcomes in patients with drug-resistant AdvSM remains to be determined in clinical trials.

EP1066 TARGETING HDAC AS A NOVEL THERAPEUTIC APPROACH TO COUNTERACT GROWTH OF NEOPLASTIC MAST CELLS IN ADVANCED SYSTEMIC MASTOCYTOSIS

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Background: Systemic mastocytosis (SM) is a hematologic stem cell neoplasm characterized by uncontrolled growth and accumulation of neoplastic mast cells (MC) in one or more organs. In a majority of patients with SM, the D816V-mutated variant of *KIT* is detectable which induces resistance against a number of tyrosine kinase inhibitors (TKI), including imatinib. Midostaurin is a TKI which is known to target *KIT* D816V. This drug has been approved for the treatment of patients with advanced SM by the FDA and EMA. However, long-lasting hematologic remissions are rarely seen and patients treated with midostaurin may also relapse.

Aims: The aim of our study was to identify novel potential drug targets and associated targeted drugs to overcome mutant-induced drug resistance of neoplastic MC.

Methods: For this purpose, a robot-based high-throughput cell viability screen using 8 different MC lines, including the *KIT* D816V+ cell lines HMC-1.2 and ROSA$^{KIT\ D816V}$ was performed.

Results: We identified a number of drugs effectively blocking survival of *KIT* D816V+ MC lines. Among these, HDAC blockers were the most potent inhibitors. The two most promising HDAC blockers, panobinostat and quisinostat, were used in subsequent validation experiments. Both HDAC inhibitors were found to block proliferation of HMC-1.1 (IC_{50}: 5-25 nM), HMC-1.2 (IC_{50}: 2.5-25 nM), ROSA$^{KIT\ WT}$ (IC_{50}: 2.5-25 nM), and ROSA$^{KIT\ D816V}$ cells (IC_{50}: 5-50 nM) as well as the multi-drug resistant cell lines MCPV-1.1, MCPV-1.2, MCPV-1.3 and MCPV-1.4 (IC_{50}:

10-100 nM). Moreover, panobinostat and quisinostat were found to suppress proliferation of primary neoplastic MC obtained from patients with advanced SM (IC_{50}: <10 nM). The two HDAC inhibitors were also found to induce apoptosis in HMC-1 cells. Moreover, combinations of HDAC blockers (panobinostat or quisinostat) and KIT-targeting drugs (midostaurin or avapritinib) produced cooperative growth-inhibitory effects in both HMC-1 subclones as well as $ROSA^{KIT\ WT}$ and $ROSA^{KIT\ D816V}$ cells. As assessed by qPCR, all MC-lines tested as well as primary neoplastic MC obtained from patients with various types of SM were found to express HDAC1 and HDAC2 mRNA. Furthermore, all cell lines investigated were found to display HDAC1 and HDAC2 which was evaluated by immunocytochemistry. In Western blot experiments, both HDAC inhibitors were found to promote the expression of acetylated histone H3 and H4 in HMC-1 and ROSA cells. By contrast, no effects of these drugs on phosphorylation of KIT were seen.

Summary/Conclusion: HDAC inhibitors are novel potent inhibitors of growth of neoplastic MC. Whether HDAC inhibitors alone or in combination with midostaurin or avapritinib are also effective *in vivo* in patients with advanced SM remains to be determined in clinical trials.

EP1067 ONCOGENE-INDUCED MALADAPTIVE ACTIVATION OF TRAINED IMMUNITY IN THE PATHOGENESIS OF HUMAN INFLAMMATORY MYELOID NEOPLASM

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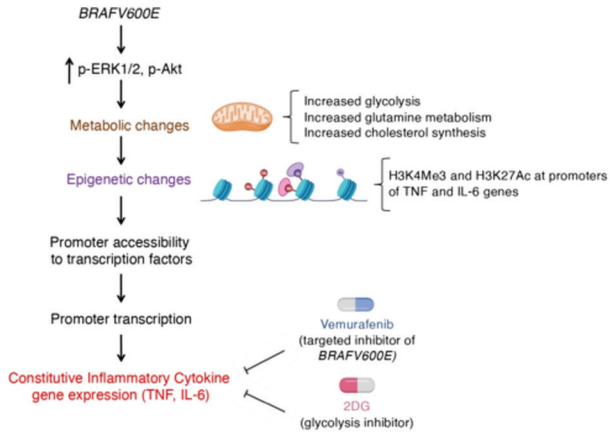
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Background: Trained immunity (TI) is a pro-inflammatory program induced in monocyte/macrophages upon sensing of specific pathogens, and characterized by immunometabolic and epigenetic changes enhancing cytokine production. Maladaptive activation of TI (*i.e.* in the absence of infection) might result in detrimental inflammation and disease development.

Aims: The present study aims at identifying the role and extent of inappropriate activation of TI in the pathogenesis of a human inflammatory myeloid neoplasm (Erdheim-Chester disease, ECD, characterized by the *BRAFV600E* oncogenic mutation in monocyte/macrophages and excess cytokine production).

Methods: Human monocytes engineered to express *BRAV600E* were investigated for the ability to recapitulate TI and ECD features by combining biochemical, genetic, metabolic, and functional approaches.

Results: Mechanistically, we provide evidence that, myeloid cells expressing *BRAFV600E* exhibit all molecular features of TI: activation of the AKT/mTOR signaling axis; increased glycolysis, glutaminolysis, and cholesterol synthesis; epigenetic changes on promoters of genes encoding cytokines; and enhanced cytokine production leading to hyper-inflammatory responses. In ECD patients, effective therapeutic strategies contrast this maladaptive TI phenotype; in addition, pharmacologic inhibition of immunometabolic changes underlying TI (i.e. glycolysis) effectively dampens cytokine production by myeloid cells.



Summary/Conclusion: This study reveals the deleterious potential of inappropriate activation of TI in the pathogenesis of human inflammatory myeloid neoplasms, and the opportunity for inhibition of TI in conditions characterized by maladaptive myeloid-driven inflammation.

EP1068 THE SYNTHETIC TRITERPENOID CDDO-ME BLOCKS SURVIVAL OF NEOPLASTIC MAST CELLS AND SYNERGIZES WITH KIT D816V-TARGETING DRUGS IN INDUCING GROWTH INHIBITION

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Background: Contrasting indolent forms of systemic mastocytosis (SM), advanced SM, including aggressive SM (ASM), mast cell leukemia (MCL), and SM with an associated hematopoietic neoplasm (SM-AHN) are characterized by SM-induced organ damage, disease progression and a poor prognosis. In most patients, *KIT* D816V is detected and is considered to act as a disease-driver. Despite encouraging results obtained with KIT D816V-targeting tyrosine kinase inhibitors (TKI), such as midostaurin, most patients fail to achieve a durable remission. This may be explained by additional oncogenic pathways. Therefore, current efforts are focusing on the identification of suitable combination partners for KIT D816V-targeting TKI. The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid methyl ester (CDDO-Me) acts anti-neoplastic in various malignancies.

Aims: The aim of the present study was to evaluate the anti-neoplastic potential of CDDO-Me, alone or in combination with KIT D816V-targeting TKI, in neoplastic mast cells (MC).

Methods: Primary bone marrow (BM) cells were obtained from 15 patients with SM (indolent SM, n=3; ASM, n=2; MCL, n=3; SM-AHN, n=7). Furthermore, we employed the MCL-like cell lines HMC-1.1 (lacking *KIT* D816V), HMC-1.2 (*KIT* D816V+), $ROSA^{KIT\ WT}$, $ROSA^{KIT\ D816V}$ and MCPV-1 (expressing RAS G12V, hTert and Large T). Proliferation was determined by measuring ^{3}H-thymidine uptake. Apoptosis was quantified by flow cytometry. Western blot experiments were performed to determine drug effects on expression and phosphorylation of target proteins.

Results: CDDO-Me was found to suppress the proliferation of HMC-1, ROSA and MCPV-1 cells, with comparable IC_{50} values (0.1-0.5 µM). Interestingly, no differences were seen between cells lacking or expressing *KIT* D816V or RAS G12V. Growth arrest was accompanied by induction of apoptosis in all cell lines tested. In addition, CDDO-Me was found to inhibit the proliferation of primary neoplastic MC, with IC_{50}-values ranging between 0.1 and 1 µM with no differences observed between SM variants and independent of previous

treatment with midostaurin. Anti-neoplastic effects of CDDO-Me were accompanied by suppression of KIT and AKT expression in HMC-1 cells. However, CDDO-Me also led to upregulation of heme oxygenase-1 (HO-1) in MC lines. Therefore, we combined CDDO-Me with the HO-1 inhibitor SMA-ZnPP. This combination resulted in synergistic effects in all cell lines tested. Finally, potential cooperative effects between CDDO-Me and the KIT D816V-targeting TKI midostaurin, avapritinib and nintedanib, were explored. In these experiments, CDDO-Me was found to synergize with KIT-targeting drugs in producing growth-inhibition in HMC-1 cells as well as in the multi drug-resistant cell line MCPV-1.
Summary/Conclusion: Together, we found that CDDO-Me counteracts growth and survival of various MCL-like cell lines and primary neoplastic MC in SM. CDDO-Me was found to potentiate anti-neoplastic effects of KIT D816V-targeting TKI and to synergize with the HO-1 blocker SMA-ZnPP in producing growth inhibition. Whether CDDO-Me is also effective *in vivo* in patients with ASM/MCL remains at present unknown.

EP1069 GENOMIC LANDSCAPE OF NON-DRIVER MUTATIONS IN MYELOPROLIFERATIVE NEOPLASMS - THE STANFORD EXPERIENCE

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Background: The myeloproliferative neoplasms (MPN) - polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF) - are clonal hematopoietic stemcell disorders with acquired genetic mutations JAK2, CALR, and MPL, that constitutively activate the signal-transduction pathways. Recently, non-driver mutations in TET2, ASXL1, SRSF1 and U2AF1 were reported to be associated with the intiation and disease transformation, independent of the driver mutations in myeloproliferatuve neoplasms.
Aims: To define the genomic landscape of non-driver mutations in myeloproliferative neoplasms.
Methods: This study was conducted at Department of Pathology StanfordUniversity from April 2017 to January 2018. We studied the association of non-driver mutations with the presenting clinical and laboratory characteristics in a cohort of 71 subjects of MPN at the time of diagnosis including 15 polycythemia vera, 17 essential thrombocytosis and 39 subjects of primary myelofibrosis. We used targeted next generation sequencing panel (Illumina) to detect somantic mutations in 54 genes. Genomic DNA was extracted from peripheral blood or bone marrow. Libraries were prepared and sequencing performed on MiSeq. NextGen analysis software was used for alignment, variant calling, annotation and reporting.
Results: Among 71 patients 55(77%) harbored JAK2, 9(13%) CALR and 2(3%) MPL mutations while 5(7%) were triple negative. 36(51%) subjects had driver mutations JAK2, CALR and MPL with co-occuring non-driver mutations in PV, ET and PMF subjects (14 vs 17 vs 69%; *P*=0.001) at the time of diagnosis. The most frequent non-driver mutations are involved in epigenetic regulation, splicing, and signaling like TET2(23%), ASXL1(15%), SRSF2(13%) and U2AF1(7%) being most prevalent in PMF with leukemic transformation (69%; *P*=0.02). The results also indicate that MPNs primarily affects older male patients (median; 66 yrs, male; 69%). At initial diagnosis 36% displayed transfusion required anemia and 56% constitutional symptoms.
Summary/Conclusion: Targeted NGS has become more widely available for the detection of specific MPN associated mutations, allowing early detection of residual disease and leukemic transformation which in turn should lead to improved clinical outcomes for patients by early therapeutic intervention. We further conclude that MPNs have frequent presence of co-occuring non driver mutations, reported in literature to play a key role in the disease initiation, progression and prognosis.

EP1070 AVAPRITINIB AND NINTEDANIB INHIBIT GROWTH AND SURVIVAL OF KIT D816V+ HUMAN MAST CELLS

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Background: Systemic mastocytosis (SM) is a hematopoietic neoplasm defined by abnormal growth and accumulation of neoplastic mast cells (MC) in various internal organs. Major drivers of SM are activating mutations in *KIT*, especially the D816V point mutation, which initiates ligand-independent signaling in MC.
Aims: Several tyrosine kinase inhibitors targeting KIT have already shown clinical activity. However, the D816V *KIT* mutation confers resistance against most KIT-targeting drugs.
Methods: We evaluated the effects of two novel KIT D816V-targeting drugs, avapritinib and nintedanib, on growth and function of neoplastic MC and compared their activity profiles with that of midostaurin.
Results: Avapritinib was found to suppress growth of HMC-1.1 (KIT V560G) and HMC-1.2 cells (KIT V560G+KIT D816V) with comparable IC_{50} values (0.1-0.25 µM). In addition, avapritinib was found to block proliferation of $ROSA^{KIT\ WT}$ (IC_{50}: 0.1-0.25 µM), $ROSA^{KIT\ D816V}$ (IC_{50}: 1-5 µM), and $ROSA^{KIT\ K509I}$ cells (IC_{50}: 0.1-0.25 µM). Even stronger effects were seen with nintedanib (IC_{50} in HMC-1.1: 0.001-0.01 µM; HMC-1.2: 0.25-0.5 µM; $ROSA^{KIT\ WT}$: 0.01-0.1 µM; $ROSA^{KIT\ D816V}$: 1-5 µM; $ROSA^{KIT\ K509I}$: 0.001-0.01 µM). Avapritinib and nintedanib also suppressed the growth of primary neoplastic MC in most patients with advanced SM (IC_{50} of avapritinib: 1-5 µM; IC_{50} of nintedanib: 0.1-5 µM). Growth-inhibitory drug effects were accompanied by signs of apoptosis and downregulation of activation-linked surface antigens CD63, CD71 and CD117 (KIT) in MC. Contrasting midostaurin, both drugs failed to inhibit IgE-dependent histamine release in MC or basophils.
Summary/Conclusion: Contrasting midostaurin, both drugs failed to inhibit IgE-dependent histamine release in MC or basophils. In conclusion, our data suggest that avapritinib and nintedanib are promising drugs for treatment of patients with advanced SM.

EP1071 CALR MUTATION CLEARANCE IN RUSSIAN PATIENTS WITH PHI-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS TREATED WITH INTERFERON-ALPHA

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Background: Mutations in CALR gene exon 9 insertion/deletions along with JAK2 or MPL gene mutations are routine diagnostic markers in phi-negative myeloproliferative neoplasms (MPN). Interferon-α (IFN) selectively targets the malignant clone in MPN patients and can induce both hematological and molecular remissions. Quantitative measurement of JAK2 (V617F) mutation burden is routinely used for treatment monitoring in the therapy of MPN. The value of CALR mutation burden monitoring still controversial.
Aims: To evaluate CALR gene mutation clearance in Russian patients with phi- negative MPNs, treated with IFN.
Methods:. Patients diagnosed in accordance with the WHO (2017) classification and treated at the Outpatient Department of the National Research Center for Hematology from 2015 to 2020 were included in the study (n=27). Among 27 patients with MPNs 16 cases were essential thrombocythemia (ET), 10 cases - primary myelofibrosis (PMF), 1 unclassified MPNs. All cases were tested for the presence of JAK2 (V617F), CALR(exon 9), and MPL (W515L/K) gene mutations by means of allele-specific PCR or fragment analysis. All patients were CALR positive (type 1 or type 2), JAK2 (V617F) and MPL (W515L/K) mutation negative at the onset of disease. Out of 27 patients, 22 were females (81%), and the mean age at diagnosis was 34.6 years (range 18-70). The median of IFN treatment duration was 30,5 months (range 10-68).
Results: Only 2 ET patients with CALR mutation type 2 achieved a minimal or partial molecular response. Both of them had at onset an initial allele load level of no more than 45%. Patients with PMF did not achieve any molecular response. 2 ET patients with the allelic load of 45 and 49% at the onset did not achieve any molecular response despite long-term treatment (49 months or more). Molecular response in patients

with type 1 mutation was 7 out of 14 (50%) - 5 patients with ET and 2 – with PMF. Two PMF patients with molecular response to treatment had an allele load at onset of no more than 30%.

	Age at diagnosis	Sex	Type Mutation	%CALR (debut)	Month of treatment	%CALR	% decrease
ET patient							
1	32	f	Type 1	49	57	26	47
2	30	f	Type 1	45	57	47	0
3	42	f	Type 1	51	16	21	59
4	45	f	Type 1	49	49	69	0
5	34	f	Type 1	48	41	40	16
6	42	f	Type 1	47	28	21	55
7	36	f	Type 1	37	12	14	62
8	29	f	Type 2	45	57	21	53
9	30	m	Type 2	33	68	44	0
10	30	f	Type 2	18	20	22	0
11	40	m	Type 2	51	30	50	0
12	33	f	Type 2	22	11	46	0
13	34	f	Type 2	34	14	25	26
14	21	f	Type 2	46	37	40	0
15	65	f	Type 2	47	15	44	0
16	49	f	Type 2	41	10	46	0
PMF patient							
1	40	f	Type 1	29	53	6	79
2	38	f	Type 1	33	24	45	0
3	23	f	Type 1	50	42	48	0
4	31	f	Type 1	27	27	16	40
5	70	m	Type 1	62	20	75	0
6	23	f	Type 1	49	33	47	0
7	38	f	Type 2	37	68	47	0
8	42	f	Type 2	39	37	42	0
9	27	m	Type 2	45	10	41	0
10	28	f	Type 2	47	63	43	0
n-MPN patient							
1	19	m	Type 1	33	30	43	0

Summary/Conclusion: All patients in our study had more than 20% level of the mutant CALR allele at baseline, in contrast to patients with the JAK2 (V617F) mutation, who often carry low levels of mutant cells. Despite complete hematological remission achieved by all patients included in the study, clearance of mutated clone measured by PCR and fragment analysis of CALR mutation was only partial in some cases. One can speculate that IFN treatment may effectively control malignant cells with CALR mutations while not affecting more differentiated ones. However further studies with separated cell populations are required to support this point and to establish the value of CALR mutation monitoring in the therapy of MPNs.

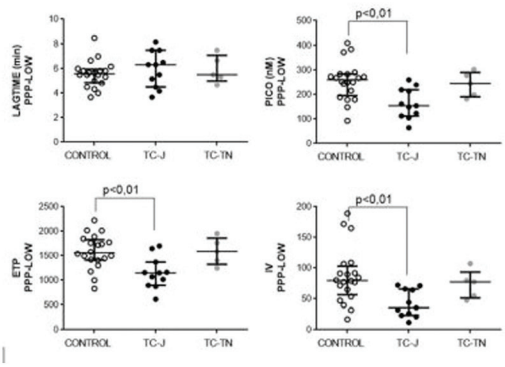
EP1072 RELATIONSHIP BETWEEN MOLECULAR PROFILE AND PLATELET FUNCTION AND THROMBIN GENERATION IN PATIENTS WITH ESSENTIAL THROMBOCYTEMIA

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Background: Myeloproliferative neoplasms (MPNs) like Essential Thrombocythemia (ET) presents with higher platelet counts and driver mutations in JAK2, CALR or MPL. Thrombotic and hemorrhagic complications are main causes of morbidity/mortality. Platelet functional alterations have been previously reported in patients with ET, also higher reticulated platelet fraction and higher aggregation potential compared to healthy controls.
Aims: To investigate platelet activity and thrombin generation (TG) in patients with ET with different molecular mutations.
Methods: Twenty-two adult patients with ET according to 2017 WHO classification and 10 healthy controls were included. Patients did not receive cytoreductive treatment, and antiaggregant drugs were stopped 7 days prior to sample collection. Patients group included JAK2 mutations (n=11), CALR (n=3), MPL (n=1) and triple-negative (TN)(n=5). Platelet characteristics and functional assessment included flow cytometry and TGT using *Calibrated Automated Thrombogram (CAT) using* PPP-low as trigger.
Results: ET patients included 21 females and 1 male with median age of 51 years (24-76). Median platelet count was 631 x10^9/L (245-1102) and median platelet volume was 8,3fL (7,2-10,8). Fibrinogen receptors on platelets from JAK2+ patients had decreased capacity to be activation by agonists TRAP *(p<0.01) and ADP (p<0.01)*. Platelets from JAK2+ and TN patients exposed P-selectin levels similar to controls after agonist stimulation. Decreased CD63 exposure was noted on JAK2+ group after TRAP stimulation *(p<0.05)*.No significant differences in vWF receptor expression were detected among groups. Plasma from JAK2+ patients had less thrombogenic potential according to the reduced values of endogenous thrombin potential (ETP) *(p<0.01)*,peak (p=0.01) and Velocity index (VI) *(p=<0,01) (Figure 1)*. Platelets from patients with MPL mutation had less fibrinogen receptors with reduced capacity to be activated by TRAP and ADP. All evaluated activation markers were decreased in CALR+ platelets. In MPL+, basal exposure of P-selectin and of CD63 were increased compared to controls. vWF receptor level in CALR+ and MPL+ was similar to controls. TG capacity in CALR+ showed decrease in ETP, peak and VI similar to findings in JAK2+. In phospholipid-dependent TG, diminished ETP and activation index was observed in CALR+. TG depending on tissue factor on microparticles was similar to controls in CALR+.

Figure 1. Thrombin generation capacity in JAK2+ and triple negative patients and healthy controls triggered by PPP-Low reactive



Summary/Conclusion: Our results suggest that molecular profile in ET patients may influence platelet activity and TG. Some alterations were also found in CALR+ and MPL+ patients, but due to the small number of patients it´s no possible to conclude a characteristic pattern in these patients Studies increasing number of patients included should be performed to identify a characteristic pattern of haemostasis and coagulation for each mutation that could help to adjust antiaggregant treatment in ET patients.

EP1073 MECHANISTIC ABSORPTION PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL FOR THE MURINE DOUBLE MINUTE 2 (MDM2) INHIBITOR KRT-232: PREDICTION OF FOOD AND PROTON PUMP INHIBITOR EFFECTS

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Background: KRT-232 is a potent, selective, and orally bioavailable inhibitor of MDM2, a key negative regulator of the tumor suppressor protein, p53. KRT-232 restores p53 function resulting in apoptosis of malignant cells. Clinical trials investigating hematologic malignancies and solid tumors are ongoing. KRT-232 is a carboxylic acid that is metabolized primarily to an acyl glucuronide and undergoes enterohepatic recirculation. A 60 mg dose of KRT-232 given after a fast or a high-fat, high-calorie meal gave generally comparable KRT-232 pharmacokinetics (PK; Wong 2020). PBPK modeling was used to extrapolate this observation to higher doses and to define sensitivity of KRT-232 absorption to intrinsic and extrinsic factors.
Aims: 1) Develop an absorption PBPK model for KRT-232; 2) Use the model to characterize regional absorption and fraction absorbed (Fa) across doses; 3) Predict whether PK exposure will be sensitive to gastric pH, gastrointestinal transit times, or meal type.
Methods: The PBPK model was developed in GastroPlus v9.7 (Simulations Plus, Inc.), using KRT-232 physicochemical properties that were mainly measured in vitro. Single dose healthy volunteer PK data (N=30) were from a 60-mg single-dose crossover study that compared a new tablet formulation administered after fasting and after a high-fat, high-calorie meal (Wong 2020). The model was verified against the single-dose clinical PK data, which led to a clearance adjustment. The final model was validated against PK results from a single ascending dose study in patients with advanced solid tumors or multiple myeloma (Gluck 2020, Ma 2019).
Results: Model simulations using the final model were consistent with observed data from healthy volunteers (60-mg single tablet dose) and from fasted cancer patients (60–480-mg single tablet dose; **Table**).
The model accurately reflected the lack of a meaningful change in KRT-232 PK after administration of a 60-mg tablet with a high-fat,

high-calorie meal. KRT-232 Fa was near 100% and was not affected by dose or meal type. Absolute bioavailability was estimated to be ~73%, assuming UGT1A3 is the primary isoenzyme mediating KRT-232 metabolism. Under fasted conditions, most KRT-232 absorption occurred in the jejunum, with the relative amount of drug absorbed in the duodenum increasing slightly after a meal.

KRT-232 exposure was simulated for other meal types; Fa and AUC were not markedly affected. Over a physiologically-relevant range of values, sensitivity analyses showed that complete absorption of KRT-232 had little or no sensitivity to dose (≤ 480 mg), dissolution volume, stomach pH, or stomach transit time.

Simulated Fa of KRT-232 had little sensitivity to solubility from 1.6 µg/mL upwards past the reference solubility of the drug in Fasted and Fed State Simulated Intestinal Fluid (FaSSIF and FeSSIF, respectively [130 µg/mL]). Simulated fasted Fa was >90% with a mean particle radius almost 3-fold higher than that of the active pharmaceutical ingredient. Simulated Fa was even less sensitive to particle size under fed conditions.

Table. Simulated versus observed PK parameters for KRT-232 after 60-mg crossover tablet administration in healthy volunteers (N=30) under fasted or fed conditions (Treatments A1, A2, B) or fasted administration to cancer patients at 60-480-mg doses.

Healthy Volunteer PK									
	C_{max} (ng/mL)[a]			T_{max} (h)[b]			$AUC_{0\text{-}inf}$ (ng·h/mL)[a]		
KRT-232 Treatment[d]	Obs[e]	Sim	Sim/Obs	Obs[d]	Sim	Sim./Obs	Obs[e]	Sim	Sim/Obs
A1 Fasted	434	429	0.99	2	1.5	0.75	2949	2596	0.88
A2 Fasted	428	429	1.00	2	1.5	0.75	3213	2596	0.81
B Fed	442	424	0.96	3	3.2	1.07	2527	2599	1.03
Cancer Patient PK									
	C_{max} (ng/mL)[c]			T_{max} (h)[b]			$AUC_{0\text{-}24}$ (ng·h/mL)[c]		
KRT-232 Dose (mg)	Obs[f]	Sim	Sim/Obs	Obs	Sim	Sim/Obs	Obs[f]	Sim	Sim/Obs
60	530	430	0.81	4.0	nc	nc	2950	1920	0.65
120	600	840	1.40	3.0	1.6	0.53	5160	3840	0.74
240	1350	1610	1.19	2.9	1.7	0.59	8480	7660	0.90
360	2380	2320	0.97	2.0	1.8	0.90	15800	11450	0.72
480	2630	2980	1.13	3.1	1.9	0.61	18800	15230	0.81

AUC, area under the curve; $AUC_{0\text{-}24}$, AUC during 24-hour period; $AUC_{0\text{-}inf}$, AUC to infinite time; C_{max}, maximum concentration; inf, infinity; nc, not calculated; NCA, noncompartmental analysis; Obs, observed; PK, pharmacokinetics; Sim, simulated; T_{max}, time of maximum concentration.
[a]Observed data are geometric means of individual values. [b]Observed data are medians of individual values. [c]Observed data are means of individual values. [d]Treatments A1 and A2 – New tablet fasted was measured in duplicate on separate occasions, Treatment B – New tablet – high fat/high calorie meal, [e]NCA PK parameter values were estimated with PKPlus™ software version 2.0 (Simulations Plus, Inc.) and are similar to Wong et al. *Blood*. 2020. [f]NCA PK parameter values are rounded from Gluck et al. *Invest New Drugs*. 2020.

Summary/Conclusion: The model adequately predicted KRT-232 PK under fasted and fed conditions. KRT-232 is completely absorbed across a wide range of doses, mainly from the jejunum. KRT-232 PK is not likely to be affected by proton pump inhibitor-mediated increases in gastric pH, in accord with its carboxylic acid structure. Because absorption is near 100% under most circumstances, major contributors to variability in KRT-232 PK will most likely be related to post-absorption intrinsic or extrinsic factors.

Myeloproliferative neoplasms - Clinical

EP1074 A PHASE 2 STUDY OF THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) FOR THE TREATMENT OF ADVANCED MYELOFIBROSIS

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Background: Patients with myelofibrosis (MF) require treatment when the clinical benefits of JAK inhibitors are exhausted; there is a clear need for novel therapies. Lysine-specific demethylase-1 (LSD1) is an enzyme critical for malignant stem cells and the differentiation, e.g., LSD1 licenses maturation of megakaryocytes, a key cell in MF pathogenesis. IMG-7289 (bomedemstat) is an orally active LSD1 inhibitor that in mouse models of MPNs reduced peripheral cell counts, splenomegaly, inflammatory cytokines, marrow fibrosis and, importantly, mutant cell burdens (Jutzi *et al.* 2018).

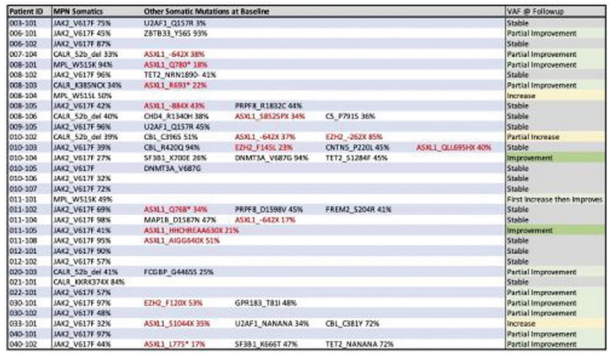
Aims: IMG-7289-CTP-102 is an ongoing, multi-national, open-label, 24-week Phase 2 study of IMG-7289 taken once daily in MF patients resistant to all approved therapies. Key objectives are safety, and reduction a in spleen volume (SVR) and total symptoms scores (TSS). A platelet count ≥100k/µL is a key inclusion criterion. Bone marrow (BM) biopsies and imaging studies are read centrally. Dosing is individually tailored using platelet count as a biomarker targeting a platelet count of 50-100k/µL.

Methods: At the censoring date (15Feb2021), 62 patients had enrolled, 24 patients remain on study. The median duration of treatment is 98 days (14-567). Median age is 68 (35-88) with 50% males; 47% had PMF, 34%, PET-MF, 19%, PPV-MF. All but 6 patients were previously treated with ruxolitinib; 47% had received up to 3 additional treatments. 33% were transfusion-dependent. 58% were IPSS high-risk, 42% intermediate risk-2. Of driver mutations, 66% were *JAK2*, 27% *CALR*, 6% *MPL* and one triple-negative. Of a panel of 261 genes mutated in AML/MPN/MDS, 65% had ≥2 mutation, 46% had ≥1 HMR mutations, 94% were in *ASXL1*.

Results: Of all enrolled patients evaluable at 24 weeks for TSS (N=13), 85% recorded a reduction in TSS (mean change -31%; -81% to 21%) with 31% reporting >50% reduction. Of all patients evaluable for SVR after 24 weeks (N=19), 81% had a reduction in SV from baseline (mean SVR: -8%; -41% to +37%). 72% of evaluable patients (N=36) had stable or improved hemoglobin (>1 g/dL). 26% of evaluable patients had an improvement in fibrosis score by 1 grade while 43% were stable. Elevated serum LDH improved or resolved in 88%.

In 32 patients to date, mutant allele frequencies (MAF) in driver and HMR mutations were reduced in 42% and stable in 50%. All driver mutations showed sensitivity to bomedemstat; most *ASXL1* clones were subject to purifying selection by treatment. When MAFs in driver mutations were stable or decreased, SV and/or TSS was stable (n=2) or improved (n= 17). In subjects with excess blasts (N=12), 8 (67%) improved or resolved during therapy. There has been no progression to AML at up to 550 days. There was no obvious relationship among mutations, final optimal dose or response rates. Germline variants will be discussed. CN-LOH remains a strong driver of mutant gene dosage.

55 patients (89%) reported 1001 AEs of which 63 were SAEs. Eight SAEs, 6 Grade 3 and 2 Grade 2, each occurring once, were deemed related by Investigators to IMG-7289: painful splenomegaly, rectal hemorrhage, cardiac failure, headache, vertigo, gastrointestinal hemorrhage, anaemia and pyoderma gangrenosum. There have been no safety signals, DLTs, or deaths related to drug.



Summary/Conclusion: In this first clinical study of an LSD1 inhibitor in MF patients, IMG-7289 as monotherapy was well-tolerated, improved symptom burdens and reduced spleen volume without safety signals. Additionally, improvements in fibrosis scores, anemia and MAF have been observed.
The study is active and is enrolling in the US, UK, EU and Hong Kong.

EP1075 ADD-ON PARSACLISIB (A PI3K-DELTA INHIBITOR) IN PATIENTS WITH MYELOFIBROSIS AND SUBOPTIMAL RESPONSE TO RUXOLITINIB: INTERIM ANALYSIS FROM A PHASE 2 STUDY

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Background: Ruxolitinib (rux) is highly effective in myelofibrosis (MF). Rux improves symptoms, reduces spleen size, and prolongs survival; however, suboptimal response may occur in a subset of patients (pts), potentially due to persistent PI3K/AKT pathway activation despite continued JAK inhibition. Parsaclisib (INCB050465) is a potent and highly selective next-generation PI3Kδ inhibitor. We hypothesized that adding parsaclisib would improve outcomes in pts with suboptimal response to stable rux treatment.
Aims: This phase 2 study (NCT02718300) evaluated optimal dosing, efficacy, and safety of add-on parsaclisib in pts with MF with a suboptimal response to rux.
Methods: Pts had primary, post–polycythemia vera, or post–essential thrombocythemia MF, ECOG performance status ≤2, and suboptimal response (palpable spleen >10 cm below left subcostal margin [LSM]; or palpable splenomegaly 5–10 cm below LSM and presence of 1 symptom score ≥5 or 2 symptom scores ≥3 each using the Screening Symptom Form) after ≥6 months of rux (5–25 mg twice daily; rux stable dose, ≥8 weeks [wks]). Pts remained on their stable rux dose and were randomized to receive add-on parsaclisib 10 mg or 20 mg once-daily (QD) for 8 wks and the same dose once-weekly (QW) thereafter (QD/QW group), or parsaclisib 5 mg or 20 mg QD for 8 wks and 5 mg QD thereafter (all QD group) (Figure 1). The primary endpoint was change in spleen volume from baseline to wk 12 by MRI/CT scan; other endpoints included change in spleen length and symptoms (Myelofibrosis-Symptoms Assessment Form Total Symptom Score [MFSAF-TSS]).
Results: At data cutoff (Aug 27, 2020) for this interim analysis, 32 pts received parsaclisib QD/QW and 35 received parsaclisib all QD. Median treatment duration was 213 days; median average daily dose was 5.0 mg/day for parsaclisib and 30.0 mg/day for rux. Baseline median spleen volume (cm^3) was 2414 in QD/QW (n=29) and 1885 in QD (n=29); median MFSAF-TSS was 10.8 (n=28) and 16.3 (n=26), respectively. Median percentage change in spleen volume at wk 12 was −1.9 (n=29) in QD/QW and −13.0 (n=27) in QD, and at wk 24 was −3.5 (n=23) and −21.8 (n=17), respectively (Figure 2: [A] spleen volume reduction; [B] palpable spleen length change). Median percentage change in MFSAF-TSS at wk 12 was −14.0 (n=21) in QD/QW and −37.4 (n=17) in QD.
Nonhematologic treatment-emergent adverse events (TEAEs) were primarily grade 1/2; grade 3/4 nonhematologic TEAEs occurring in >1 pt overall were urinary tract infection (n=3; all QD/QW), fall, increased alanine aminotransferase, increased aspartate aminotransferase, hypocalcemia, and hypertension (each n=2; all QD/QW), dyspnea (n=2; both QD), and fatigue and pneumonia (each n=2; each 1 QD/QW, 1 QD). New-onset grade 3 thrombocytopenia was observed in 6/32 (19%) pts in QD/QW and 9/35 (26%) pts in QD; grade 4 thrombocytopenia was observed in 6/32 (19%) pts in QD/QW and 1/35 (3%) pts in QD. TEAEs of special interest included grade ≥2 diarrhea (n=4) and grade ≥2 rash (n=1) (all QD/QW). No colitis was reported. TEAEs led to parsaclisib interruption in 18/32 pts in QD/QW and 18/35 pts in QD, and rux interruption in 6/32 and 8/35 pts, respectively; and to parsaclisib discontinuation in 7/32 pts in QD/QW and 3/35 pts in QD, and rux discontinuation in 2/32 and 1/35 pts, respectively.

Figure 1: Parsaclisib dosing schedules in combination with ruxolitinib

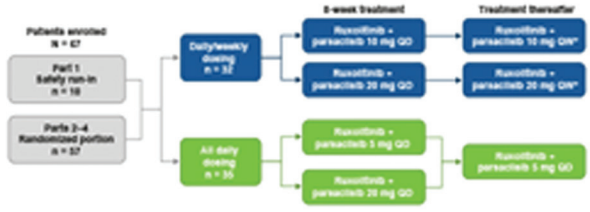
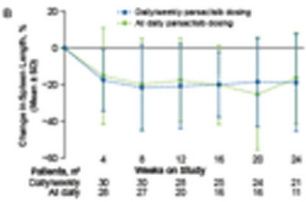


Figure 2: Spleen volume reduction at week 12 and 24 (A) and change in palpable spleen length over time (B), by parsaclisib dosing schedule

A.

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n = 29	n = 27
>10% to <25% reduction	8 (28)	11 (41)
≥25% to <35% reduction	1 (3)	3 (11)
≥35% reduction	0	1 (4)
Week 24	n = 23	n = 23
>10% to <25% reduction	2 (7)	6 (26)
≥25% to <35% reduction	3 (10)	5 (21)
≥35% reduction	1 (3)	2 (9)



Summary/Conclusion: Add-on parsaclisib showed preliminary efficacy in pts with MF experiencing suboptimal response to rux; QD dosing appeared more efficacious than QD/QW dosing. Combination therapy was generally well tolerated with limited grade 3/4 AEs and TEAE-related discontinuations.

EP1076 TOWARDS A POTENTIAL OPERATIONAL CURE IN PATIENTS WITH POLYCYTHAEMIA VERA? RESULTS FROM FIVE YEARS' ROPEGINTERFERON ALPHA-2B THERAPY IN A RANDOMIZED SETTING

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Background: Following long-term interferon-α therapy for polycythaemia vera (PV), hematologic responses persist despite treatment discontinuation in some patients, demonstrating that operational cure can be achieved. Relapse-free discontinuation is more likely in patients who achieved a *JAK2*V617F mutation <10% prior to stopping treatment (Daltro De Oliveira R et al., Blood 2020) but prognostic factors for deep molecular responses to interferon-α are unknown.
Aims: To explore predictive baseline factors in patients who achieved a *JAK2*V617F allele burden <10% after 5 years' ropeginterferon alfa-2b (BESREMi®) therapy and to distinguish this population from patients with allele burden ≥10% regarding clinical outcome parameters.

Methods: Patients with PV diagnosed by WHO 2008 criteria who were cytoreduction-naïve or hydroxyurea (HU) pre-treated were randomised 1:1 to receive ropeginterferon alpha-2b or HU for one year in PROUD-PV. In CONTINUATION-PV, patients received long-term treatment in the study arms originally allocated. Efficacy assessments included complete haematological response (CHR) and *JAK2*V617F allele burden. Patients with a baseline *JAK2*V617F allele burden ≥10% who were treated with ropeginterferon alpha-2b for ≥5 years were analysed using univariate and multivariate logistic regression models to determine predictive baseline factors (including demographics, non-driver mutations, spleen size and PV-related symptoms) and Fisher's or Wilcoxon test to determine other associated factors (including 4-weekly dose level, CHR, duration of maintained CHR, splenomegaly and symptoms) for achieving a *JAK2*V617F allele burden <10% at 5 years.
Results: In CONTINUATION-PV, 66/95 patients enrolled in the ropeginterferon alfa-2b arm had a baseline *JAK2*V617F allele burden ≥10% and had been treated for ≥5 years at the time of analysis, of whom 37 achieved allele burden <10% at Month 60 (last observation carried forward).
Lower age and lower *JAK2*V617F allele burden were identified as predictive baseline factors for achieving a *JAK2*V617F allele burden <10% at 5 years (median age 54.0 years for patients with allele burden <10% vs. 63.0 years in those with allele burden ≥10%; univariate and multivariate analyses p=0.005 and p=0.002; median allele burden 36.8% vs. 46.3%, p=0.03 and p=0.02 respectively). Absence of non-driver mutations was predictive only in the univariate analysis (p=0.02). Time since PV diagnosis, PV-related symptoms and spleen size were not predictive.
Allele burden <10% was associated with a higher CHR rate at Month 60 (CHR in 86.5% of patients with allele burden <10% vs. 58.6% with allele burden >10%; p=0.02) and longer maintained CHR (median: 41.8 vs. 30.3 months respectively; p=0.03). All 37 patients with allele burden <10% had platelets <400 x 10^9/L and leukocytes <10 x 10^9/L at Month 60, but a few patients still required phlebotomy in the 5th year (n=6) or had mild splenomegaly (n=2; spleen size 14.9 cm and 13.4 cm) or pruritus (n=1). Dosing level had no impact on allele burden (p=0.9).
Operational cure defined as allele burden <10%, maintained CHR for the last ≥2 years, and no disease progression, thromboembolic events, or worsening of symptoms in the entire 5-year period was achieved in 27 patients.
Summary/Conclusion: A sizable proportion of patients with PV achieved operational cure after 5 years' ropeginterferon alfa-2b treatment. Lower age and lower allele burden at baseline predicted allele burden <10% at 5 years, suggesting that ropeginterferon alfa-2b should be initiated early in PV to achieve the greatest long-term benefit.

EP1077 PELABRESIB (CPI-0610) IMPROVED ANEMIA ASSOCIATED WITH MYELOFIBROSIS: INTERIM RESULTS FROM MANIFEST PHASE 2 STUDY

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Background: Pelabresib (CPI-0610), a first-in-class, oral, small-molecule inhibitor of bromodomain and extraterminal domain (BET) proteins, has the potential to promote disease-modifying activity through altered gene regulation of key oncogenic, fibrotic, and inflammatory factors in the clonal disease cells of origin in myelofibrosis (MF). Furthermore, pelabresib promotes maturation and ex vivo differentiation of erythroid progenitors (Mertz, ASH 2020). Many MF patients (pts) treated with ruxolitinib (rux) develop worsening anemia and may become red blood cell (RBC) transfusion-dependent (TD) which represents a significant unmet medical need. Here we report improvement of anemia in advanced MF pts as evidenced by achievement of RBC-transfusion independence (TI) in TD pts or sustained mean hemoglobin (Hgb) increase of ≥1.5g/dL for 12 wks in non-transfusion dependent (non-TD) pts.
Aims: Evaluation of pelabresib monotherapy or as add-on to rux in advanced MF pts.
Methods: MANIFEST is an ongoing, open-label Phase 2 study. In Arm 1, pts that were refractory, intolerant or ineligible for JAKi were treated with pelabresib monotherapy. A washout of ≥2 wks since last systemic MF therapy was required. In Arm 2, pts receiving rux but not deriving adequate benefit were treated with pelabresib add-on to rux. Pts are stratified to cohorts 1A and 2A if they were TD (receiving ≥6U RBCs/12 wks) and into cohorts 1B and 2B as non-TD if they did not meet TD criteria. Primary endpoint was achievement of TI ≥12 wks in TD cohorts; ≥35% spleen volume reduction at wk 24 in non-TD cohorts.
Results: As of 29 Sep 2020, 19 TD pts and 27 non-TD pts were treated in Arm 1 (monotherapy). 76% of pts had baseline Hgb <10g/dL (Median: 9, range: 6-15). Median number of prior therapies was 2 (1-6). Median time since last rux dose in non-TD cohort was 9.2 mo (range 0.5-46 mo). In TD cohort, 21% (3/14) of pts achieved TI (median duration of transfusion-free period: 44 wk, range 32-50). In non-TD cohort, mean Hgb increase ≥ 1.5 g/dL sustained over a 12-wk transfusion-free period was achieved by 59.1% (13/22) of pts among which only 1 pt received rux within 4 months of study entry, suggesting the increase in Hgb was not a consequence of rebound due to rux discontinuation.
In Arm 2, 52 TD pts and 26 non-TD pts were treated with pelabresib as add-on to rux. 76% of pts had baseline Hgb <10g/dL (median: 9, range: 6-13). In TD cohort, 36% (13/36) of pts achieved TI (median duration of transfusion-free period: 39 wk, range 18-148). 17.4 % (4/23) of non-TD pts had mean Hgb increase ≥ 1.5 g/dL sustained over a 12-wks transfusion-free period.
In pts with an anemia response, the observed Hgb improvement or achievement of TI has been generally associated with an increase in reticulocyte count and/or increased CD71+ progenitor cells in the bone marrow, suggesting a positive pelabresib effect on erythroid differentiation.
Pelabresib was generally well tolerated. The most common treatment emergent adverse events include diarrhea (46%, ≥Gr3: 4%), thrombocytopenia (40%, ≥Gr3: 22%), nausea (36%, ≥Gr3: 2%), asthenic conditions (32%, ≥Gr3: 2%), respiratory tract infections (32%, ≥Gr3: 4%), dysgeusia (26%, ≥Gr3: 1%) and cough (25%, no ≥Gr3).

Table 1	Monotherapy Non-TD (1B)	Add-on to rux Non-TD (2B)	Monotherapy TD (1A)	Add-on to rux TD (2A)
Mean Hgb increase of ≥1.5 over 12 wks[1,2]	59.1% (13/22)	17.4% (4/23)	-	-
Achievement of TI ≥12 wks[3]	-	-	21% (3/14)	36% (13/36)

[1]Patients are evaluable if they received ≥12wks of treatment; baseline: the latest Hgb assessment prior to C1D1
[2]Post-baseline mean Hgb increase of at least 1.5g/dL is required for any 12 wks RBC transfusion free period
[3]Patients are evaluable for achievement of transfusion independent (TI) ≥12 wks if they have been on treatment for at least 24 weeks by the data cutoff date or if they have been on treatment for at least 12 weeks by the data cutoff day and have achieved the conversion or would have failed to achieve the conversion by week 24

Summary/Conclusion: Pelabresib monotherapy was associated with a mean increase in Hgb ≥ 1.5 g/dL in majority of non-TD pts and conversion of one-fifth of TD pts to TI in heavily pretreated MF pts in Arm 1. Addition of pelabresib to rux in Arm 2 pts with suboptimal response on stable doses of rux resulted in mean increase in Hgb ≥ 1.5 g/dL in 17% of non-TD pts and conversion to TI in more than one-third of TD pts.

EP1078 NAVITOCLAX AND RUXOLITINIB FOR PATIENTS WITH MYELOFIBROSIS AND JAK INHIBITOR EXPERIENCE: RESPONSE DURATION IN PHASE 2 STUDY

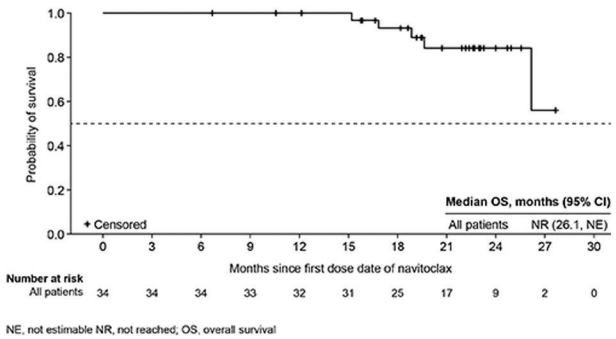
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Background: Navitoclax (Nav) is an oral small-molecule inhibitor of antiapoptotic B-cell lymphoma 2 proteins (BCL-X_L, BCL-2, BCL-W) that has shown pronounced antitumor activity in xenograft models. Interim analyses of an ongoing, multicenter, Phase 2 trial (NCT03222609) of Nav plus the Janus kinase 1/2 (JAK1/2) inhibitor ruxolitinib (Rux) in 34 patients (pts) with myelofibrosis (MF) were previously reported (Pemmaraju et al. ASH 2020, #52).
Aims: To provide an update on the findings from this Phase 2 trial of Nav plus Rux in pts with MF.
Methods: Pts with primary or secondary MF who had previously received Rux for ≥12 weeks continued their current stable dose of Rux, and Nav was initiated at 50 mg/day and escalated to a maximum of 300 mg/day, as tolerated based on platelet count. The primary endpoint was spleen volume reduction of ≥35% (SVR_{35}) from baseline (BL) at Week (Wk) 24. Secondary endpoints included improvement in total symptom score (TSS, as measured by the Myelofibrosis Symptom Assessment Form v4.0), bone marrow fibrosis (BMF), anemia response (per International Working Group [IWG] criteria), and safety. Exploratory endpoints were duration of response (DOR) of SVR_{35}, and overall survival (OS).
Results: At the data cutoff, August 30, 2020, 34 pts with MF received ≥1 dose of Nav plus Rux. Median age was 68 years (range 42–86). At BL, the median spleen volume was 1,695 cm^3 (range 465–5,047). At BL, 9 pts were transfusion independent (TI) with hemoglobin (Hbg) <10g/dL and 2 pts were transfusion dependent per IWG criteria. Of 33 pts with BL testing, 79% and 21% had *JAK2* and *CALR* mutations (4/7 *CALR* type 1, 3/7 *CALR* type 2), respectively, and 19 pts had high molecular risk mutations (HMR); 17 pts had ≥3 genes mutated at enrollment. Median duration of Rux exposure prior to study was 82 wks (range 19–308).
Twenty-four (71%) pts received the maximum Nav dose of 300 mg/day. Median Nav exposure since study onset was 81 wks (range 4–126); 24 pts remain on-study and 17 pts remain on-treatment. Of 17 pts who discontinued Nav, the most common reasons were progressive disease (29%) and adverse events (AEs, 18%).
SVR_{35} from BL to Wk 24 was reported for 9 (27%) pts, independent of HMR, and SVR_{35} at any time was achieved in 15 (44%) pts; responses were seen at wk 12 in 6 (18%) pts. Median DOR of SVR_{35} was 13.8 months (95% confidence interval [CI]: 8.2–not reached), which was similar in pts with and without HMR. TSS was reduced by ≥50% in 6/20 (30%) pts who were evaluable at Wk 24. BMF improved by ≥1 grade at any time on study in 11/33 (33%) pts. Hgb levels improved on-study; 7/11 (64%) pts with Hgb <10 g/dL or transfusion dependency at BL had improvement in Hgb of ≥2 g/dL (n=6) or became TI (n=1). At a median follow-up of 105 wks, median OS was not reached (**Figure**); OS estimate at 24 months was 84% (95% CI: 63.0%–93.9%).
All pts experienced an AE, most common AEs were thrombocytopenia (88%), diarrhea (71%), and fatigue (62%), with most gastrointestinal AEs of Grade 1/2. Thirty (88%) pts experienced a Grade 3/4 AE, and 15 (44%) had a serious AE (SAE). The most common Grade ≥3 AEs were thrombocytopenia (without clinically significant bleeding; 56%) and anemia (32%), and the most common SAE was pneumonia (12%). Thrombocytopenia led to Nav dose reduction in 19 (56%) pts.

Figure. Kaplan-Meier Curve of Overall Survival



NE, not estimable NR, not reached; OS, overall survival

Summary/Conclusion: SVR was durable and encouraging, and improvement in TSS, anemia response, BMF, and OS were clinically meaningful. These data suggest that Nav plus Rux may exert disease-modifying activity in MF and warrant further testing in Phase 3 clinical studies.

EP1079 HIGH MOLECULAR RISK MUTATIONS ARE BIOMARKERS OF CLINICAL RESPONSE AND OUTCOME IN INTERMEDIATE-1 RISK MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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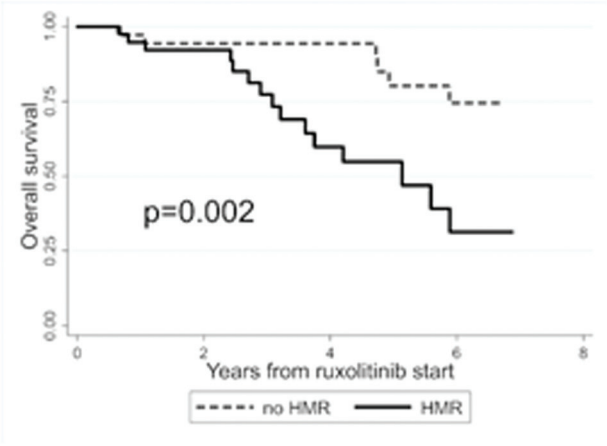
Background: In intermediate (int)-2/high-risk patients (pts) with myelofibrosis (MF), presence of ≥3 high molecular risk (HMR) mutations (*IDH1/2*, *ASXL-1*, *SRSF2*, *EZH2*) was associated with lower response rates to ruxolitinib (RUX) (Newberry, Blood 2016). Although RUX is widely used in int-1 risk pts, the impact of HMR on response and outcome is unknown in this setting.
Aims: To investigate the impact of HMR mutations on treatment success and outcome in int-1 risk RUX-treated MF pts.
Methods: After IRB approval, the "RUX-MF" retrospective study collected 739 RUX-treated MF pts in 25 Hematology Centers. Overall, 361 (48.9%) pts received RUX while at int-1 risk according to DIPSS (primary MF, PMF) or to MYSEC-PM (secondary MF, SMF). In 79 int-1 pts, HMR status was evaluated by next generation sequencing (NGS) before or soon after RUX start. Clinical/laboratory characteristics and RUX starting dose were comparable in these 79 pts and in the 282 with no HMR data available. Spleen (SR) and symptoms (SyR) response were evaluated according to IWG-MRT criteria. Overall survival/RUX stop/blast phase (BP)/infection-free survival were estimated from RUX start to death/RUX stop/BP/infection or last contact and compared with the log-rank test.
Results: The characteristics of the 79 int-1 MF pts at RUX start were: median age 65.7y (24-83); males 55.7%; PMF 44.3%; *JAK2*, *CALR* and *MPL* mutated: 73.4%, 25.3% and 0 (1.3% triple negative), Hb<10 g/dl: 12.7%, PLT>200 x10^9/l: 76%; blast cells≥1%: 33%; spleen length >10 cm: 44.3%, TSS >20: 56.5%, time from MF diagnosis to RUX start >2y

in 46.8%. Starting and cumulative RUX dose >10 mg BID: 74.4% and 57.9%, respectively. Overall, ≥1 HMR was detected in 39 pts (49.4%) (≥2HMR in 12 pts). Specifically, *ASXL-1* was found in 33 pts, *IDH1* in 5, *IDH2* in 3, *SRSF2* in 6 and *EZH2* in 7. While *SRSF2* mutations were detected only in PMF (p=0.005), distributions of the other HMR mutations were comparable in PMF and SMF. HMR pts started RUX more frequently with large spleen (p=0.03) and lower PLT count (p=0.04) compared to no-HMR pts.

At 3 and 6 mos, 26.9% and 31.3% of pts achieved a SR, while 65.6% and 75% were in SyR, respectively. SR was less frequently achieved by HMR pts at both 3 (11.4% vs 43.8%, p=0.003) and 6 mos (18.8% vs 43.8%, p=0.03). SyR was not influenced by HMR status.

PLT count at 3 and 6 mos was always >50 x10^9/l in all cases but two. At 3 and 6 mos, in 33.3% and 29% of transfusion independent pts, Hb decreased <10 g/dl, while 18.7% and 19.7% became transfusion-dependent, respectively, regardless of HMR. At least one infection, mainly including lung (32.8%), urinary tract (11.7%) and gastrointestinal tract (7.6%) occurred in 28 pts, regardless of HMR (log-rank p=0.13).

After a median RUX exposure of 2.7y (0.1-7.7), 36 (45.6%) pts discontinued RUX, 4 (5.2%) progressed to BP and 22 (27.9%) died. In HMR pts, RUX discontinuation (38.9% vs 20.8% at 3y, log-rank p=0.01) and BP progression (10% vs 0 at 3y, log-rank p=0.04) were significantly higher. Overall survival was also significantly shorter for HMR pts (log-rank p=0.002) (**Fig.1**).



Summary/Conclusion: In int-1 pts treated with RUX, HMR mutations are associated with lower responses, increased BP progression and worse survival. HMR evaluation is crucial for personalized management of these pts.

EP1080 BET INHIBITOR PELABRESIB DECREASES INFLAMMATORY CYTOKINES, IMPROVES BONE MARROW FIBROSIS AND FUNCTION, AND DEMONSTRATES CLINICAL RESPONSE IRRESPECTIVE OF MUTATION STATUS IN MYELOFIBROSIS PATIENTS

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Background: Myelofibrosis (MF) is characterized by abnormal megakaryopoeisis and overproduction of pro-inflammatory cytokines (Ck), which lead to bone marrow (BM) fibrosis, progressive anemia, and extramedullary hematopoiesis resulting in hepatosplenomegaly. Driver and high molecular risk mutations are well characterized and impact survival of MF patients (pts). Bromodomain and extraterminal domain (BET) proteins regulate neoplastic myeloproliferation and pro-inflammatory Ck expression mediated by nuclear factor kappa B (NF-κB), serving as a rational target for drug development in MF. Pelabresib (CPI-0610) is a potent, selective BET inhibitor under investigation in the ongoing Phase 2 MANIFEST trial (NCT02158858), given as a monotherapy to ruxolitinib (rux) intolerant/refractory MF pts in arm 1; as an 'add-on' to rux in MF pts who have suboptimal or lost response to rux in arm 2; and as combination therapy with rux in JAK inhibitor naïve MF pts in arm 3. Pelabresib demonstrated reductions in spleen volume and symptoms, improvements in hemoglobin levels, and conversions to transfusion independence.

Aims: Evaluation of translational studies from MANIFEST Phase 2 trial.

Methods: We assessed pharmacodynamic (PD) activity of pelabresib including changes in inflammatory Ck in blood, improvement of BM biology, including fibrosis (BMF), erythroid (Ery) progenitor and megakaryocyte (Mk) histotopography, and impact of mutations status on clinical response.

Results: Rapid PD response was demonstrated by 55% median reduction of blood *IL8* mRNA level compared to baseline (BL) 4 hours post the 1st dose of pelabresib in 101 pts, with similar reduction across arms. Elevated blood Ck levels were observed at BL across arms, consistent with prior MF studies. Reduction of NF-κB and non-NF-κB regulated inflammatory Ck was observed on cycle 1 day 14 (C1D14) across arms and maintained at C5D1 and C9D1.

BMF grading was assessed by local pathologists for BL and post-treatment (most at 24 weeks) biopsies available from 116 evaluable pts. Relative BMF improvement of ≥1 grade was observed in 33% (38/116) of all pts, with 21% (6/29) in arm 1, 41% (16/39) in arm 2 and 33% (16/48) in arm 3. BMF grade worsening was observed in only 6% (7/116) of pts. Exploratory analysis of Ery and Mk lineages by immunohistochemistry staining for CD71 and CD61 were conducted centrally on BM biopsy pairs collected at BL and week 24 for 37 pts. Semi-quantitative analysis revealed an increase in Ery progenitors in 59% (22/37) of pts. Tight clusters of Mk, characteristic in MF BM, were observed at BL, and improvement in Mk histotopography was observed in 65% (24/37) of pts.

Mutation analysis revealed similar mutation profiles at BL across arms, with *JAK2* (65%) and *ASXL1* (47%) as the most frequently mutated genes. The 14 most frequently mutated genes at BL were assessed for correlation with spleen volume reduction by ≥35% (SVR35) or ≥50% reduction of total symptom score (TSS50) at 24 weeks. SVR35 and TSS50 at 24 weeks were similar in pts regardless of mutational status for each of the 14 genes analyzed.

Summary/Conclusion: Our interim translational data demonstrate a robust PD effect of pelabresib in MF pts, indicate broad clinical responses of pelabresib monotherapy and combination with rux irrespective of mutation status, including *ASXL1*, and suggest at a disease-modifying potential of pelabresib by improving BM histotopography and function. MANIFEST-2; a global, randomized, double-blind phase 3 trial (NCT04603495) is currently underway evaluating combination of pelabresib with rux versus placebo with rux in JAK inhibitor treatment naïve MF pts.

EP1081 IMPROVED TRANSFUSION INDEPENDENCE RATES FOR MOMELOTINIB VS RUXOLITINIB IN ANEMIC JAKI NAÏVE MYELOFIBROSIS PATIENTS INDEPENDENT OF BASELINE PLATELET OR TRANSFUSION STATUS

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Background: Momelotinib (MMB) is a potent JAK1, JAK2 and ACVR1 inhibitor with clinical activity against the hallmark features of myelofibrosis (MF), namely anemia, constitutional symptoms and splenomegaly, across the continuum of JAKi naïve or previously JAKi treated intermediate/high risk MF patients as demonstrated in the previously conducted Phase 3 SIMPLIFY-1 & -2 clinical trials (S1, S2). S1 was conducted in JAKi-naïve patients with MF (n=432) double-blind randomized 1:1 to MMB or ruxolitinib (RUX).
MMB demonstrated a statistically non-inferior splenic response rate (SRR) to RUX at the W24 landmark analysis in S1 but did not meet significance for total symptom score (TSS) response. Low SRR and TSS response was observed for RUX in patients with low platelets, while MMB elicited consistent SRR and TSS response across the platelet subsets, comparable to the response in the ITT. Transfusion independence (TI) at W24 was higher for MMB vs RUX patients across all PLT strata.
Aims: Progressive anemia is a common occurrence in MF with nearly all MF patients requiring transfusions as their disease advances. Given the prognostic importance of Hgb and transfusion status in MF patients including evidence that achieving or maintaining transfusion independence by Week 24 with momelotinib is associated with improved OS in S1 and S2, we expanded the previously reported retrospective platelet subset analysis.
Methods: Week 24 TI response rates for MMB and RUX randomized patients in S1 by baseline Hgb and PLT levels and transfusion status were explored.
Results: The data presented here suggest that the prognostically-important W24 TI rate was substantively higher in anemic patients receiving MMB versus RUX, irrespective of the degree of anemia. MMB is also more effective relative to RUX in achieving or maintaining TI in JAKi naïve patients irrespective of baseline PLT count or baseline transfusion status.

	TI Response at Week 24	
	MMB	RUX
ITT Population	67% (143/215)	49% (107/217)
Baseline Hgb Level		
Hgb <8	29% (8/28)	18% (4/22)
Hgb <10	47% (40/86)	27% (26/95)
Hgb <12	62% (99/159)	37% (61/164)
Hgb <14	67% (136/204)	45% (87/195)
Hgb ≥14	64% (7/11)	91% (20/22)
Baseline PLT Count		
PLTs <150	62% (29/47)	43% (24/56)
PLTs <300	68% (93/136)	48% (62/128)
PLTs ≥300	63% (50/79)	51% (45/89)
Baseline Transfusion Status		
TI	81% (119/147)	62% (94/152)
TR	53% (8/15)	31% (4/13)
TD	30% (16/53)	17% (9/52)

Hgb=hemoglobin, ITT=intent-to-treat, MMB=momelotinib, PLT=platelet, RUX=ruxolitinib, TD=transfusion dependent, TI=transfusion independent, TR=transfusion requiring

Summary/Conclusion: Together with data suggesting that TI response at W24 with momelotinib is associated with a survival advantage, these data further support the potential TI benefits of inhibiting ACVR1 in addition to JAK1 and JAK2 with MMB in MF patients.

EP1082 INTENSIVE AND NONINTENSIVE BLAST REDUCTION THERAPY IN ACCELERATED AND BLAST PHASE OF BCR-ABL NEGATIVE MPN

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Background: Accelerated phase (AP) and/or blast phase (BP) of *BCR-ABL* negative myeloproliferative neoplasms (MPN) are associated with poor outcomes. Comparative efficacy of AML-type induction regimens versus non-intensive hypomethylating agent (HMA)-based regimens is not well studied. Further, the lack of standardized response criteria to evaluate the treatment of MPN-AP/BP poses challenges in understanding treatment efficacy between various studies.
Aims: To determine the efficacy of intensive and non-intensive blast-reduction therapy in patients with MPN-AP/BP using uniformly applied study-defined response criteria.
Methods: All patients with MPN-AP/BP assessed at Princess Margaret Hospital between 01/1998 and 12/2020 were identified from the program database. Only patients treated with intensive induction chemotherapy and non-intensive azacytidine (AZA)-based therapy were included.
Intensive treatment included 3+7 (daunorubicin 60 mg/m^2 IV day (d) 1-3; AraC 100-200 mg/m^2 d1-7), FLAG-IDA (fludarabine 30 mg/m^2 IV & AraC 2000 mg/m^2 IV day 1-5; idarubicin 10 mg/m^2 IV d1-3; granulocyte-colony stimulating agent SC d1-6), or NOVE-HiDAC (mitoxantrone 10 mg/m^2 IV & etoposide 100 mg/m^2 d1-5; AraC 1000-1500 mg/m^2 every 12 hours for d1-2).
Non-intensive therapy consisted of AZA or AZA with venetoclax (AV). Targeted sequencing with a myeloid gene panel was performed. The primary endpoint was overall survival (OS) (time of AP/BP transformation until death or last follow-up), and overall response (CR, CRi or reversion back to chronic phase of MPN), using study-defined criteria.
Results: All patients (n=124) with MPN-AP (n=27) and MPN-BP (n=97) treated with intensive chemotherapy (3+7 [n=31]; FLAG-IDA/NOVE-HiDAC [n=46]) or non-intensive therapy (AZA [n=36] AV [n=11]) were included. The proportion of patients >70 years old, with ECOG ≥2, adverse ELN risk, and AP was higher in the non-intensive group. In evaluable patients, higher overall response rates were observed in patients treated intensively (78% [60/77] vs 38% [17/45], p<0.001). There was a trend towards improved response with AV (55% [6/11]) over AZA (32% [11/34]). Similar response rates were observed in patients receiving upfront 3+7 (74% [23/31]) or FLAG-IDA/NOVE-HiDAC (80% [37/46], p=0.58). However, patients receiving upfront 3+7 required more second inductions (29% [9/31] vs 9% [4/46], p=0.03). No difference in HCT rates was observed between induction regimens (43% [9/21] in 3+7 vs 58% [21/36] in FLAG-IDA/NOVE-HiDAC, p=0.4). The median OS for the cohort was 9.7 months (95% CI 8.4-12). There was no difference in OS between the intensive and non-intensive groups (HR 1.13 [95% CI 0.75-1.72].
OS was improved among patients receiving HCT (HR 0.3 [95%CI 0.17-0.54]). Factors significantly associated with shorter OS in multivariable analysis included non-response, BP (vs AP), number of mutated genes, and TP53 mutation. Factors negatively associated with response in multivariable analysis were non-intensive therapy and TP53 mutation.

Outcome	Blast Reduction Therapy					
	INTENSIVE THERAPY			NON-INTENSIVE		
	3+7 (N=31)	FLAG-IDA or NOVE-HIDAC (N=46)	P-value	HMA (N=34)	HMA+Ven (N=11)	P-value#
Best Response* (%)						
CR	9 (29)	14 (30)		1 (3)	3 (27)	
CRi	1 (3)	5 (11)		0	0	
CMPN	13 (42)	18 (39)		10 (29)	3 (27)	
No response	3 (10)	3 (7)	NS	19 (56)	5 (45)	
Progressive Disease	3 (10)	1 (2)		1 (3)	0	
Early Death	2 (6)	5 (11)		3 (9)	0	
Composite Best Response (CR/CRi/CMPN)	23 (74)	37 (80)	NS	11 (32)	6 (55)	NA
Need for re-induction (%)	9 (29)	4(9)	<0.05			
HCT-Eligible‡ (≤70 yo in CR/CRi/CMPN1)	N=21	N=36		N=5	N=3	
HCT performed (%)	9 (43)	21 (58)	NS	3 (60)	3 (100)	NA

*assessed after 1-2 cycles of induction and at time of best response with HMA; NS: not statistically significant
#Intensive vs non-intensive NA: not applicable
‡ patients ≤70 years-old and in CR/CRi/CMPN1

Summary/Conclusion: In this observational study, more rapid responses were observed with higher dose AraC containing regimens FLAG-IDA or NOVE-HIDAC compared to 3+7 in MPN-AP/BP. Azacytidine and venetoclax combination therapy appear to have higher response rate in comparison to azacytidine alone, and merit prospective investigation.

EP1083 CLINICAL AND MOLECULAR FACTORS AFFECTING SURVIVAL AFTER JAK-INHIBITOR FAILURE IN MYELOFIBROSIS: LONG-TERM DATA FROM A MOLECULARLY ANNOTATED COHORT

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Background: JAK-inhibitor (JAKi) therapy has become standard of care for symptomatic patients with myelofibrosis. While effective in ameliorating symptoms of MF, JAKi therapy is limited by variable duration of therapeutic benefit. Survival following JAKi failure is short, and the impact of clinical and molecular factors at JAKi failure is not well studied.
Aims: To characterize the clinical and molecular factors that influence the outcomes of JAKi failure in a myelofibrosis cohort with mature follow-up.
Methods: We conducted a retrospective cohort study analyzing a well-curated dataset of 113 patients in chronic phase MF patients treated with first line ruxolitinib (n=85) or momelotinib (n=28) at the Princess Margaret Cancer Centre between 11/2009 and 02/2019. Patients were included if they had a sample available for targeted mutational profiling of clinically relevant genes in myeloid neoplasms prior to start of JAKi therapy. Paired samples were available for a subset of 55 patients at the time of JAKi failure (n=49), or after sustained clinical response >3 years (n=6). The Canadian MPN Group consensus criteria was used to define JAKi failure along with its pattern: loss or lack of spleen response, cytopenias, progression to acceleration/blast phase (AP/BP), second malignancy, or non-hematologic toxicity (Gupta et al, JCO Oncology Practice, 2020).
Results: Median follow-up in survivors was 74 (range 21-120) months. A total of 107 (95%) patients experienced JAKi failure, and cumulative incidence of JAKi failure at 1,3 and 5 years was 34%, 71%, 87%, respectively. JAKi therapy failure rates were similar for those treated with ruxolitinib or momelotinib. Median overall survival (OS) was 41.8 months after JAKi start and 13.6 months in 107 patients after first line JAKi failure. In multivariate analysis, survival after JAKi failure was associated with high DIPSS score (HR 4.06, 95%CI 1.61-10.21), ECOG ≥2 (HR 5.58, 95%CI 2.27-13.72) and transformation to AP/BP (HR 2.44 95%CI 1.04-5.7)
Paired samples were available for mutation analysis in 49 patients at time of failure, and 6 patients with ongoing clinical response. A total of 30 emergent mutations were observed in 20 (43%) patients with JAKi failure. The most common emergent mutations were in *KRAS* (n=4) and *ASXL1* (n=4); with *RAS* pathway genes (*KRAS*, *NRAS*, *CBL*, and *PTPN11*) the most common class of emergent mutations occurring in 9 (45%) patients. *RAS* pathway mutations at time of JAKi failure, including persistent (n=8) and emergent (n=9) mutations, were present in: 7/23 (30%) patients with spleen progression, 5/10 (50%) with AP/BP, and 1/10 (10%) with cytopenia, 2/4 (50%) with non-heme toxicity, and 1/2 (50%) with secondary malignancy. The presence of persistent or emergent *RAS* pathway (P=0.03, Figure 1), *TET2* (P=0.04), or high molecular risk (HMR; *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1 Q157*)(p=0.009) mutations were associated with inferior survival.

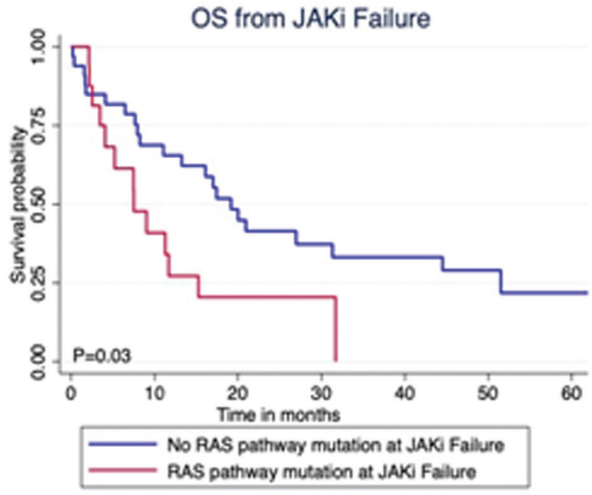


Figure 1: Overall survival following JAKi failure in patients with and without mutations in the *RAS* pathway (*NRAS/KRAS/CBL/PTPN11*)

Summary/Conclusion: Survival following first line JAKi failure is poor. Higher DIPSS/ECOG at time of failure and patients with disease transformation to AP/BP have worse survival compared to other types of JAKi therapy failure. *RAS* pathway gene mutations were the most common emergent mutations at JAKi therapy failure. The presence of persistent or emergent *RAS* pathway (Figure 1), *TET2*, or HMR mutations appear to predict inferior survival following JAKi failure.

EP1084 GENOMIC PROFILING OF MYELOPROLIFERATIVE NEOPLASMS WITH SPLANCHNIC VEIN THROMBOSIS

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Background: Myeloproliferative neoplasms (MPN) are associated with an increased risk of thrombosis that can affect atypical sites, such as splanchnic vein thrombosis (SVT). In some cases, SVT precedes the MPN diagnosis whereas in other cases it occurs sometime after. MPN patients presenting with SVT are usually younger, have less abnormal blood counts and lower *JAK2V617F* allele burden than other MPN patients. However, it is unknown whether clinical and genetic characteristics are different according to SVT chronology.
Aims: The main aim of the present study is to describe the clinical and genomic profile of MPN associated with SVT occurring before, concurrent or after the diagnosis of MPN.
Methods: Ninety-two patients with MPN and SVT were selected. Cases were divided in three categories: Group 1 included patients diagnosed of SVT before MPN; group 2, cases with concurrent diagnoses of MPN and SVT; and group 3, patients with SVT being diagnosed after MPN. Next Generation Sequencing was performed and patients were classified according to the genomic classification proposed by Grinfeld.

Results: In 15 cases (16%) SVT was diagnosed before MPN, in 56 patients (61%) SVT and MPN were concurrently diagnosed and in 21 cases (23%) SVT was found after the diagnosis of MPN. Fifty-two patients (56.5%) were women. The median age was 51, 42 and 43 years in groups 1, 2, and 3, respectively.
Regarding their MPN, 52 cases (57%) fulfilled diagnostic criteria for polycythemia vera (PV), 23 cases (25%) for essential thrombocythemia and 2 (2%) for primary myelofibrosis. Thirteen cases (14%) were classified as MPN, unclassifiable (MPN-U). Group 1 was enriched in MPN-U cases (33% of group 1 cases vs 11.5% and 9.5% in groups 2 and 3, p=0.02), while group 2 was enriched with PV (69% of cases vs 47% and 43% in groups 1 and 3, p=0.02).
In comparison with group 2 and 3, group 1 patients had lower hematocrit value (median 41% vs 46% and 49%, p=0.02) and lower leukocyte count (5.8x10^9/L vs 9.9x10^9/L and 10.9 x10^9/L, p=0.02) whereas patients from group 3 showed higher platelet counts (630x10^9/L vs 339 x10^9/L and 410 x10^9/L in groups 1 and 2, respectively, p=0.02).
JAK2 gene was mutated in 85 patients: *V617F* mutation in 81 cases (88%), exon 12 mutation in 3 cases and non-canonical mutation in 1 case. *JAK2V617F* allele burden was higher in group 3 (43% vs 21% and 28% in groups 1 and 2, respectively, p=0.001). Genomic classification showed MPN with *TP53* disruption/aneuploidy, MPN with chromatin/spliceosome mutation, MPN with *CALR* mutation, MPN with homozygous *JAK2* and MPN with heterozygous *JAK2* mutation in 5%, 17%, 3%, 10%, and 61% of cases, respectively. Analysis according to SVT chronology showed that groups 1 and 2 were enriched in MPN with heterozygous *JAK2* mutation (60% and 77% of cases, respectively, vs 37% in group 3, p=0.01). MPN with *TP53* disruption/aneuploidy was observed in 0%, 7%, and 21%, of cases in groups 1, 2 and 3, respectively. MPN with chromatin/spliceosome mutation was detected in 20%, 15% and 26% of cases in groups 1, 2, and 3 respectively. A higher number of pathogenic mutations was observed in group 3 (median: 2; range:1-6) than in group 2 (median: 1; range: 1-3) or group 1 (median 1; range: 0-4) (p=0.001).
Summary/Conclusion: Patients developing SVT after the diagnosis of MPN have higher *JAK2V617F* allele burden and more genomic complexity than patients with SVT diagnosed before or at MPN diagnosis. Mild or absent hematological alterations due to low genomic complexity might explain the delay in MPN diagnosis in patients with SVT preceding MPN.

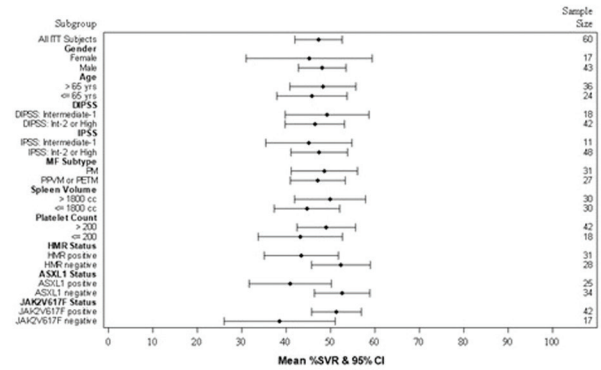
EP1085 CLINICAL BENEFIT OF PELABRESIB (CPI-0610) IN COMBINATION WITH RUXOLITINIB IN JAK INHIBITOR TREATMENT NAÏVE MYELOFIBROSIS PATIENTS: INTERIM EFFICACY SUBGROUP ANALYSIS FROM ARM 3 OF MANIFEST PH2 STUDY

M. Kremyanskaya [1,*], J. Mascarenhas [1], A. Patriarca [2], V. Gupta [3], T. Devos [4], C. Harrison [5], F. Passamonti [6], R. Rampal [7], A. Mead [8], J. Scandura [9], G. Hobbs [10], M. Talpaz [11], N. Granacher [12], T. Somervaille [13], R. Hoffman [1], P. Bose [14], G. Colak [15], J. Shao [15], J. Cui [15], S. Bobba [15], K. Luptakova [15], S. Verstovsek [14], F. Palandri [16]

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Background: The bromodomain and extraterminal domain (BET) family of proteins bind to chromatin to regulate the transcription of target genes involved in multiple pro-fibrotic pathways and is a potential novel therapeutic target for reducing fibrosis in myelofibrosis (MF). Pelabresib (CPI-0610), a first-in-class, oral, small-molecule inhibitor of BET proteins (BETi), has potential to promote disease-modifying activity through altered gene regulation of key oncogenic, fibrotic, and inflammatory factors in the clonal disease cells of origin in MF. Treatment with JAK inhibitor (JAKi) ruxolitinib (rux) or fedratinib in the frontline setting is associated with approximately 30-40% splenic response defined as spleen volume reduction ≥ 35% (SVR35) at 6 months (Verstovsek 2012, Pardanani 2015). The BETi pelabresib monotherapy demonstrated clinical activity in heavily pretreated MF patients (pts) (Talpaz, ASH 2020). In preclinical MF models, the combination of a BETi and rux demonstrated synergistic reduction of splenomegaly (Kleppe 2018). Therefore, combination of pelabresib with rux is expected to achieve higher SVR35 response rate in JAKi treatment naïve MF pts.
Aims: Evaluation of pelabresib in combination with rux in JAKi treatment naïve MF pts.
Methods: Pts with MF who were not previously treated with JAKi were enrolled in Arm 3 of the MANIFEST study. Primary endpoint is SVR35 response (≥35% reduction in spleen volume) at wk 24. Pts were treated with pelabresib 125 mg daily on days 1-14 in a 21-day cycle, in combination with rux which was dosed based on the baseline platelet count.
Results: As of 29 September 2020, 78 pts were treated, and 66 pts were ongoing. Baseline characteristics were mean age: 67 yo; 72% male; primary MF: 54% pts; DIPSS ≥Int-2: 76% pts; IPSS ≥Int-2: 83%; Hgb <10g/dL: 65%; median platelet: 294 x 10^9/L (range: 100, 1849); median spleen volume: 1719 cc (range: 451, 4782); median TSS: 16 (range: 0, 38); high-molecular-risk mutations: 55%, *JAK2* mutation: 72%.
At wk 24, 67% (42/63) pts achieved SVR35 (median % change from baseline: -50%; range: -84.4%, 23.7%). Subgroup analysis showed that mean percentage change in spleen volume at wk 24 was consistent across subgroups based on gender, age, risk score, MF subtype, baseline platelet count and baseline spleen size (Fig. 1). Importantly, subgroup analysis based on molecular findings show a significant benefit regardless of the mutational status, including the presence of *ASXL1* mutation which generally carries a poor prognosis.
Pelabresib was generally well tolerated. The most common treatment emergent adverse events include anemia (33%, ≥Gr3: 30%), thrombocytopenia (32%, ≥Gr3: 8%), diarrhea (30%, no ≥Gr3), dysgeusia (19%, no ≥Gr3), and asthenic conditions (19%, no ≥Gr3).

Figure 1. Subgroup analysis of percentage reduction in spleen volume from baseline at wk 24



Summary/Conclusion: Pelabresib treatment in combination with rux in JAKi treatment naïve MF pts resulted in spleen volume reduction that was greater than what would be expected with rux alone, regardless of baseline patient disease and demographic characteristics.

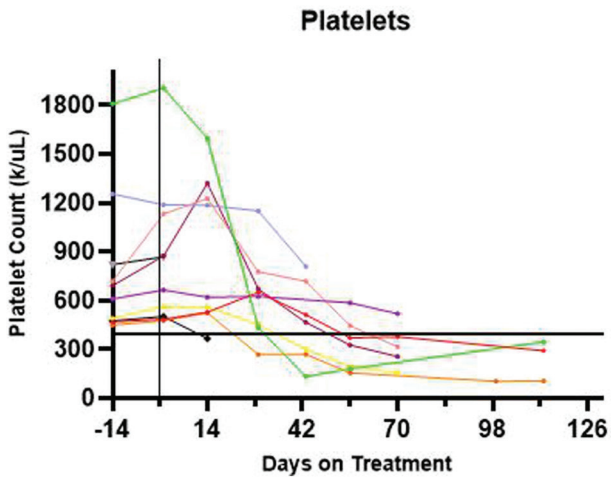
EP1086 A PHASE 2 STUDY OF THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) FOR THE TREATMENT OF ESSENTIAL THROMBOCYTHEMIA (ET)

D. Ross [1,*], T. Cochrane [2], S. Lane [3], S. Larsen [4], A. Gerds [5], A. Halpern [6], J. Shortt [7], J. Rossetti [8], A. Jones [9], J. Peppe [10], G. Natsoulis [11], W. Stevenson [12], N. Vianetti [13], C. Harrison [14], H. Rienhoff [10]

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Background: For patients with essential thrombocythaemia (ET) intolerant of or resistant to hydroxyurea (HU), interferon or anagrelide, there is a need for therapies with distinct MOAs that reduce thromboses, improve the patient experience and potentially offer distinct clinical benefits. Lysine-specific demethylase-1 (LSD1) is a histone H3K4 demethylase critical for the self-renewal potential of malignant myeloid cells and the differentiation of myeloid progenitors, *e.g.*, LSD1 licenses progenitors to mature into megakaryocytes, a cell central to the pathogenesis of ET. IMG-7289 (bomedemstat) is an orally active LSD1 inhibitor that reduced peripheral cell counts, splenomegaly, inflammatory cytokines, and mutant cell burdens in mouse models of MPNs (Jutzi *et al*. 2018). In an ongoing study of IMG-7289 for the treatment of myelofibrosis (MF) (NCT03136185), symptoms, platelets, neutrophils, mutant allele burdens and inflammatory cytokines were favorably impacted (Pettit *et al*. 2020).
Aims: IMG-7289-CTP-201 is an ongoing, multi-national, open-label, 24-week Phase 2b study of bomedemstat taken once daily in patients with ET who are resistant to or intolerant of at least one standard of care treatment (NCT04254978). Key objectives are safety and reduction in the platelet count to ≤400k/μL in the absence of thromboembolic events. Dosing is individually tailored targeting a platelet count between 200-400k/μL. All patients were started at a dose of 0.6mg/kg/d and titrated as needed to the target platelet count range.
Methods: At the censoring date (16 Feb 2021), 10 patients had enrolled. All patients remain on study. The median duration of treatment is 85 days (6-141).
Median age, 66 years (55-84), 20% males. 60% were deemed resistant to or intolerant of HU (by ELN criteria), 20% to anagrelide and 10% to interferon or busulfan. 40% had received at least one additional previous treatment. After a 14- to 28-day washout of prior ET treatment, the mean platelet and WBC counts at Day 1 were 866k/μL (477-1905) and 10.2k/μL (4.4-20.0), respectively.
Results: Of 7 patients who reached Day 71, the mean platelet count was 289k/μL (145-519k/μL), an overall -58% reduction from baseline (mean, -582k/μL). 86% achieved a platelet count of <400k/μL. (See Figure 1.) Mean WBC count at Day 71 was 7.8k/μL (6.8-9.5k/μL), a reduction of -24%. All patients had stable haemoglobins. At baseline, 2 patients had MPN10 TSS >10 (scale 0-100); at Week-12, both had a TSS reduction of >50% while the symptom scores of the remaining patients were stable at <5. There was no obvious relationship among driver mutations, starting platelet counts, final optimal dose or response rates. Germline variants, individual mutational burden and changes in mutant allele frequencies will be presented.
Eight patients have reported 67 AEs, all Grade 1/2. The most common related non-hematologic AEs were headache and diarrhoea, each reported by 2 patients with all instances Grade 1 in severity. There have been no SAEs. There have been no safety signals, DLTs, or deaths related to drug.



Summary/Conclusion: In this first clinical study of an LSD1 inhibitor in ET patients, IMG-7289 as monotherapy was generally well-tolerated, reduced platelets in all patients, moderated WBC counts, improved symptom scores and maintained haemoglobin levels without safety signals. The study is active and enrolling in the US, UK, EU, Australia and New Zealand.

EP1087 SAFETY AND EFFICACY OF MEPOLIZUMAB IN HYPEREOSINOPHILIC SYNDROME: AN OPEN-LABEL EXTENSION STUDY

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Background: Mepolizumab, an anti-interleukin-5 monoclonal antibody, has been shown to reduce disease flares and blood eosinophil counts (BEC) with a favorable safety profile in patients with uncontrolled *FIP1L1-PDGFRA*-negative hypereosinophilic syndrome (HES).
Aims: To further investigate the safety and efficacy of mepolizumab in patients who had previously completed the 32-week, randomized, double-blind, placebo-controlled, Phase III study, 200622 (NCT02836496).
Methods: In this open-label extension study (205203), patients who previously received mepolizumab or placebo during 200622 received 4-weekly mepolizumab 300 mg subcutaneously (SC) for 20 weeks, plus standard of care (SoC) adapted at their physicians' discretion. All patients provided written informed consent. Investigators and patients were blinded to BEC until Week 4. Primary safety endpoints included the number of patients with adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), and anti-drug antibodies (ADAs). Efficacy and pharmacodynamic endpoints included the annualized rate of flares (physician-identified based on worsening symptoms/BEC), plus changes from baseline in mean daily oral corticosteroid (OCS) dose and BEC.
Results: Of the 104 patients who completed 200622, 102 (98%) enrolled in 205203 (previous placebo n=52, previous mepolizumab n=50; 54% female; mean [SD] age 46.0 [15.5] years). Exposure to mepolizumab during both studies was 70.0 patient-years. Overall, 62 (61%) patients experienced on-treatment AEs (**Table**); the maximum severity was mild and moderate for 18% and 31% of patients, respectively. Treatment-related AEs were reported by 15 (15%) patients and one SAE was considered treatment-related; AESIs were uncommon and no events were fatal (**Table**). One patient was positive for ADAs at baseline (but negative thereafter) and no neutralizing antibodies were detected. The mean annualized rates of flares (95% confidence intervals) during 205203 were 0.37 (0.16, 0.86) and 0.14 (0.04, 0.49) events/year for the previous placebo and previous mepolizumab groups, respectively, versus a mean of 2.7 events for each treatment arm in the year preceding 200622. Of the 72 patients using OCS during Weeks 0–4, 20 (28%) achieved a ≥50% reduction in daily dose during Weeks 16–20 (**Table**). Reductions in BEC observed with mepolizumab in 200622 were maintained in 205203; for the previous placebo group, the adjusted mean reduction from baseline at Week 20 was 89%.

Table: Summary of safety and efficacy endpoints

	Mepolizumab 300 mg SC		
	Previous placebo (n=52)	Previous mepolizumab (n=50)	Total (n=102)
Safety endpoints, n (%) patients			
Any AEs	40 (77)	26 (52)	66 (65)
On-treatment AEs	38 (73)	24 (48)	62 (61)
Most frequent* on-treatment AEs, by preferred term			
Diarrhea	8 (15)	4 (8)	12 (12)
Pruritus	4 (8)	3 (6)	7 (7)
Headache	4 (8)	2 (4)	6 (6)
Vomiting	6 (12)	0	6 (6)
Treatment-related† AEs	11 (21)	4 (8)	15 (15)
Leading to study treatment discontinuation	1 (2)	0	1 (<1)
Leading to study withdrawal	1 (2)	0	1 (<1)
Any SAEs	6 (12)	3 (6)	9 (9)
On-treatment SAEs	6 (12)	2 (4)	8 (8)
Treatment-related† SAEs	1 (2)	0 (0)	1 (<1)
Fatal AEs/SAEs	0	0	0
Most frequent* AESIs			
All infections	18 (35)	18 (36)	36 (35)
Local injection site reactions	3 (6)	3 (6)	6 (6)
Efficacy/ pharmacodynamic endpoints			
Rate of HES flares, adjusted mean rate/year (95% CI)	0.37 (0.16, 0.86)	0.14 (0.04, 0.49)	0.26 (0.13, 0.52)
Patients achieving a mean daily OCS dose reduction ≥50%, n (%)‡	14 (37)	6 (18)	20 (28)
Week 20 LS mean ratio to baseline BEC, (95% CI)§	0.11 (0.08, 0.15)	0.52 (0.67, 1.26)¶	N/A

Reductions in mean daily OCS dose were calculated for patients with a mean OCS dose >0 mg/day at Weeks 0–4.
*Reported for >5% of patients overall; †as determined by the treating investigator; ‡in this analysis, n=38 in the previous placebo group and n=34 in the previous mepolizumab group; §in this analysis, n=50 in the previous placebo group and n=48 in the previous mepolizumab group. AE, adverse event; AESI, adverse event of special interest; BEC, blood eosinophil count; CI, confidence interval; HES, hypereosinophilic syndrome; LS, least squares; OCS, oral corticosteroid; SC, subcutaneous; SAE, serious adverse event

Summary/Conclusion: Mepolizumab 300mg SC plus SoC has a favorable safety profile without the development of neutralizing antibodies, and is associated with reductions in flares, OCS use, and BEC. These findings support previous safety and efficacy data for mepolizumab in patients with uncontrolled *FIP1L1-PDGFRA*-negative HES. Funding: GSK [205203/NCT03306043]

EP1088 INCREASED RISK OF PRETERM BIRTH IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS – A POPULATION BASED COHORT STUDY FROM SWEDEN

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Background: A significant proportion, 10-15%, of patients with myeloproliferative neoplasms (MPNs) are of fertile age at diagnosis. Pregnancy in MPN patients is associated with increased risks of numerous complications, including bleeding, thrombosis, and fetal loss. Population-based studies of pregnancy outcomes in MPN patients are rare, and even less is known about risks for the child.
Aims: The aim of this study is to assess adverse pregnancy outcomes in patients with MPN in a population-based setting.
Methods: Patients with MPN were identified in the Swedish Cancer Register and Patient Registers, from 1953 to 2019. All pregnancies in these patients between 1973 and 2019 were identified from the Medical Birth Register, which captures all pregnancies in Sweden starting from gestational week 22 (before 2008 from week 28), thus only viable pregnancies at that gestational week are included in this study. Women with an MPN diagnosis prior to delivery or during the postpartum period (2 months) were included. From the general population, one pregnant control per pregnant MPN patient was randomly selected, matched by maternal age, year of delivery, maternal parity, and whether it was a singleton or duplex pregnancy. Main outcomes were stillbirth, birthweight, small-for-gestational-age, and preterm birth. The two-sided Fisher exact test was used to assess associations, with p-values <0.05 considered statistically significant. In the test comparison, only the first pregnancy after MPN was included.
Results: We identified 342 pregnancies in 229 women with MPN, and equally many in controls, 337 of these were singleton pregnancies and 5 duplex pregnancies, table. Among the 342 pregnancies in MPN patients, 43 were in patients with polycythemia vera, 238 in patients with essential thrombocythemia, 55 in patients with primary myelofibrosis and 6 in patients with MPN-unclassifiable. The mean maternal age at delivery among MPN patients and controls was 31.9 years, range 20-45. Mean birthweight was 3,378 g in children to MPN patients and 3,573 g in controls.

Table. Descriptive statistics and number and proportion of pregnancies in MPN patients and controls respectively with stillbirth, low birthweight, small for gestational age and prematurity. P-values are calculated with two-sided Fisher exact test, including only first pregnancy after MPN diagnosis.

	All identified pregnancies		First pregnancy after MPN diagnosis		
	Number of pregnancies in MPN patients (%)	Number of pregnancies in controls (%)	Number of pregnancies in MPN patients (%)	Number of pregnancies in controls (%)	p-value
Total	342	342	229	229	
Singleton	337	337	225	225	
Duplex	5	5	4	4	
Polycytemia vera	43 (13)	-	27 (12)	-	
Essential thrombocythemia	238 (70)	-	158 (69)	-	
Myelofibrosis	55 (16)	-	40 (17)	-	
MPN-Unclassifiable	6 (2)	-	4 (2)	-	
Stillbirth	2 (0.6)	0 (0)	1 (0.4)	0 (0)	1.0
Low birthweight <2500 g	29 (8)	11 (3)	22 (10)	10 (4)	0.042
Very low birthweight <1500 g	7 (2)	0 (0)	7 (3)	0 (0)	0.015
Small for gestational age	15 (4)	7 (2)	11 (5)	7 (3)	0.47
Preterm < week 37	42 (12)	14 (4)	33 (14)	10 (4)	<0.001
Moderate preterm, week 32-37	31 (9)	12 (4)	22 (10)	9 (4)	0.024
Very preterm, week 28-32	6 (2)	2 (0.6)	6 (3)	1 (0.4)	0.122
Extremely preterm, >week 28	5 (1)	0 (0)	5 (2)	0 (0)	0.061

When restricting to first pregnancy after MPN, there were 229 pregnancies. There was a significantly increased proportion of preterm birth (<37 weeks) in MPN patients (n=33, 14%) compared to controls (n=10, 4%). Furthermore, 11 deliveries were very (week 28-32) or extremely (<28 weeks) preterm in MPN patients, compared to 1 in the control group. The proportion of neonates with low birthweight was also significantly higher in MPN patients (n=22, 10%) versus in controls (n=10, 4%). No significant differences were observed in proportion of small-for-gestational-age or stillbirth, although very few events. There was one neonatal death in the MPN group and one in the control group, both on day 2.
Summary/Conclusion: This large register- and population-based study demonstrated a significantly increased risk of preterm birth in patients with MPN. The higher proportion of low birthweight in children of MPN patients was mainly but not solely driven by the higher proportion of preterm birth. Our novel findings indicate the need for further clarification of the underlying pathophysiology as well as identification of adequate preventative measures. Preterm birth may affect neonatal morbidity and mortality, and have consequences on future health and capabilities, therefore optimizing care in MPN pregnancies to prevent maternal and neonatal complications is of great importance.

EP1089 LONG-TERM FOLLOW-UP OF RECOVERED MPN PATIENTS WITH COVID-19

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Background: To our knowledge, there is no information on long-term follow-up of recovered patients with chronic myeloproliferative neoplasms (MPN) with COVID-19. It can be hypothesized that cytokine storm of the acute phase and the post-COVID persistence of a residual inflammatory state may contribute to elicit hematopoietic stem cell insults and continuous vascular endothelial damage, leading to MPN disease progression and persistent high risk of thrombosis.
Aims: To describe sequelae of COVID-19 in surviving patients with MPN following COVID-19.
Methods: MPN-COVID study involved 38 European blood centers, and accrued 180 patients with MPN diagnosed with COVID-19 from Feb to Jun 2020, assessing mortality and incidence of thrombosis and bleeding during the acute phase of the pandemic [Barbui T et al. Leukemia. 2021;35(2):485-493. Barbui T et al. Blood Cancer J. 2021;11(2):21]. One-hundred-twenty-five (69%) of these patients survived and were followed up for at least 6 months. Centers were asked to update symptoms, treatments, hematological changes, major outcomes (i.e., thrombosis, disease evolution and death).
Results: Among the 125 surviving patients, all eligible for the follow-up update, with a median age 70 years (IQR: 58-79), the following phenotypes were registered: PV (n=38, 30%), ET (n=37, 30%), early PMF (n=14, 11%) and MF (n=36, 29%). During the acute phase of infection, 38 (30%) were managed at home, 80 (64%) in a regular ward and 7 (6%) in ICU.
Symptoms
(i)The 3 prevalent symptoms during the acute phase of the disease were fever (79%), cough (56%) and dyspnea (53%), while gastrointestinal, neurological, musculoskeletal symptoms, as well as fatigue and anosmia/dysgeusia, were present in a minor proportion, ranging from 1.6% to 17%.
(ii) In the post-acute COVID-19 phase, 36 of 125 patients (32%) declared the persistence of some of these symptoms, fatigue being the most frequent (19%), while none presented persistence of fever and only 10% of dyspnea.
Major outcomes
(i) Major thrombosis was documented in 5 patients and involved 3 patients with MF (one fatal intestinal ischemia, two non-fatal events: splenic infarction and peripheral artery thrombosis), one case in PV (acute myocardial infarction) and one with ET (DVT of the legs with pulmonary embolism). Age varied from 61 to 80 years. The first event occurred five months after COVID-19 recovery and the Kaplan Meier thrombosis-free survival probability after 9 months was 82%.
(ii) Acute myelogenous leukemia (AML) was ascertained in 3 patients (1 in MF, 1 in early-PMF, 1 in ET); one was fatal and occurred in a 49-year-old patient, the other 2 in 78- and 82-year-old patients, respectively. One non-Hodgkin´s lymphoma (in ET) and one progression of a previous parotid carcinoma (in MF) were seen in two patients aged 60 and 77 years, respectively.
(iii) Deaths were reported in 8 patients (6.4%), due to AML (n=1), thrombosis (n=1), progression to prior carcinoma (n=2, 1 suspected), multi organ failure (n=1) and heart failure (n=2); the cause was unknown in a single patient. Five deaths (63%) occurred in MF patients.
(iv) Overall, the event-free survival pooling together thrombosis, disease evolution and death reached 66% after 9 months from COVID-19 recovery, indicating that, during this time of observation, 1 out of 3 patients died or have experienced at least one of the other two severe events.
Summary/Conclusion: These results indicate that MPN patients who have survived SARS-CoV-2 infection continue to experience severe events suggesting an increased vigilance in the post-COVID period.

EP1090 AN EPIDEMIOLOGICAL STUDY OF THE CARDIOVASCULAR HEALTH AND THROMBOTIC RISK PROFILES OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS IN PRIMARY CARE ACROSS THE UNITED KINGDOM

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Background: Patients with myeloproliferative neoplasms (MPN) are at increased risk of venous and arterial thromboembolic events (TEEs). Although MPN-specific treatment is generally delivered by specialist haematology centres in the United Kingdom (UK), cardiovascular risk is managed in the primary care setting. In the UK, primary care is provided by the government-funded National Health Service, and patient data is collected by the Clinical Practice Research Datalink (CPRD).
Aims: In this retrospective cohort study, we interrogated the CPRD, a centralized national dataset comprising clinical and prescription records for patients in primary care across the entire UK, for descriptive data on the cardiovascular health and thrombotic risk of all patients with MPN.
Methods: During the study period (1 Jan 2012–21 Aug 2019), adults were indexed at the date of first recorded diagnosis for polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (MF), with a ≥6-month pre-index lookback and ≥24-month post-index follow-up. The study objectives were to determine the MPN epidemiological landscape, extent of co-morbidities (using the Charlson score), thrombotic/cardiovascular risk profiles (before diagnosis) and occurrence of TEEs/cardiovascular events (CVEs) (after diagnosis). MPN diagnoses and co-morbidities were determined using medical and ICD-10 codes; medications were identified using product codes.
Results: Overall, 2,477 patients with MPN (PV, n=1,315; ET, n=336; MF, n=146; unspecified MPN, n=680) of the 19,474,733 patients in the CPRD were identified with a median age at diagnosis of 68 years (range 7 months–101 years); 56% were male. Among all MPN patients, 96.2% had a low Charlson co-morbidity score of 0–5. The prevalence of MPN was 12.72 per 100,000; PV was the most prevalent MPN subtype (6.75 per 100,000), followed by ET (1.73 per 100,000) and MF (0.75 per 100,000). In the total MPN population, the most prevalent pre-diagnosis risk factors were smoking (59.8%) and ischaemic heart disease (27.7%); few patients had hypertension (14.6%), diabetes (13.1%), dyslipidaemia (12.8%) or obesity (8.8%). For risk management, most hypertensive (88.9%), dyslipidemic (82.4%) and diabetic (77.9%) patients were prescribed appropriate medications for management of their blood pressure, dyslipidemia, and diabetes, respectively. Among the patient cohort, 372 TEEs/CVEs occurred after diagnosis (PV, 214 events; ET, 64 events; MF, 9 events; unspecified MPN, 85 events), the most common being stroke (27.2%), deep vein thrombosis (17.7%) and myocardial infarction (MI; 14.8%) (**Table**). Notably, the occurrence of MI was greater for patients with PV (15.9%) than for those with ET (10.9%) or MF (0%).

Table | Occurrence of TEEs and/or CVEs post-diagnosis in the total MPN population and by MPN subgroup.

TEE/CVE Category	Number of TEEs and/or CEEs by MPN subgroup – n (%)				
	All MPN (372 events)	PV (214 events)	ET (64 events)	MF (9 events)	Unspecified (85 events)
Myocardial Infarction	55 (14.8)	34 (15.9)	7 (10.9)	0 (0)	14 (16.5)
Stroke	101 (27.2)	57 (26.6)	15 (23.4)	4 (44.4)	25 (29.4)
Deep Vein Thrombosis	66 (17.7)	43 (20.1)	5 (7.8)	2 (22.2)	16 (18.8)
Peripheral Arterial Disease	8 (2.2)	4 (1.9)	2 (3.1)	0 (0)	2 (2.4)
Pulmonary Embolism	45 (12.1)	20 (9.3)	16 (25)	0 (0)	9 (10.6)
Splanchnic Vascular Thrombosis	9 (2.4)	1 (0.5)	1 (1.6)	1 (11.1)	6 (7.1)
Rare Site Venous Thrombosis	14 (3.8)	10 (4.7)	1 (1.6)	1 (11.1)	2 (2.4)
Migraine	49 (13.2)	29 (13.6)	14 (21.9)	0 (0)	6 (7.1)
Vascular Dementia	25 (6.7)	16 (7.5)	3 (4.7)	1 (11.1)	5 (5.9)

Summary/Conclusion: This study is the first of its kind to describe the cardiovascular health and thrombotic risk profiles of UK patients with MPN in primary care within the CPRD. The prevalence of PV and MF in this study was largely consistent with most known epidemiological reports, but the prevalence of ET was lower. However, MPN subtype was not specified in the CPRD for a sizeable proportion (680 of 2,477 patients). Importantly, in the UK MPN population, the majority were smokers and a considerable proportion of patients (11.1–22.1%) were not prescribed appropriate medications for management of co-morbidities associated with thrombotic risk (hypertension, dyslipidemia or diabetes), highlighting a potential unmet need for improved cardiovascular risk management and coordination between primary and secondary care.

EP1091 ANALYSIS OF THROMBOTIC AND BLEEDING COMPLICATIONS IN 1381 ESSENTIAL THROMBOCYTHEMIA PATIENTS ASSESSED BY R-IPSET THROMBOSIS RISK SCORE: A MULTICENTER RETROSPECTIVE STUDY

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Background: Vascular complications such as thrombosis and hemorrhage are major causes of morbimortality in patients with essential thrombocythemia (ET). The 2016 revised IPSET-thrombosis (R-IPSET-thrombosis) score stratifies patients into very-low (VLR), low (LR), intermediate (IR) and high (HR) risk groups according to thrombosis history, age≥60 years and *JAK2*mut. Such stratification is important as lower risk patients receive less intensive treatment.
Aims: Confirm the prognostic impact of the R-IPSET-thrombosis risk score and other risk factors for thrombosis and major bleeding in a large cohort of adult patients with ET.
Methods: Medical records were retrospectively reviewed for data on thrombotic events, major hemorrhages; and anti-aggregation, anticoagulation, and cytoreductive treatment for 1381 adult ET from 1 French, 1 Italian, 3 Spanish and 5 Polish hospitals. Patients were treated according to local protocols. Statistical analyses were performed using R Core Team 2020 software v4.0.2.
Results: Patient median age was 62 years (54.4% ≥60 years). In terms of driver mutation, 898 were mutated in *JAK2* (65.0%), 264 (19.1%) in *CALR*, and 24 (1.7%) in *MPL*; 176 (12.7%) were triple negative (19 patients were negative for *JAK2* and *CALR* but *MPL* was not determined).
Data on thrombosis and major bleeding was available for 1378 and 1380 patients, respectively. With an average follow-up period of 87.7 months, a total of 91 hemorrhagic events (6.6%) were reported. Thrombotic events occurred in 260 patients (18.8%) before or at diagnosis (dx), and in 173 patients (12.6%) after dx. There were 88 deaths (6.4% of the study population).
Following distribution into risk groups according to the R-IPSET-thrombosis score, thrombosis-free survival (TFS) at 10 years for the VLR, LR, IR and HR groups was 99%, 88%, 83% and 75%, respectively (p<0.0001). Overall survival (OS) according to thrombosis risk group was 96%, 93%, 76% and 71%, respectively (p<0.0001) (**Figure 1**). Comparing the LR and VLR groups, the difference in TFS was significant (Fisher Exact test, p<0.001) but OS was not (HR 1.43, p=0.451).
Logistic regression univariate analysis confirmed the R-IPSET-thrombosis variables of age at dx, cardiovascular risk factors, thrombosis history, and *JAK2*mut as thrombotic risk factors (HR 2.5, 1.9, 2.3, and 1.6, respectively). *CALR*mut was a protective factor (HR 0.43, p=0.0021). In multivariate analysis, only age, previous thrombosis and *CALR*mut retained statistical significance. For thrombotic event prior to dx or at dx, *JAK2*mut was a risk factor (Fisher exact, OR 2.8, p<0.001) while *CALR*mut was a protective factor (OR 0.32, p<0.001); *MPL*mut was not a significant risk factor.
For major bleeding, leukocyte count was a significant risk factor while hemoglobin count was a significant protective factor in multivariate analysis.
Anti-aggregation after dx had a protective effect on thrombosis (HR 0.31, p=0.005) in multivariate analysis but was not protective for major bleeding (χ^2, p=0.708). Thrombosis at 10 years was not a significant risk factor (HR 1.3, p=0.35) for OS while severe bleeding was (HR 2.3, p=0.0011). Among the 249 patients in the VLR group, 12 had severe bleeding (4.8%), of which 9 received anti-aggregation (75%).

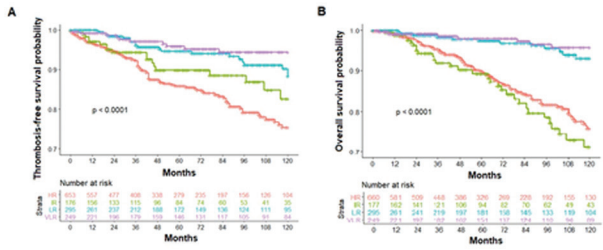


Figure 1. Kaplan-Meier survival curves for the high risk (HR), intermediate risk (IR), low risk (LR) and very-low risk (VLR) groups according to the R-IPSET score, for **A.** Thrombosis-free survival, and **B.** overall survival.

Summary/Conclusion: TFS was significantly different between the risk groups; specifically, the VLR group had a higher TFS than the LR group. Therefore, our results validate the R-IPSET score. Anti-aggregation after dx was protective for thrombosis but not for major bleeding. Major bleeding at 10 years was associated with mortality but thrombosis was not.

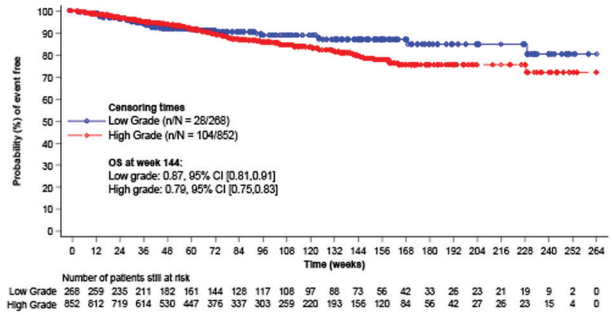
EP1092 IMPACT OF BONE MARROW FIBROSIS GRADE ON RESPONSE AND OUTCOME IN PATIENTS WITH PRIMARY MYELOFIBROSIS TREATED WITH RUXOLITINIB: A POST-HOC ANALYSIS OF THE JUMP STUDY

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Background: Bone marrow (BM) fibrosis is one of the key histological features of myelofibrosis (MF); high-grade BM fibrosis is associated with worse outcome in patients (pts) with MF. Prefibrotic MF is characterized by low-grade BM fibrosis (0-1) and is described as a separate entity from overt MF in the WHO 2016 classification. Ruxolitinib (RUX) is a potent JAK1/JAK2 inhibitor that has shown improvement of MF-related symptoms and increased overall survival (OS) in pts with MF. The JUMP phase 3b, expanded-access trial (NCT01493414) assessed the safety and efficacy of RUX in pts with symptomatic MF without access to RUX outside of the clinical trial setting (N=2,233).
Aims: To investigate the impact of BM fibrosis grade on response and outcome in pts with primary MF (PMF) treated with RUX.
Methods: Pts ≥18 years (y) with PMF, and with an enlarged spleen (≥5 cm from costal margin) were included in this analysis. BM fibrosis was assessed locally by biopsy and graded 0 to 3. Although the primary endpoint of the study was safety, efficacy of RUX was assessed by secondary endpoints including changes in spleen length by palpation, progression-free survival (PFS), and OS. The present work is a post hoc analysis, and thus was not statistically powered.
Results: A total of 1,326/2,233 pts with PMF had a documented biopsy (grade 0, n=25; grade 1, n=243; grade 2, n=433; grade 3, n=419). The median age at baseline was 67 years (range, 18–89 years). Median time since initial diagnosis was similar between pts with lower grade fibrosis (LGF, grade 0-1; 31.8 months [range, 0.3–296.4]) and higher grade fibrosis (HGF, grade 2-3; 25.5 months [range, 0.1–456.0]). Pts with HGF had more cases of anemia and thrombocytopenia at baseline (HGF vs LGF: 46.4% vs 32.5% pts with hemoglobin <100 g/L; 8.6% vs 4.1% pts with platelets <100 x 10^9/L). Mean (SD) palpable spleen length (cm below costal margin) at baseline was similar between patient groups (LGF vs HGF: 11.3 [7.1] vs 12.9 [7.2]), as were mean FACIT – Fatigue and FACT – Lymphoma total scores (34.5 and 115.4 for pts with LGF vs 32.8 and 114.9 for pts with HGF, respectively).
A larger proportion of pts with LGF achieved a ≥50% spleen length reduction at week 24 (62.4% vs 55.1% in pts with HGF). Furthermore, a clear trend was observed between grade of fibrosis and spleen response at week 24 (66.7% for grade 0, 62.0% for grade 1, 59.5% for grade 2, and 50.2% for grade 3). Spleen response at week 24 was higher for pts who initiated RUX ≤2 y after diagnosis irrespective of fibrosis grade (64.0% vs 61.1% in >2 y in LGF; 61.5% vs 49.2% in >2 y in HGF).

PFS estimates at week 144 were 82% for pts with LGF and 70% for pts with HGF. LGF was associated with higher OS at week 144 (91% for grade 0, 87% for grade 1, 80% for grade 2, and 78% for grade 3). OS probability estimate at week 144 was 87% for pts with LGF (n=73), and 79% for pts with HGF (n=156); median OS was not achieved by either pt group (**Figure**). More deaths were recorded for pts with LGF who initiated RUX >2 y after diagnosis (death events: 12.4% vs 8.1% for pts ≤2 y); this effect was not observed in pts with HGF (death events: 11.4% vs 13.0% for pts ≤2 y).



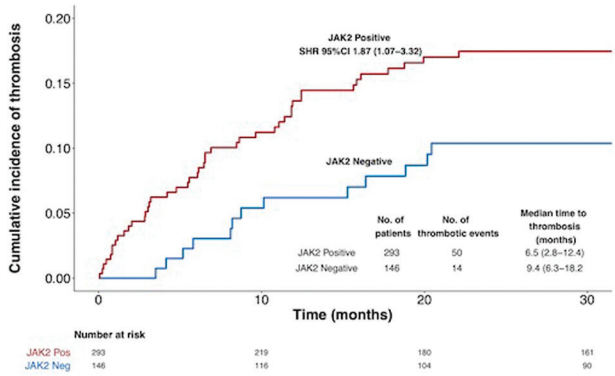
Summary/Conclusion: PMF symptomatology and splenomegaly are comparable in LGF and HGF pts, suggesting an unmet need in LGF pts. RUX therapy is associated with improved spleen responses and survival in both cohorts, but more so in LGF pts; however, LGF could also be a marker of better clinical characteristics at baseline. Early treatment with RUX may improve clinical benefits for both LGF and HGF pts.

EP1093 CLINICAL AND MOLECULAR FACTORS ASSOCIATED WITH THROMBOSIS IN MYELOFIBROSIS

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Background: The clinical and molecular factors for thrombosis in myelofibrosis are not well studied.
Aims: To measure the association of molecular and clinical factors with thrombotic events in MF.
Methods: Design: Retrospective, single-centre study.
Study Population and Setting: All chronic phase MF patients from 2004 to 2018 seen at Princess Margaret Cancer Centre, Toronto, Canada.
Exposure: Our primary exposure variable was *JAK2* mutation; and *DNMT3A*, *ASXL1* and *TET* mutations in a subset with myeloid next generation sequencing availability. Clinical variables were age, sex, cardiovascular risk factors (smoking, hypertension, diabetes mellitus, and hypercholesterolemia), thrombosis prior to MF diagnosis, blood counts, DIPSS risk.
Outcomes and measures: The primary outcome was cumulative incidence of first thrombosis (arterial or venous) 30 days after diagnosis. The effect of covariates was measured as sub-distribution hazard ratio (SHR) using Fine-Gray method to account for competing risks from death.
Results: Total 439 MF patients were included in the study, 229 (52%) were primary, 153 (35%), secondary, and 57 (13%) pre-fibrotic. The median age was 68.6 years (SD 12.7), 59% were male. The median follow-up was 4.2 years (Range 0-18). *JAK2* mutations were detected in 293 patients (66.7%), *CALR* in 82 (18.6%), *MPL* in 26 (5.9%), and 38 (8.6%) were triple negative with no canonical MPN driver mutations. 228 (52%) had next generation myeloid sequencing results: 120 (52.6%) had at least 1 Tier I/II mutation in *ASXL1* (n = 83, 36.4%), *EZH2* (n = 22, 9.6%), *IDH1* (n = 3, 2.8%), *IDH2* (n = 2, 1.8%), *SRSF2* (n = 11, 10%); *DNMT3A* (n=18, 7.9%) or *TET2* (n=68, 29.8%).
There were 64 (14.6%) thrombotic events (37 venous, 27 arterial) after diagnosis. The median time to thrombosis was 8.1 months (IQR 3.1-15.6). The 1-year cumulative incidence of thrombosis was 11.2% (95% CI 8.3-14.5) [6.6% (95% CI 4.3-8.2) arterial and 6.7% (95% CI 5.1-8.1) venous]. The incidence rate ratios for thrombosis per 100 person-years for those with *JAK2* mutation compared to those without was 2.6 (1.9-4.9, p-value <0.001). The univariate Fine Gray analysis showed only *JAK2* mutation and prior thrombosis were associated with increased thrombosis risk (Figure 1) and also remained significant in the multivariable model [SHR: *JAK2* mutation 1.93, 95% CI 0 1.07-3.59; prior thrombosis 4.06, 95% CI 2.38-6.90]. For model validation, bootstrap cross-validation with 1000 samples was used. The Wolber's concordance index at 1-year was 0.65, suggesting adequate discrimination. The model showed good calibration graphically.
We then studied the influence of clonal hematopoiesis associated mutations (*DNMT3A*, *ASXL1*, *TET2*) on thrombosis in a subset cohort of 228 patients. Patients with *TET2* mutation had a significant association with thrombosis in univariate analysis; *DNMT3A* or *ASXL1* mutations did not. In the multivariable model, *TET* mutations did not show an independent effect on thrombotic risk. Patients with co-occurrence of *JAK2* and *TET2* mutations (SHR 4.95, 95% CI 1.8-13.7) had similar thrombotic risk compared to patients with *JAK2* (SHR 3.02, 95% CI 1.10-8.3) mutation alone (p-value 0.1). Prior thrombosis remained a significant variable in this model.



Summary/Conclusion: In MF, the 1-year cumulative incidence of thrombosis after diagnosis was 11.2%. *JAK2* mutation and prior thrombosis independently predicted a higher risk of thrombosis. *DNMT3A*, *TET2* or *ASXL1* did not show an independent effect on risk of thrombosis. These data provide useful information to further develop thrombo-prophylaxis strategies in MF patients.

EP1094 WHEN MYELOPROLIFERATIVE NEOPLASMS MEET COVID-19: INFLAMMATION, ENDOTHELIOPATHY AND COAGULOPATHY

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Background: Myeloproliferative Neoplasms (MPNs) - polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) - are marked by thrombosis. COVID-19 infection is marked by thrombosis as reported in China and confirmed in autopsies of patients experiencing sudden death. The thrombosis in MPNs is related to inflammation and endotheliopathy. The thrombosis in COVID-19 may be related to devastating enhancement of inflammation ("cytokine storm") and profound endotheliopathy, known as COVID-19-associated coagulopathy (CAC). It is showed that patients with hematological malignancies and COVID-19 had worse outcomes. It is unclear if COVID-19 exerts additive or synergistic thrombotic effects.
Aims: Therefore, we evaluated Interleukin-6 (IL-6) and Tissue Factor (TF), as inflammatory and endothelial mediators, D-dimer (DD), thrombin antithrombin complex (TAT) and Fibrinogen (Fib), as coagulation activation mediators, platelet factor 4 (PF4), as platelet activation mediator, and whole blood viscoelastic analysis, as indicator of whole hemostatic activation.
Methods: The cohort study included 120 WHO-defined MPNs patients with COVID-19 ascertained by positive RT-PCR on nasopharyngeal swab (n= 40 PV, n= 40 ET, n= 40 PMF) (60 men, 60 women; mean age 51 years, range 32-60) and 90 WHO-defined MPNs patients without

COVID-19 (n= 30 PV, n= 30 ET, n= 30 PMF) (45 men, 45 women, mean age 50 years, range 30-60). All patients gave written informed consent for study enrollment. The mean duration of disease was 12 years. All patients were on ASA 100 mg once daily. Concerning presentation and therapy, our MPNs patients with COVID-19 and without COVID-19 had not comorbidities and drug treatment was consistent with therapeutic standards (hydroxyurea, interferon, anagrelide, ruxolitinib). All patients were on ASA 100 mg once daily. IL-6 was measured by multiplex bead array (Millipore Sigma), TF and DD, and TAT by ELISA and Fib by Clauss method. PF4 was determined by ELISA. Whole blood viscoelastic analysis including clotting time (CT), and clot formation time (CFT) were measured by thomboelastometry method.

Results: MPNs with COVID-19 had high IL-6 and TF (50±12pg/ml and 1950±500 pg/ml) compared with MPNs without COVID-19 (3±2pg/ml and 19±2 pg/ml), as well as DD, TAT and Fib (549±100 □g/l, 69±10 □g/l and 590±20mg/dl) compared with MPNs without COVID-19 (59±5□g/l, 2±1□g/l and 149±10 mg/l). PF4 was elevated (150.1□62.7 IU/ml) in MPNs with COVID-19 compared with MPNs without COVID-19 (2□1 UI/ml). A positive correlation was found between inflammatory, endothelial and coagulation mediators. A p-value of <.05 was considered statistically significant. Shortened CT (CT, unit: s. n.v. 100-240 s) (40±20 s) and shortened CFT (CFT, unit: s, n.v. 30-160 s (14±10 s) there were in MPNs with COVID-19 compared with MPNs without COVID-19 (CT 99±10 s and CFT 39±5 s).

Summary/Conclusion: These data suggest that COVID-19 infection in MPNs patients may increase the thrombotic risk and get worse prognosis. In our opinion, this study can serve as a baseline study of COVID-19 thrombotic risk in MPNs and it is worthy of dissemination amongst patients and clinician communities.

EP1095 FIRST REAL-LIFE RESULTS ON PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS TREATED WITH MIDOSTAURIN IN FRANCE

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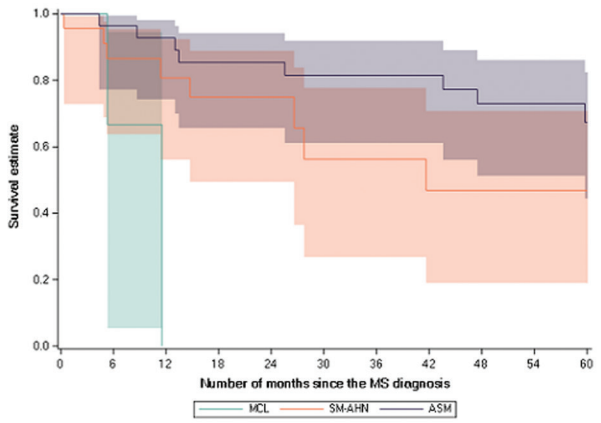
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Background: Mastocytosis is a heterogeneous group of rare diseases related to the proliferation and/or abnormal accumulation of mast cells in one or more organs. The most common form, observed mostly in children, is cutaneous mastocytosis where the infiltration of mast cells is limited to the skin. When it reaches other organs, the disease is called systemic mastocytosis (SM). SM is frequently indolent with normal life expectancy but is life threatening in patients with advanced SM. In France, midostaurin, a tyrosine kinase inhibitor, is the only approved treatment for the three advanced SM subtypes [Aggressive Systemic Mastocytosis (ASM), Systemic Mastocytosis with Associated Haemotological Neoplasms (SM-AHN) and Mast Cell Leukemia (MCL)].

Aims: This study aimed to describe in real-life the characteristics and outcomes of patients treated with midostaurin for advanced systemic mastocytosis.

Methods: A retrospective cohort study was conducted using the French National Healthcare Database (SNDS). The study population included all adults patients with advanced SM treated with midostaurin between January 1, 2012 and September 30, 2018. Kaplan Meier model was used to assess survival and competing risk survival model was used to assess treatment duration, using death as competing risk. Survival analysis was realized on a sub-group of 61 patients exclusively affiliated to the French general insurance scheme.

Results: Overall, 81 patients treated with midostaurin for advanced SM were identified and their data collected, mainly from 2016 and later on (68%). The most frequent subtype was ASM (n=37), followed by SM-AHN (n=31) and MCL (n=4). The SM subtype was undetermined in 9 patients. The median age was 67 years and 64% of patients were men. Over the 11.4 months mean follow-up, median midostaurin treatment duration was 8.4 months and 28 patients were still on treatment at the end of the study. Discontinuation from the study was firstly due to a treatment discontinuation (42%) followed by the end of the study period (Dec 31, 2018, 35%), death (16%) and switch to another treatment (7%). The estimated overall survival (considering any deaths) from time since diagnosis was 83% at one year and 56% at five years. The overall survival in the different MS sub-types was statistically different (p=0.0095) with ASM>SM-AHN>MCL: 1-year overall survival was respectively 93% for ASM patients, 81% for SM-AHN patients and 0% for MCL patients. Over the follow-up period, 12 serious adverse events were identified, with the most frequent one being pneumonia (N=6 patients).



Summary/Conclusion: This study described for the first time the characteristics and outcomes of patients treated in real-life with midostaurin for advanced SM. It highlights that in routine clinical practice the characteristics of the patients, their disease management, treatment tolerance (treatment discontinuation) and survival were in line with previous published results (compassionate use and clinical trials). This study confirms the positive outcomes of midostaurin in AdvSM patients in France.

EP1096 OVERALL AND CAUSE SPECIFIC CHANGES IN MORTALITY OF PATIENTS WITH MYELOFIBROSIS OVER THE LAST 3 DECADES

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Background: Patients with myelofibrosis (MF) have decreased overall survival with a median of 5 years. Leading causes of death are believed to be directly or indirectly related to MF progression or complications, including transformation to acute leukemia (AML) and infections.

Aims: We aimed to compare survival, mortality rate and causes of death of MF patients referred to our institution before (≤) and after the years of 2010.

Methods: This retrospective study included patients with MF diagnosed within one year prior to their presentation to our institution (between January 1990 and February 2020, 4% presented < year 2000). Patients with unknown cause of death or loss to follow-up were excluded (final cohort, n = 995). Causes of death were divided into groups: i) MF progression; ii) AML (≥ 20% blasts); iii) sudden multi-organ failure or vascular event (possibly related to MF, Vasc/MOF); iii) infections (MF had to be controlled or in remission); iv) other (unrelated medical conditions). We calculated crude mortality rate per 1000 person - years of observation (comparison by Poisson's regression) and overall survival (by Kaplan Meier method with log rank test). To account for variations in age groups (< 49; 50-59; 60-69; and 70+ years), we assessed age-adjusted mortality rates per 1000 person-years standardized for the entire cohort.

Results: The study included 378 and 617 patients ≤ and > 2010, respectively, 59% of which were males. Sixty-five percent of patients were ≥60 years. Distribution of age groups between periods was comparable, except for higher proportion of 70+ year old patients > 2010, counterbalanced by lower proportion of < 60 years.

Over the observation time of 1942 and 1608 person-years for ≤ and > 2010, 206 (55%) and 100 (16%) of patients died, respectively (p < 0.001, RR 0.54, CI 0.48-0.63). Crude, age-adjusted and cause-specific mortality per 1000 person-years in both periods is outlined in Table.

Overall mortality, both crude and age-adjusted, was significantly higher ≤ 2010 irrespectively of gender and age. As expected, crude mortality steadily increased with age in both periods. For each of the respective age groups, more patients died ≤ 2010 than > 2010. In both periods, males

had higher mortality than females; but it has decreased > 2010 for both genders. Whilst comparable death rate was observed between < 49 years males and females, it was significantly higher in males for all other ages regardless of periods.
Leading cause of mortality for all combined ages was AML, followed by MF, infections, Vasc/MOF and other causes. However, when MF related and possibly related causes of death (Vasc/MOF, or /i+iii/) were combined, this group was leading cause of mortality ≤ 2010, and was comparable to AML > 2010. Cause specific crude mortality has decreased > 2010 for all subcategories, except for AML, which remained unchanged between periods. MF and AML related cause of deaths were increasing with age irrespectively of periods (Table).

Mort. per 1000 person-years	All patients		< 49yo	50-69yo	60-69yo	70+yo
	< 2010	≥ 2010	< / ≥ 2010	< / ≥ 2010	< / ≥ 2010	< / ≥ 2010
Died, N (%)	206 (55)	100 (16)	18 (31) /5 (4)	56 (51) /16 (13)	73 (56) / 40 (66)	59 (75) / 41 (20)
Crude Mort.	106	62	46 / 13	89 / 46	115 / 66	205 / 94
Age Adj Mort.	74	35				
Females, N (%)	76 (45)	22 (9)	9 (30) / 1 (4)	20 (39) /4 (9)	29 (48) / 10 (10)	18 (62) /7 (11)
Crude Mort.	77	35	43 / 12	57 / 30	87 / 36	193 / 53
Age Adj Mort.	54	16				
Males, N (%)	130 (63)	78 (21)	9 (31) / 2 (5)	36 (62) / 12 (16)	44 (62) / 30 (25)	41 (82) / 34 (24)
Crude Mort.	136	79	49 / 16	130 / 56	147 / 90	210 / 112
Age Adj Mort.	89	48				
MF, N (%)	56 (15)	28 (5)	3 (5)/0	16 (15)/1 (1)	18 (14)/9 (4)	19 (24)/18 (9)
Crude Mort.	29	17	8 / 0	25 / 3	28 / 15	66 / 41
Age Adj Mort.	23	14				
AML, N (%)	61 (16)	40 (6)	7 (12)/2 (3)	21 (19)/9 (8)	19 (15)/13 (9)	14 (18)/10 (5)
Crude Mort.	31	25	18 / 10	33 / 26	30 / 49	49 / 23
Age Adj Mort.	18	12				
Vasc/MOF, N (%)	21 (6)	4 (1)	--	5 (5)/1 (1)	7 (5)/1 (1)	9 (11)/2 (10)
Crude Mort.	11	3	--	8 / 3	11 / 2	31 / 5
Age Adj Mort.	10	2				
Infections, N (%)	44 (12)	21 (3)	6 (10)/1 (2)	12 (11)/4 (3)	19 (15)/7 (3)	7 (9)/9 (5)
Crude Mort.	23	13	15 / 5	19 / 11	30 / 12	24 / 21
Age Adj Mort.	11	8				
Others, N (%)	24 (6)	7 (1)	2 (3)/0	2 (2)/1 (1)	10 (8)/4 (2)	10 (13)/2 (10)
Crude Mort.	12	4	5 / 0	3 / 3	16 / 7	35 / 5
Age Adj Mort.	12	3				

Summary/Conclusion: In our study, we provide specific details on overall and cause specific mortality for patients with MF and show declining rates in the last decade (> 2010). However, the leading cause of death still remain MF and AML, implying ongoing need for clinical research and novel therapies.

EP1098 ACQUIRED VON WILLEBRAND SYNDROME IN MYELOPROLIFERATIVE NEOPLASMS WITH EXTREME THROMBOCYTOSIS

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Background: Acquired von Willebrand syndrome (AvWS) is a rare bleeding disorder that resembles inherited von Willebrand disease. AvWS may be associated with myeloproliferative neoplasms (MPN), due to the adsorption of von Willebrand Factor (vWF) on platelets (PLT), and enhanced cleavage of vWF multimers. Current guidelines recommend to test VWF activity in MPN with PLT above 1000 x10^9/L. However, there is no convincing evidence that correlates PLT count, VWF activity and risk of bleeding.
Aims: We aimed to describe vWF parameters, in terms of antigen and functional activity, and correlate the frequency of AvWS with risk of bleeding in MPN patients with extreme thrombocytosis, considering different PLT thresholds and different severity of AvWS. Moreover, we analysed the impact of patients' genotype.
Methods: We interrogated our MPN database to identify patients affected with essential thrombocythemia and polycythemia vera and extreme thrombocytosis (PLT higher than 1.000 x10^9/L) and identified 58 patients (15 at diagnosis, 43 during follow-up), as reported in table. vWF testing included vWF antigen (vWF: ag) and vWF ristocetin cofactor activity (vWF:RCo). AvWS was diagnosed when vWF:RCo was below the normal range (50-200%), vWF:RCo / vWF: ag was below 0.7 and in the absence of a familial history. Analyses were performed in 3 clusters of PLT count (1000-1200, 1200-1400, >1400 x10^9/L, defined as mild, intermediate ad severe thrombocytosis respectively). Severe AvWS was diagnosed for vWF:RCo below 30%.
Results: We found an inverse relationship between PLT count and vWF:RCo (Spearman's Rho=-0.4 P 0.002). VWF:RCo was significantly different (*P* 0.022) in the 3 clusters of thrombocytosis, with a median of 44.4% (IQR 35.7-65.6) in mild thrombocytosis, 32.6% (IQR 26.9-38.2) in intermediate and 35.2% (IQR 29.8-44.9) in severe. Frequency of AvWS was higher among *JAK2* mutated patients (26/30, 86.7%) as compared to *CALR* mutated ones (5/24, 62.5%, *P* 0.056). Also median vWF:RCo was different according to genotypes (*P* 0.004), being 35.9% (IQR 27.9-44.4) in *JAK2* mutated patients, 44.2% (IQR 32.4-63.9) in *CALR* mutated patients, and 68.5% (IQR 67.4-76.6) in triple-negative ones. In a ROC analysis we found PLT ≥ 1211 x10^9/L and PLT ≥ 1153 x10^9/L as the better cut-offs to identify AvWS and severe AvWS, respectively. In bivariable logistic model, AvWS was associated with PLT ≥ 1211 x10^9/L (OR=16.8 P 0.012), adjusting for mutational profile (presence versus absence of *JAK2* mutation, OR=7.4 P 0.005). Similarly, severe AvWS was associated with PLT ≥ 1153 x10^9/L (OR=12 P 0.004), after adjusting for diagnosis (TE vs PV, OR=0.25 p=0.091). Of 58 patients, 23 (39.7%) experienced bleeding events (all mild and muco-cutaneous). We did not find association between bleeding and vWF level (P 0.632), also after adjusting for antiplatelet treatment (P 0.640). This result might be influenced by the introduction of cytoreduction (32 patients, 55.2%), that was coincident with vWF assessment (n= 10) or prescribed shortly after (n= 22). Accordingly, number of patients experiencing bleedings significantly decreased after starting cytoreduction: 35% (12/32) before compared to 6.3% (2/32) after therapy (P=0.002).

	n=58
Age, median (IQR)	43.1 (33.5-51.7)
Sex, n (%)	
female	35 (60.3%)
male	23 (39.7%)
MPN diagnosis	
ET	46 (79.3%)
PV	12 (20.7%)
Patients with PLT > 1000x10^9/L	
At diagnosis	15 (25.8%)
During follow-up	43 (74.2%)
Antiplatelet drugs at vWF assessment	50 (86.2%)
Genotype	
CALR	24 (41.4%)
CALR type 1	12 (20.7%)
CALR type 2	12 (20.7%)
JAK2	30 (51.7%)
Triple negative	4 (6.9%)
Plt, median (IQR)	1132 (1053-1301)
Plt, n (%)	
<1200	39 (67.2%)
1200-1400	13 (22.4%)
≥1400	6 (10.4%)
vWF antigen, median (IQR)	73.4 (55.3-89.5)
vWF:RCo, median (IQR)	38.6 (31.3-63.7)
vWF:RCo <50%, n (%)	41 (70.7%)
vWF:RCo <30%, n (%)	13 (22.4%)

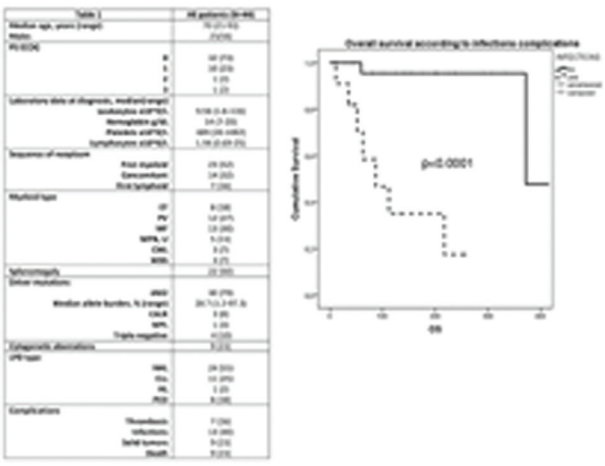
Summary/Conclusion: vWF:RCo reduction is associated with PLT count and mutational profile. Extreme thrombocytosis is associated with muco-cutaneous bleedings, as expected in primary haemostasis defects. The introduction of cytoreduction significantly reduces the number of bleeding events.

EP1099 INFECTIOUS AND THROMBOTIC COMPLICATIONS AND THEIR PROGNOSTIC IMPACT IN PATIENTS WITH CONCOMITANT MYELOID AND LYMPHOID NEOPLASMS. A SINGLE-CENTER COHORT STUDY

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Background: patients with myeloproliferative neoplasms (MPNs) have an intrinsic risk of lymphoproliferative disease (LPD) compared to the general population, ranging from 2.79 to 3.44 folds increased as reported in literature. Less is known about the clinical characteristics of this setting of patients and their outcome in terms of infectious and thrombotic complications.
Aims: to assess the occurrence of infections and thrombosis in patients with concomitant myeloid and lymphoid neoplasms.
Methods: We retrospectively evaluated a single center cohort of 1351 myeloid neoplasms (930 MPN and 421 myelodysplastic syndromes [MDS]) followed up for a median of 9 (0.8-35) years. We evaluated the time from diagnosis to LPD development, LPD type, treatment requirement for both myeloid disorder and LPD, and the occurrence of infections, thrombosis, and overall survival (OS).
Results: A total of 44 patients developed an LPD after a median of 37 (0-318) months from myeloid disease, in 32% of patients myeloid and lymphoid neoplasms were diagnosed concomitantly. Table 1 shows clinical and laboratory characteristics: patients were mainly males, 61% >65 years, and all but 3 had a diagnosis of MPN. JAK2V617F-mutated patients were 30 (68%), while 25% and 11% were CALR- and MPL-mutated, respectively. Mutated patients showed a longer time to LPD development (mean 120±92 versus 31±17 months in unmutated, p=0.01).
As regards treatment, 29 MPN patients were on anti-platelet therapy, 2 on anticoagulants, 36 (82%) of MPN patients required myeloid specific treatment, the majority with hydroxyurea (71%). Lymphoid disease required treatment in 45.5% of cases, after a median time from diagnosis of 8 months (0-115). A thrombotic event was reported in seven patients (4 ET and 3 MF), and, unexpectedly, JAK2 resulted unmutated in more than half of the cases (57.1%). Thirteen patients (30%) experienced a grade ≥3 infectious episode (9 pneumonias, 3 urinary tract infection, and 1 sepsis), all due to bacterial agents, occurring mainly in elderly subjects (12/13, p=0.006).
Nine patients (20%) died due to solid tumor (4), leukemic progression (2), infectious complications (2), and brain bleeding (1). Deaths were more frequent among elderly patients (89%), ECOG ≥1 (42% versus 13%, p=0.02), and triple-negative status (50% versus 12.5%, p=0.02); deaths were also associated with a significantly shorter time to LPD development (37±8 versus 115±94 months, p=0.002) and with lymphoid treatment requirement (35% versus 9%, p=0.04). In addition, fatalities were more frequent in patients with infections (58% versus 6%, p=0.001). By Kaplan Meyer method, a longer OS was observed in younger patients (p=0.001), with better performance status (p=0.02) and with the presence of driver mutations (p=0.003). Contrarily, a worse survival was significantly associated with the occurrence of infections (p<0.0001). Multivariate analysis by Cox regression model showed that the occurrence of infections was the only independent predictor of worse survival within the cohort (HR 3.18, 95%CI 2.9-19, p=0.003).



Summary/Conclusion: The co-occurence of LPD and myeloid neoplasms was associated with a high rate of infectious complications (30%) being the latter the only independent predictor of shorter OS. Interestingly, our data support the adverse prognostic impact of triple-negative molecular status also in this specific setting.

EP1100 MYELOPROLIFERATIVE NEOPLASMS IN PEDIATRICS AND YOUNG ADULTS: GENOMIC FEATURES, CLINICAL OUTCOMES, PROGRESSION AND OVERALL SURVIVAL

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Background: The myeloproliferative neoplasms (MPN) comprise a group of hematological malignancies, consisting of essential thrombocytosis (ET), polycythemia vera (PV), and primary myelofibrosis (MF) which are diagnosed primarily in older adults (OA). MPN is characterized by clonal overproduction of mature blood cells and a driver mutation in the *JAK2*, *MPL*, or *CALR* gene. However, MPN in pediatric and young adults (PAYA) has not been well-described and optimal management is unknown.
Aims: We sought to compare genomic features, disease progression, and clinical outcomes between the PAYA and OA patient groups.
Methods: The Hopkins MPN cohort is comprised of 630 patients with an MPN enrolled between 2005-2015. All had driver mutation genotyping for *JAK2V617F*, *CALR*, and *MPL*. PAYA was defined as those diagnosed ≤39 years of age; OA were diagnosed at >40 years. STADA was used for statistical analysis. Familial MPN was defined as MPN with a 1st or 2nd degree relative with myeloid malignancy.
Results: Of 630 patients, 27% (n=171) were PAYA (average age 30 years; range 1 week-39 years) and 63% (n=459) were OA (average age 58 years; range 40-89 years). Females comprised the majority in both cohorts, but were more prevalent in PAYA (71% v. 58%; $p<0.05$). ET was more frequent in PAYA compared to OA (67% v. 39%; $p<0.05$), whereas PV [26% v. 46%; $p<0.05$) and MF [7% v. 16%; $p<0.05$) were less common. Mutations in *JAK2 V617F* (64% PAYA, 80% OA) or exon 12 mutations (2% PAYA, 1% OA) comprised 100% of PV for both groups, while *JAK2* mutations were less common in PAYA ET (55% v. 67%; $p<0.05$) and similar in MF (42% v. 66%). *CALR* mutations were similar in PAYA and OA in ET, but less common in PAYA MF (42% v. 16%; $p<0.05$). *MPL* mutations were more common in PAYA MF (42% v. 17%). Triple negative disease (absence of mutations in *JAK*, *CALR*, *MPL*) was more common in PAYA (9% v. 4%; $p<0.05$). Familial MPN was more prevalent (19% v. 9%; $p<0.05$). Cancer predisposition syndromes were rare in both cohorts (2 PAYA, 1 OA). Venous thromboses comprised the most frequent (n=39; 23%) complication in PAYA. Additional cancers, most frequently skin, developed in 9% of PAYA compared to 20% ($p<0.05$) of OA. In PAYA, 12.9% progressed to MF or AML, with majority progressing to MF (11%). In PAYA, ET progressed to MF (n=8, mean age 51 years, mean time to progression 22 years) and PV to MF (n=11, mean age 40 years, mean time to progression 10 years). Progression to AML occurred in 2% (3/171) PAYA, with average time to AML from original MPN diagnosis of 27 years, compared to OA, where AML occurred in 5% (25/459), with average time to AML progression of 11 years ($p<0.05$). There were fewer deaths in the PAYA v. OA (12% v. 39%; $p<0.05$). Overall survival was longer in PAYA (29 v. 12 years, $p<0.05$); however, average age of death was lower in the PAYA v. OA (60 v. 74 years; $p<0.05$).
Summary/Conclusion: PAYA comprised almost 1/3 of our MPN cohort and were more likely to present with lower-risk disease (ET), although almost 13% ultimately progressed to MF or AML. PAYA MPN had longer latency periods before progression and longer overall survival but earlier age of death compared OA MPN. The higher prevalence of familial MPN in PAYA and the secondary cancers suggest that an inherited predisposition to cancer may contribute to MPN development. Together, our findings suggest that PAYA patients should be followed closely for progression, venous thromboses, and possibly additional cancers. The long latency underscores the need to limit exposure to potentially genotoxic therapies.

EP1101 HEMORRHAGIC EVENTS BUT NOT THROMBOTIC EVENTS CONTRIBUTE TO WORSE SURVIVAL IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA: A RETROSPECTIVE NATIONWIDE SURVEY IN JAPAN

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Background: The treatment goals for essential thrombocythemia (ET) are to prevent thrombotic and hemorrhagic events, genetic transformation, and secondary malignancies. In recent years, the risk factors (including epigenetic mutations) of thrombosis and genetic transformation have been intensively investigated. However, the risk factors of hemorrhagic events have not been sufficiently investigated because the incidence of hemorrhagic events after diagnosis of ET is lower than that of thrombosis. Serious hemorrhagic events can lead to impaired activities of daily life and poor survival, and thus, prevention is of extreme importance.
Aims: We conducted a large-scale, nationwide retrospective study on Japanese patients with ET to investigate the clinical characteristics, survival rate, and incidence of thrombotic and hemorrhagic events and identify the risk factors of these events.
Methods: We included patients aged ≥20 years who were newly diagnosed with ET according to the World Health Organization's 2008 or 2017 criteria between April 2005 and March 2018. We reviewed data on patient characteristics including driver gene mutations, treatment, thrombotic and hemorrhagic events after diagnosis, genetic transformation, incidence of secondary malignancies, overall mortality, and the cause of death collected from patient medical records. This study was conducted by the Japanese Society of Hematology.
Results: In total, 1232 patients with ET were enrolled. Of these patients, 80 patients were excluded according to the selection criteria. The remaining 1152 patients were included in the analysis. At the time of diagnosis, the median patient age was 65 years old, the median platelet count was 832 × 10^9/L, and the positive mutation rates of *JAK2*V617F, *CALR*, and *MPL* were 62.8%, 25.1%, and 4.1%, respectively. The median follow-up period was 45 months (range: 0-188 months). During the study period, fifty-nine (5.1%) patients experienced hemorrhagic events. The hemorrhagic event-free survival rate was 94.2% and 89.4% at 5 and 10 years, respectively. There was no significant difference in hemorrhagic event-free survival among patients with different driver gene mutations (*JAK2*V617F, *CALR*, *MPL*, and triple-negative). In multivariate analysis, platelet count ≥1000 × 10^9/L (hazard ratio, 2.007), previous history of hemorrhage (hazard ratio, 3.793), and splenomegaly (hazard ratio, 2.888) were identified as risk factors for of hemorrhagic events. Furthermore, multivariate analysis with hemorrhagic events (hazard ratio, 7.180) as a time-dependent variable showed that hemorrhagic events were a life-threatening risk factor, and the same results were seen for landmark analysis.
Summary/Conclusion: In this large-scale retrospective study of Japanese ET patients, platelet count ≥1000 × 10^9/L, previous history of hemorrhage, and splenomegaly were risk factors of hemorrhagic events, and hemorrhagic events after diagnosis of ET was a risk factor of mortality. Since an increased platelet count is not a risk factor for thrombosis but for hemorrhagic events, appropriate cytoreductive therapy is required to prevent hemorrhagic events.

EP1102 JAK2V617F ALLELE BURDEN: AN INDEPENDENT PREDICTOR OF OVERT FIBROSIS IN PRIMARY MYELOFIBROSIS

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Background: *JAK2V617F* mutation is on the genetic basis of myelofibrosis (MF) onset and the role of its mutant allele frequency (VAF) in disease evolution as well as survival remains controversial. Monocyte-derived fibrocytes are involved in MF pathogenesis. A recent study demonstrated that monocytes with higher *JAK2V617F* allele burden were associated with the onset of MF in patients with myeloproferative neoplasms harbouring *JAK2V617F*. In addition, it has been previously shown that *JAK2V617F* with ≥ 50% allele burden was associated with more advanced BM fibrosis.
Aims: To evaluate the association between *JAK2V617F* allele burden and MF disease presentation and prognosis.
Methods: Retrospective unicentric analysis of patients diagnosed with MF between January 2010 and December 2019. The cutoff value of *JAK2V617F* VAF was established applying a logistic regression ROC curve. All variables with p<0.05 in the univariate model were included in the multivariate analysis. The Cox regression model and Kaplan-Meier method were used for the analysis of progression free survival (PFS) and overall survival (OS).
Results: Sixty-four (71.1%) out of 90 patients newly diagnosed with MF harboured the *JAK2V617F* mutation. VAF was evaluated in 54 (60%) patients, with a median mutant allele burden of 33% (range, 1-95%). Median age in this sub-cohort was 66 years old and 64.8% were males. *JAK2V617F* allele burden did not correlate with levels of hemoglobin (Hb), platelets neither with the presence of constitutional symptoms (p=NS). Based on our sample, there was a statistically significant association between VAF and leucocytes, and as VAF increase, leukocytes increase (rs=0.51; p<0.001). The presence of splenomegaly is associated with higher median VAF (26 *versus* 47%; p=0.02). About half of the patients (51.9%) were in the overt fibrotic stage (FMF) at diagnosis, which is associated with a trend for higher VAF (26 *versus* 47%, for prefibrotic (PFMF) and FMF, respectively; p=0.08). Variable dichotomization for allele burden established VAF=40% has the cutoff value to distinguish between PFMF and FMF (sensibility 60.7%; specificity 76.9%; PPV 73.9%; NPV 64.6%), therefore demonstrating VAF>40% as a good predictor of FMF (OR 5.15, p=0.007), even after adjusting to the variables older age, Hb<10g/dL, leucocytes≥11x10^9/L, elevated lactate dehydrogenase and circulating blasts >1% (OR 9.33, p=0.003). VAF>40% associated with leucocytes >11x10^9/L (p=0.019) and splenomegaly (p=0.017), at presentation. VAF had no positive predictive value in estimating prognosis according to the International Prognostic Scoring System nor in predicting need of treatment or disease progression to acute leukemia (p=NS).
In our sample, median PFS and OS were identically estimated in 124.6 months. While median PFS and OS were not reached for PFMF patients, FMF patients reached a median PFS and OS of 50.2 (P=0.0196) and 51.7 months (0.0015), respectively. Contrastingly, *JAK2V617F VAF>40%* had no impact on both PFS (124.6 vs NR months; HR 0.890, p=0.826) and OS (124.6 vs 54.4 months; HR 1.169, p=0.782).
Summary/Conclusion: We showed that MF patients with overt fibrosis at diagnosis had worse survival times, compared to PFMF patients. Also, and although the allele burden of *JAK2V617F* had no impact on PFS and OS of patients with MF, we demonstrated that VAF>40% has an independent positive predictive value for diagnosis of FMF. Thus, our findings identify *JAK2V617F* allele burden as a valuable tool to discriminate between pre-fibrotic and overt fibrotic stages in MF and suggest higher *JAK2V617F* VAF as a useful non-invasive marker of fibrosis onset in MF.

EP1103 CLONAL MUTATION PATTERNS OF ESSENTIAL THROMBOCYTHEMIA REVEALED BY SINGLE-CELL TARGETED SEQUENCING

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Background: Single-cell sequencing of hematopoietic stem cells (HSCs) provides an unprecedented opportunity to directly reveal origins of driver mutations in essential thrombocythemia (ET)–a unique model for dissecting clonal architecture of tumors.
Aims: The study aimed at revealing the clonal mutation patterns of ET with different driver mutations.
Methods: Whole-exome sequencing of bulk bone marrow cells from 33 ET patients were conducted, and targeted region sequencing of single

HSCs from two representative patients was performed, one with JAK2 V617F and the other one with the CALR mutation.
Results: Seventeen patients (51.5%) had the JAK2 V617F mutation, four (10.8%) harbored the CALR mutations, and one (3.0%) had the MPL mutation. More somatic non-silent mutations were observed in JAK2 V617F+ patients (median 13; range 5–94) than in CALR-mutated patients (median 8.5; range 2–10; P = 0.048). Mutations with known roles in myeloid neoplasms (e.g., mutations in DNMT3A, TET2, and ASXL1) were more likely to co-occur with JAK2 V617F, but not with CALR mutations. Single-HSC sequencing revealed that not every possible key mutation identified in bulk cells was an 'essential mutation'. Single-HSC sequencing revealed an unexpected complexity in genetic composition of the HSC pool. In the JAK2 V617F+ patient, tumor cells were oligoclonal in origin. The JAK2 V617F mutation occurred after the LIN54, TET2, and DNMT3A mutations. These pre-JAK2 mutations randomly occurred and continually accumulated in almost all cells from the HSC pool. JAK2 V617F occurred in cells with at least one of the pre-JAK2 mutations. As a consequence, a cluster of cells with these four mutations in every cell were emerged and acquired a growth advantage. Unlike JAK2 V617F, the CALR mutation was an early event, and the clone containing a single CALR mutation acquire a survival advantage. JAK2 V617F+ cell amplification mainly occurred in the HSC compartment in ET30, but CALR-mutated cells were mainly amplified in HPCs in ET35. This observation helps explain why JAK2 V617F causes erythrocytosis, granulocytosis, and thrombocytosis, while the CALR mutations mainly cause thrombocytosis.
Summary/Conclusion: Single-HSC sequencing provides direct evidence for revealing subject-specific key mutations and clonal evolution patterns in patients with ET.

EP1104 RECURRENT ACTIVATING STAT5B N642H MUTATION IN MYELOID NEOPLASMS: CLINICO-PATHOLOGIC AND GENOMIC CHARACTERIZATION

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Background: Oncogenic activating *STAT5B* N642H driver mutation, observed recurrently in aggressive T-cell malignancies, was recently reported as a clonal biomarker in association with myeloid neoplasms (MNs) with eosinophilia. This mutation provides potential therapeutic opportunities using small molecule inhibitors (under development) and tyrosine kinase inhibitors.
Aims: In this study, we sought to characterize the frequency, clinicopathologic and genomic features, and outcomes of all MNs with *STAT5B* N642H mutation at a single-institution.
Methods: All patients (pts) with a myeloid malignancy with *STAT5B* N624H mutation detected by using next-generation sequencing and an 81-gene myeloid panel were included (2017-2019). Pts with concurrent T-cell neoplasms or aberrant T/NK cells detected by flow cytometry immunophenotypic analysis were excluded. Bone marrow (BM) morphologic features were reviewed. Clinicopathological data were collected by chart review.
Results: Of 4551 pts who underwent baseline NGS profiling, we identified 14 (0.3%) pts with MNs associated with *STAT5B* N642H mutations. These pts included 8 men and 6 women with a median age of 76 years (26-87). Using the WHO classification criteria, the diagnoses included myelodysplastic/myeloproliferative neoplasm (MDS/MPN, n=5), MDS (n=4), acute myeloid leukemia (AML, n=3), *CALR* mutated MPN (n=1) and chronic eosinophilic leukemia (CEL, n=1). Peripheral blood (PB) or BM eosinophilia was noted in 8 (57%) pts: 5 (36%) with PB hypereosinophilia (defined >1500/μL), 3 (21%) with PB eosinophilia (500-1500/μL). Five pts (36%) showed increased eosinophils in BM. Patients with increased eosinophils were negative for rearrangements involving *BCR/ABL1*, *PDGFRA*, *PDGFRB,* and *FGFR1* assessed by FISH. BM fibrosis (grade ≥ MF-2) was seen in 2 pts. Seven (50%) pts had normal diploid karyotypes; recurrent abnormalities included +8 and monosomy 7. The median variant allele frequency (VAF) of *STAT5B* mutation was 21% (range, 2-61). In 9 (64%) pts the mutation was dominant (defined as VAF >20%) and in 5 pts the mutation was sub-clonal. The median number of mutations per pt was 4 (range, 1-7). Frequent concurrent gene mutations included *U2AF1* (n=7, 50%), *ASXL1* (n=6, 42.9%) and *TET2* (n=5, 35.7%). Eleven of 14 (79%) pts had a concurrent mutation in a splicing factor gene. Using the molecular grouping scheme by Cross et al. (PMID: 30573779), 13 (93%) pts were in group 3 (with additional mutations, not *SF3B1*), 1 in group 2 (with *SF3B1* mutations). No cases belonged to group 1 (sole abnormality).
To compare molecular characteristics, we identified 9 pts with *STAT5B* N642H positive T-cell neoplasms (6 T-prolymphocytic leukemia, 2 T-lymphoblastic leukemia, 1 cytotoxic mature T-cell lymphoma) over the same time-period. Compared to MNs, T-cell malignancies showed a higher median *STAT5B* VAF [41% (3-72); p=0.25] and fewer concurrent mutations [median 3 (range, 1-4) mutations per pt.; p=0.001]. None showed splicing mutations.
Over a median of 20 months (range, 0-42), 7 (50%) pts died. Follow-up data were available for 11 pts. Six pts transformed to AML; all died except 1 pt with sub-clonal *STAT5B* mutation with concurrent *NPM1* and *FLT3* mutations. Four patients showed clearance of *STAT5B* mutation post therapy.
Summary/Conclusion: *STAT5* N642H mutations are recurrent in MNs. Although eosinophilia is frequent, this is the first study of an unbiased pt cohort showing that a substantial proportion [6 (43%)] of pts lack eosinophilia. Further investigation of these cases is warranted due to the potential targetable nature of *STAT5* N642H using small molecular inhibitors.

EP1105 A NATIONWIDE SURVEY OF JAPANESE PATIENTS WITH POLYCYTHEMIA VERA

Y. Edahiro [1,*], Y. Hashimoto [1], T. Ito [2], A. Gotoh [3], M. Nakamae [4], F. Kimura [5], M. Koike [6], K. Kirito [7], H. Wada [8], K. Usuki [9], T. Tanaka [10], T. Mori [11], S. Wakita [12], T. I. Saito [13], A. Kada [13], A. M. Saito [13], K. Shimoda [14], Y. Sugimoto [15], T. Kurokawa [16], A. Tomita [17], K. Akashi [18], I. Matsumura [19], K. Takenaka [20], N. Komatsu [1]

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Background: A nationwide survey of Japanese patients with Philadelphia-negative myeloproliferative neoplasms (MPNs) was reported in 2006, including 266 patients with polycythemia vera (PV) and 381 patients with essential thrombocythemia (ET). Since then,*JAK2* and other driver gene mutations have been found in MPNs, and new diagnostic criteria such as the World Health Organization (WHO) 2008 and 2017 classifications have emerged, warranting a new survey to obtain novel insights regarding Japanese patients with MPNs.
Aims: To analyze the clinical characteristics of patients with PV in Japan, we conducted a retrospective study.
Methods: Patients who were diagnosed with PV according to either the WHO 2008 or 2017 classification between April 2005 and March 2018 were enrolled. This study was conducted by the Japanese Society of Hematology.
Results: In total, 1867 patients with PV or ET from 41 institutions in Japan were registered. Among them, 596 patients with PV were analyzed. The median age was 65 years, including 5.2% and 16.8% of patients <40 and <50 years of age, respectively. *JAK2* V617F mutations

were detected in 83.1% (456/549) of patients. Thrombotic and hemorrhagic events before or at the time of diagnosis occurred in 16.2% and 3.7%, respectively.
During a median follow-up of 47 months (range: 0–182 months), 49 deaths (8.2%) occurred. The median overall survival was not reached, likely due to the short follow-up time. The major causes of death were secondary malignancies (n=11; 1.8%), leukemic transformation (n=6; 1.0%), non-leukemic progressive disease (n=5; 0.8%), thrombotic complications (n=3; 0.5%), and hemorrhagic complications (n=3; 0.5%). Progression to secondary myelofibrosis was observed in 17 cases (2.9%), which subsequently progressed to acute leukemia in 1 case. Thrombotic and hemorrhagic events occurred in 24 (4.0%) and 20 (3.4%) cases, respectively. While extreme thrombocytosis (≥1000 × 10^9/L) was a risk factor for survival, leukocytosis (≥10 × 10^9/L) was a risk factor for survival and thrombosis-free survival. Age >60 years was a risk factor for leukemic transformation. Interestingly, splenomegaly was a predictor of hemorrhagic events in univariate analysis. The international PV prognostic score (age, venous thrombosis, and leukocytosis) clearly distinguished the Japanese PV population into three distinct risk groups.
Summary/Conclusion: This was the largest study of Japanese patients with PV, showing that leukocytosis is a risk factor for survival and thrombosis, and splenomegaly is a risk factor for hemorrhagic complications. Although splenomegaly has been reported as a risk factor for hemorrhage in patients with ET or whole MPN, to the best of our knowledge, it has not been specifically predicted in patients with PV. While few hemorrhagic events occurred before or at the time of diagnosis of PV, the number of thrombotic and hemorrhagic events after diagnosis showed only a slight difference (24 and 20, respectively). Among the 20 patients with hemorrhagic complications, 14 received an anti-thrombotic drug. These findings suggest that instead of preventing thrombotic complications during PV treatment, many hemorrhagic events may occur as iatrogenic events. Both thrombotic and hemorrhagic complications are significantly correlated with survival; thus, the risk of both thrombotic and hemorrhagic complications should be considered in the treatment algorithm.

EP1106 IMETELSTAT DEMONSTRATES AN ACCEPTABLE SAFETY PROFILE IN MYELOID MALIGNANCIES

J. Mascerenhas [1,*], V. Santini [2], J.-J. Kiladjian [3], P. Fenaux [4], R. S. Komrokji [5], K. Van Eygen [6], F. Palandri [7], A. Raza [8], B. Martino [9], U. Germing [10], D. Niederwieser [11], P. Font [12], A. Reiter [13], M. Diez-Campelo [14], B. L. Scott [15], S. Thepot [16], M. R. Baer [17], E. Vellenga [18], R. Hoffman [1], M. M. Patnaik [19], O. Odenike [20], J. H. Jang [21], A. Vannucchi [2], L. Sherman [22], S. Dougherty [22], F. Huang [22], T. Berry [22], L. Sun [22], Y. Wan [22], A. Rizo [22], F. M. Feller [22], U. Platzbecker [23]

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Background: Imetelstat is a first-in-class telomerase inhibitor that induces selective apoptosis of malignant hematopoietic stem and progenitor cells in the bone marrow. Imetelstat has shown clinical benefit in symptom response rate and a potential overall survival (OS) impact in Janus kinase (JAK) inhibitor relapsed and refractory (R/R) intermediate 2 (Int-2) and high risk (HR) myelofibrosis (MF) patients (pts) in the Phase 2 MYF2001 (IMbark) study, as well as meaningful and durable transfusion independence (TI) in high transfusion burden low risk (LR) and intermediate 1 (Int-1) risk myelodysplastic syndrome (MDS) pts R/R to erythropoiesis stimulating agents (ESAs) in the Phase 2 portion of the MDS3001 (IMerge) study. Clinical and biomarker data in both studies indicate potential disease-modifying activity of imetelstat. The most frequently reported adverse events (AEs) in both studies were manageable and reversible cytopenias, with limited clinical consequences, suggesting on-target activity of imetelstat (Platzbecker ASH 2020, Mascarenhas ASH 2020).
Aims: To further characterize hematologic and non-hematologic AEs, including the AEs of Interest (AEI), hepatic AEs and grade ≥3 liver function tests (LFTs) in these Phase 2 studies.
Methods: These safety analyses focus on MYF2001 study pts randomized to imetelsat 9.4 mg/kg IV q 3 weeks (wks) (N=59) as of 7 Feb 2020 and the Phase 2 of the MDS3001 study in LR/Int-1 non-del(5q) transfusion dependent ESA R/R MDS pts, all lenalidomide and hypomethylating agent-naïve (N=38), who received 7.5 mg/kg IV every 4 wks as of 21 Oct 2020. AEs were monitored and reported from the time of screening until 30 days after treatment discontinuation. Dose modification was performed based on protocol-defined criteria. An independent hepatic expert committee (HEC) reviewed all LFT and AEI data quarterly.
Results: On MYF2001 41% and 32% of pts had grade (G) ≥3 (G≥3) thrombocytopenia and neutropenia respectively and on MDS3001 61% and 55% of pts had G≥3 thrombocytopenia and neutropenia respectively. Median time to onset of these G≥ 3 cytopenias was 3 cycles in MF pts and approximately 1 cycle in MDS pts. Median duration of G≥3 cytopenias was <2 wks and >72% were reversible within 4 wks (Table 1). Median time to first dose reduction was 21 wks in MF and 11 wks in MDS. Cytopenias leading to treatment discontinuation occurred in 15% and 18% of MF and MDS pts, respectively. Importantly, clinical consequences of cytopenias including G≥3 hemorrhagic events or febrile neutropenia occurred in <10% of pts. Non-hematological AEs occurring in >20% pts in either study were nausea, diarrhea, abdominal pain, fatigue, asthenia, pyrexia, dyspnea, and back pain and were generally G1-2 events. One pt on each study experienced imetelstat related G3 AST increase that recovered with dose reduction. HEC reviews found no significant imetelstat-related liver injury.

Table 1: Characteristics of Cytopenias

	MYF2001 9.4 mg/kg q 3 weeks (n=59)		MDS3001 7.5 mg/kg q 4 weeks (n=38)	
	G3/4 Thrombocytopenia	G3/4 Neutropenia	G3/4 Thrombocytopenia	G3/4 Neutropenia
Median duration	2.0 weeks	1.3 weeks	1.1 weeks	1.7 weeks
Median time to onset	9.0 weeks (~3 cycles)	9.0 weeks (~3 cycles)	4.0 weeks (~1 cycle)	4.7 weeks (~1 cycle)
% Reversible within 4 weeks	47/65 events 72.3%	47/56 events 83.9%	86/95 events 90.5%	68/79 events 87.3%
Cytopenias leading to treatment discontinuation	6/59 (10%)	3/59 (5%)	6/38 (15.8%)	1/38 (2.6%)
Median time to first dose reduction	21.4 weeks (Cycle 6.5)		10.8 weeks (Cycle 3)	

Summary/Conclusion: Imetelstat related cytopenias are on-target effects based on the selective reduction of malignant cells through telomerase inhibition. Furthermore, they are of short duration, reversible and with limited clinical consequences when managed with the dose modification guidelines in the protocols. Pts in these two studies had no evidence of imetelstat-related liver injury. Differences in disease pathology (proliferation vs dysplasia) could account for the differences in toxicity profiles in MF vs MDS pts. Ongoing Phase 3 studies in MF and MDS will confirm the safety profile of imetelstat in a controlled setting.

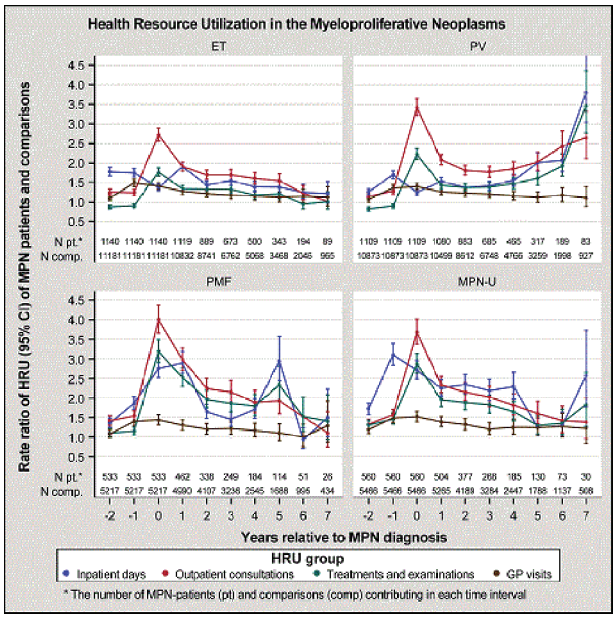
EP1107 HEALTHCARE RESOURCE UTILIZATION IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS: A NATIONWIDE MATCHED COHORT STUDY

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Background: Myeloproliferative neoplasms (MPNs) are associated with severe complications and a substantial symptom burden – frequently emerging several years before diagnosis. Due to the chronic nature of the diseases, MPN patients have a lifelong need for treatment and care. However, only few studies have assessed MPN healthcare resource utilization (HRU) compared with matched cohorts, and no detailed assessments of HRU in the years preceding MPN diagnosis exist.
Aims: To assess the pre- and post-diagnostic HRU of MPN patients compared with matched cohorts of $_{non}$MPN comparisons.
Methods: We conducted this descriptive, register-based nationwide cohort study, utilizing data from the Danish National Chronic Myeloid Neoplasia Registry on all MPN patients diagnosed between January 2010 and December 2016, and data on HRU from the Danish National Patient Registry and the Danish National Health Service Registry. Population-based cohorts of $_{non}$MPN comparisons were constructed by 1:10 matching on age, sex, level of education, and region of residence. Data were linked using the unique civil registration number, which identifies all Danish citizens. HRU was summarized over each year for all cohorts from two years before date of MPN diagnosis and until emigration, death, or end of study (31 December 2017). HRU was calculated as annual number of healthcare contacts (inpatient days, outpatient consultations, treatments and examinations, and general practitioner [GP] visits) divided by person-years at risk and compared using rate ratios with 95% CI.
Results: The study population included 3,342 MPN patients (1,140 essential thrombocythemia [ET]; 1,109 polycythemia vera [PV]; 533 primary myelofibrosis [PMF]; and 560 unspecified MPN [MPN-U]) and 32,737 $_{non}$MPN comparisons (11,181 $_{non}$ET; 10,873 $_{non}$PV; 5,217 $_{non}$PMF; and 5,466 $_{non}$MPN-U). The median age was 67 (ET), 69 (PV), 73 (PMF), and 72 years (MPN-U), and the mean follow-up was 3.8 (ET), 3.8 (PV), 3.1 (PMF), and 3.3 years (MPN-U). A total of 750 (22.4%) MPN patients and 4,627 (14.1%) $_{non}$MPN comparisons died during follow-up. In nearly all years of follow-up, MPN patients had a higher HRU than $_{non}$MPN comparisons (Figure, rate ratio>1). Rate ratios for *outpatient consultations* were largest at the time of diagnosis: ET, 2.7 (95%CI, 2.6-2.9); PV, 3.4 (95%CI, 3.2-3.6); PMF, 4.0 (95%CI, 3.7-4.4); and MPN-U, 3.7 (95%CI, 3.4-4.0). For most MPN subtypes, rate ratios also peaked at time of diagnosis for *treatment and examinations*. In contrast, the largest rate ratio for PV was in the last year of follow-up: 3.5 (95%CI, 2.8-4.3). Across MPN subtypes, rate ratios for *GP visits* varied from 1.0 to 1.5 during follow-up without any considerable fluctuations. Interestingly, increased rate ratios for *inpatients days* were evident 2 years before diagnosis: ET, 1.8 (95%CI, 1.7-1.9); PV, 1.3, (95%CI, 1.2-1.3); PMF, 1.4 (95%CI, 1.2-1.5); and MPN-U, 1.7 (95%CI, 1.6-1.9). During follow-up, notable increases in rate ratios were observed, e.g., PMF 3.0 (95%CI 2.4-3.6) and PV 3.8 (95%CI 3.0-4.8) in year 5 and 7, respectively.



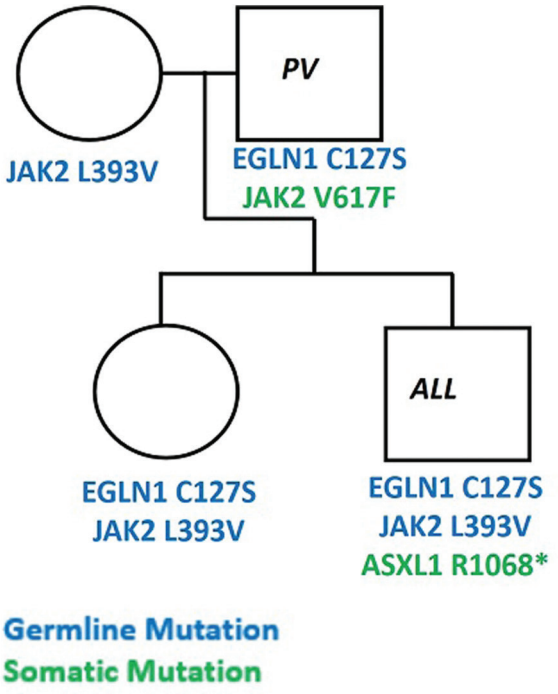
Summary/Conclusion: Overall, compared with matched $_{non}$MPN comparisons, MPN patients had a higher HRU throughout the study period. This was consistent across MPN subtypes and HRU measures. Within the limitations of small numbers toward end of follow-up and lack of matching on comorbidity, our findings confirmed a consistent HRU burden after MPN diagnosis. Equally important, our study revealed substantial increases in HRU two years before MPN diagnosis, warranting further exploration of the pre-diagnostic period, including the potential benefits of early detection.

EP1108 ASSOCIATION OF JAK2 AND PHD2 MUTATIONS IN A FAMILY WITH ERYTHROCYTOSIS

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Background: Absolute erythrocytosis is characterized by persistently raised Haemoglobin (Hb) and haematocrit (Ht) levels. Polycythaemia Vera (PV) is a clonal disease associated in 95% of cases with *JAK2*V617F mutation, while familial erythrocytoses are poorly understood.
Idiopathic erythrocytosis (IE) has not a definite cause, even after an accurate diagnostic investigation. Recently, also HFE mutations have been observed frequently in erythrocytotic patients. The recent availability of NGS technique has offered us the possibility to recognize mutations in known and unknown genes involved in the pathogenesis of erythrocytosis.
Aims: We report a venetian family with erythrocytosis in whom we found an undescribed association of mutations all consistent with the clinical phenotype.
Methods: The family comprehends a man, his wife, and their two children, a male and a female. Hematocrit, ferritin at diagnosis and necessity of phlebotomies were recorded if available. An NGS panel constituted by *JAK 2, EGLN 1 (PHD2), HBB, HBA1, HBA2, ASXL1, HFE, HFE2, TFR2, HAMP, SLC40A1, SLC11A2, VHL, BPMG, EPAS1* was used.
Results: Results are showed in Table I.
Genealogic tree of the family is reported in Figure I.



Summary/Conclusion: In this study we show the presence of contemporary mutations involved in erythrocytosis in more members of the same family.
Father and the two children have the same germline mutation *(EGLN1 C127S)* among with a mutation in *JAK2* gene, somatic in the father (*V617F*) and germline in the two children *(L393V)*. The mother has also this *JAK2* germline mutation. The son has also a somatic mutation in *ASXL1* R1068*. Interestingly, the son developed an acute lymphoblastic

Member	Age	History	Somatic Mutations	Germline Mutations	HT (%)	Ferritin (μG/L)	Phlebotomies
Father	68	Treated for PV since 2014, symptomatic for chest pain when Ht is high, no coronaropathy.	JAK2V617F	EGLN1 C127S	56	n.a.	4/year since 2014, recently increasing
Mother	57	Asymptomatic	-	JAK2 L393V	40	n.a.	no
Son	26	Treated for acute lymphoblastic leukemia (ALL) in 2012 with high transfusion need and iron overload, developed erythrocytosis in 2017	ASXL1 R1068*	EGLN1 C127S JAK2 L393V	50	510	4/year since 2017
Daughter	30	Asymptomatic	-	EGLN1 C127S JAK2 L393V	n.a.	n.a.	no

leukemia (ALL) at the age of 18 and developed erythrocytosis after recovery. The daughter and the mother are still asymptomatic.
It has been hypothesized that *JAK2* germ line mutations may precede the acquisition of *JAK2V617F* lesion during the evolution of PV phenotype. The *PHD2* mutation of this family is frequently observed in Tibetans, that establish an escape mechanism against erythrocytosis at high altitude, while in conditions of normoxia, the *EGLN1 p.C127S* variant has still an unclear function. We surmise that the association of *PHD2* and *JAK2* mutations could be associated with a more significant increase in hematocrit in this family. Moreover, usually ASXL1 is an epigenetic modifier, a marker of high risk for shorter survival in primary myelofibrosis (PMF). IE patients during their clinical history do not usually evolve in overt PV, nor in PMF or AML, and the role of *ASXL1* mutation in these patients is therefore unknown.
In conclusion, the use of a specific NGS panel for erythrocytosis is a useful tool to explore new and combined genes variants and to study other members of the family to find the link between their haematological complications, in order to predict eventual clinical variations of the phenotype.

EP1109 DIAGNOSTICS OF ERYTHROCYTOSIS OFTEN STOPS AFTER POLYCYTHAEMIA VERA EXCLUSION

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Background: Erythrocytosis is a condition of increased red cell mass, manifested by high haemoglobin (Hb) and/or haematocrit (Hct). Most frequently, it is secondary (SE) to hypoxia caused by various cardiac, pulmonary or renal diseases. Congenital causes are very rare. The only clonal erythrocytosis is polycythaemia vera (PV), almost uniformly associated with *JAK2* mutation. When no cause of erythrocytosis is identified, the erythrocytosis is idiopathic (IE). As thromboembolic events are frequent in PV, patients are usually treated with antiaggregation and cytoreduction. Management of all other types of erythrocytosis is less clear and differs according to the underlying cause of erythrocytosis
Aims: The aim of our study was to retrospectively analyze the etiology and management of patients with non-clonal erythrocytosis referred to an adult haematology outpatient clinic in an 8-year period.
Methods: First step was inclusion of patients with Hb> 185 g/L and/or Hct> 0.52 in men and Hb> 165 g/L and/or Hct> 0.48 in women on two visits ≥ two months apart, thus confirming absolute erythrocytosis. Secondly, PV was excluded by determination of *JAK2* mutation and erythropoietin level, sometimes also by bone marrow biopsy. Concomitantly, causes of SE were identified using various biochemistry and imaging techniques (iron stores, haemochromatosis testing, pulse oximetry, blood gas analysis with COHb determination, CT or ultrasound for detection of cardiac or pulmonary disease or origin of ectopic erythropoietin, polysomnography). Thirdly, IE patients were referred to targeted next-generation sequencing for congenital erythrocytosis. Informed consent was obtained from all participants.
Results: Between March 2011 and April 2019, 655 patients met the inclusion criteria for absolute erythrocytosis. After excluding PV 116 patients were evaluated for other causes of erythrocytosis; 75 (65%) were men and 41 (35%) women. Median age in men and women was 51.4 years (41.1 – 62.9, interquartile range), and 60.7 years (54.4 -68.2), respectively (p = 0.002). For 34/116 (29%) patients secondary causes of erythrocytosis were identified, namely obstructive sleep apnoea (38%), smoking (21%), lung (18%) and cardiovascular diseases (6%), neurological disorders affecting respiratory function (6%), kidney diseases (renal cell carcinoma, renal cysts, polycystic kidney disease) (12%), tumors with ectopic erythropoietin secretion (6%), hemochromatosis (3%) and drugs (6%). 15/116 (13%) patients remained idiopathic despite extensive diagnostics. 67/116 (58%) patients stayed incompletely characterized (ICE) due to insufficient diagnostics. Patients from all three groups were similarly treated, either with aspirin or phlebotomies. Differences in SE, IE and ICE patients are presented in Table 1. Thrombotic events were registered in 12%, 20% and 15% of SE, IE and ICE patients, respectively. Congenital erythrocytosis type 4 (ECYT4) was diagnosed in one patient, who had already suffered several thromboembolic complications.

Table 1. Characteristics of patients with secondary (SE), idiopathic (IE) and incompletely characterized (ICE) erythrocytosis (N=116).

Laboratory characteristics	Median (25% – 75%)			
	Patients with SE (N=34)	*Patients with IE (N=15)*	**p value** (SE vs IE)	*Patients with ICE (N=67)*
Age	57.7 (47.3 – 63.8)	41.1 (35.4 – 52.0)	**0.01**	58.0 (45.6 – 67.9)
Male /female	25/9	12/3	NS	38/29
Haemoglobin	189 (182 – 197)	182 (176 – 183)	**0.02**	180 (172 – 185)
Haematocrit	0.55 (0.53 – 0.58)	0.52 (0.52 – 0.53)	**0.002**	0.53 (0.51 – 0.54)
Erythropoietin	9.8 (7.6 – 17.2)	8.2 (6.1 – 12.5)	NS	8.6 (6.2 – 11.3)
Treatment with phlebotomies	19 (56%)	8 (53%)	NS	27 (40%)
Prescribed aspirin	25 (74%)	10 (67%)	NS	47 (70%)
Thrombotic events	4 (12%)	3 (20%)	NS	10 (15%)

Haemoglobin and haematocrit in the table reflect the patients' first measurements before phlebotomies.

Summary/Conclusion: Our study demonstrated that diagnostics of erythrocytosis often stopped after PV exclusion. Thromboembolic events were not rare among patients with non-clonal erythrocytosis, which could be attributable to yet unidentified causes of congenital erythrocytosis in the ICE group but also to inadequate management of secondary causes. The optimal management for each patient can be chosen only by identifying the etiology of erythrocytosis.

EP1110 IS MIR-155 USEFUL AS A MARKER OF CLONAL HEMOPOESIS IN MYELOID PROLIFERATION?

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Background: MiR-155 is involved in various physiological processes in the cell, including hematopoiesis, immunity, inflammation and differentiation. Increased expression of miR-155 is observed in many malignant diseases, including lymphomas, acute myeloid leukemia and CLL (Morales-Martinez M., et.al., 2020). Earlier (Stolyar M.A., et.al.,2020) we have demonstrated an increased miR-155 level in patients with chronic Ph-negative myeloproliferative neoplasms (MPN). Both an increase (Long L., et.al., 2013) miR-155 in blood mononuclear cells

and a decrease (Kolarz B., et.al., 2020) in its level in the blood plasma of patients with rheumatoid arthritis have been described. At the same time, there are no results of a special study of miR-155 expression in reactive (non-clonal) leukocytosis.
Aims: To assess the diagnostic capability of determining miR-155 for the differentiation of non-clonal leukocytosis and MPN.
Methods: The study used anonymous (blind) EDTA venous blood samples from 107 patients with MPN (66-PV, 24-ET,17-PMF) and 20 patients with reactive neutrophilic leukocytosis above 12 * 10^9/μL, as well as 51 samples of voluntary blood donors. Determination of miR-155 in blood leukocytes was carried out by RT-PCR (Gene Formula Ltd.). The results were statistically evaluated using the R statistical package.
Results: In our study, the level of miR-155 in whole blood samples did not depend on the number of blood leukocytes. At the same time, its level in blood samples from patients without oncohematological disease does not significantly differ from the values typical for healthy people. On the contrary, in the group of patients with verified forms of MPN, the level of miR-155 in leukocytes was significantly increased (Table; p<0.001), although leukocytosis was less pronounced. There were no significant differences in the level of miR-155 between different variants of the MPN phenotype (PV, ET or PMF). Obviously, miR-155 overexpression is characteristic of cancer-transformed blood cells during myeloid proliferation.

Table. Characteristics of the studied groups

Patients		Leukocytosis Me*10^9/μL (C_{25}-C_{75})	miR-155 (relative units)	P-value
1	Blood donors	< 7,2	0,74 (0,28-1,48)	
2	With reactive (non-clonal) neutrophilic leukocytosis	17,4 (14,9-20,6)	0,25 (0,18-0,38)	0.001
3	With MPN	7,1 (5,3-10,1)	1,7 (0,9-2,9)	

Summary/Conclusion: The data obtained confirm the participation of miR-155 in the pathogenesis of MPN and suggest the possibility of using the miR-155 test as an additional diagnostic test for the differentiation of the clonal nature of the disease.

EP1111 A REAL-WORLD STUDY ON DIAGNOSIS AND TREATMENT STRATEGIES OF PEDIATRIC ESSENTIAL THROMBOCYTHEMIA IN CHINA

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Background: Essential thrombocythemia (ET) is rare in pediatric patients, with uncertain criteria for diagnosis, prognosis and treatment strategies in real-world clinical practice.
Aims: The study aimed at revealing the patterns of diagnosis, prognosis and treatment strategies in real-world clinical practice in a cohort of children diagnosed with ET in China, and trying to optimize the diagnostic and therapeutic regimens based on existing evidence.
Methods: A total of 86 pediatric patients (age≤16 years) with an initial diagnosis of ET according to the 2016 WHO diagnostic criterion were enrolled. A total of 137 genes associated with myeloid malignancies were analyzed in 55 children. The immunophenotype of bone marrow mononuclear cells was detected by flow cytometry. Informed consent was obtained from the guardians of the patients.
Results: The median age was 10 years (range 1-16 years). The JAK2 V617F mutation was positive in 16 patients (18.6%). The CALR mutations were found in 3 out of 62 (4.8%) patients. The MPL mutation was analyzed in 65 patients, and none of them was positive. Surprisingly, although bone marrow histology was consistent with a diagnosis of ET in all the 67 cases without driver molecular markers, a spontaneous normalization of the platelet count without cytoreductive therapy occurred in 7 cases (10.4%), after a median follow-up of 37 months (8-96 months). We found that several factors might be 'true ET'-specific, but rarely seen or absent in those with spontaneous recovery, including palpable splenomegaly, presence of immunophenotypic abnormality (mainly showing reduced CD38 expression on myeloid blast cells and reduced CD36 expression on nucleated red blood cells), positive endogenous erythroid colonies, subnormal erythropoietin, and presence of molecular markers other than JAK2, CALR or MPL mutations (such as mutations in NRAS, ASXL1). In 79 patients still with sustained thrombocytosis, 4 children (5.1%) displayed major thrombosis, and 3 (3.8%) evolved to myelofibrosis. The International Prognostic Score of thrombosis for adults was not applicable to childhood patients, and so does the International Prognostic Score of survival. We found that severe splenomegaly was a risk factor of myelofibrosis transformation in childhood patients. The Efficacy and safety between pegylated interferon and regular interferon were compared for the first time in childhood patients. Similar efficacy was seen between pegylated interferon and regular interferon, but better tolerance was seen in children using pegylated interferon. Furthermore, pegylated interferon was still effective and tolerant in 8 children that were resistant or intolerant for regular interferon.
Summary/Conclusion: Based on the 2016 WHO diagnostic criterion for ET, several 'true ET'-specific features might be considered for the diagnostic screening of childhood ET. Prognostic factors of thrombosis and survival in pegylated interferon were different from that in adult patients. Pegylated interferon has an extensive application prosperity for childhood ET.

EP1112 EFFECT OF DRIVER MUTATIONS ON THE PHENOTYPE OF ESSENTIAL THROMBOCYTHEMIA AND PRIMARY MYELOFIBROSIS

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Background: Myeloproliferative neoplasms (MPN) are a group of clonal hematological malignancies. In which there are three classic pathologies (WHO 2017): polycythemia vera, essential thrombocythemia (ET) and primary myelofibrosis (PMF). According to the accumulated data, it becomes clear that the traditional division of MPN into the above mentioned subtypes does not fully reflect the main biological heterogeneity of these diseases, and that their clinical and laboratory parameters are the result of the various genetic factors interaction. Somatic point mutations of genes encoding tyrosine kinase (*JAK2*), calreticulin protein (*CALR*), and thrombopoietin receptor (*MPL*) (driver mutations, DM) had a great influence on the diagnosis of this group of pathological conditions. However, the question of the each of the mutations influence on the fenotype remains open.
Aims: To determine the correlation of the gene mutations *JAK2, CALR, MPL* with the clinical and laboratory features of MPN.
Methods: Retro- and prospective study of the 192 ET and 141 PMF patient's medical histories were performed. All of them were observed at The Federal State-Financed Scientific Institution Kirov Research Institute of Hematology and Blood Transfusion under the Federal Medical Biological Agence from 1995 to 2019. Gene mutations *JAK2* V617F, *CALR*, and *MPL* W515L/K were determined using kits from GenoTechnologiya LLC (Moscow, Russia) by real-time PCR using TaqMan technology. The mutational status of the gene *CALR* included two like mutations - p.L367fs * 46 (52 bp deletion - type 1, or group *CALR1+*) and p.K385fs * 47 (5 bp insertion - type 2, or group *CALR2+*). Patients without DM were assigned to the triple negative group. The statistical significance of quantitative indicators differences was assessed by the Kruskal-Wallace test.
Results: JAK2-mutated (*JAK2+*) ET patients display a higher hemoglobin levels (median Hb levels are 147 (102-219) and 134 (93-176) g/l, respectively, p <0.0001). Patients with *CALR2+* had a higher number of platelets compared with those who did not have this mutation (median platelet counts 1197x10^9/l (676-3766) and 750x10^9/l (357-2074), respectively, p <0.0001). A comparative analysis of the data obtained showed that the *CALR2+* ET patients were significantly younger at the onset of the disease than the patients from other groups (medians of age 39 (31-78) and 57 (18-90) years, respectively, p = 0.001)
Patients with *JAK2* V617F mutated PMF also had higher hemoglobin levels (median Hb levels are 146 (125-162) and 114 (59-160) g/l, respectively, p <0.0001). The number of platelets in *CALR2+* mutation carriers was statistically significantly higher than their number in patients from other groups (median platelet counts are 1330x10^9/l (272-2529) and 487x10^9/l (38-2000), respectively, p = 0.01). The presence of a type 1 *CALR* gene mutation in patients was associated with a lower leukocyte count of the median leukocyte count of 6.3x10^9/l (3.35-13.64) and 12.2x10^9/l (2.3-49.1), respectively, p = 0.0004).

Summary/Conclusion: In patients with ET and PMF, the association of the gene *JAK2* V617F mutation with a higher hemoglobin level was confirmed. Patients with type 2/like gene *CALR* mutations in comparison with all other patients had the highest platelet count. In the case of PMF, it was found that the leukocyte count in patients with a type 1 gene *CALR* mutation was lower than in patients from other groups. A statistically significant difference in the age at the disease onset for ET was established.

EP1113 ACUTE CORONARY SYNDROME AND JAK2 V617F MUTATION POSITIVE MYELOPROLIFERATIVE NEOPLASMS: A CARDIOLOGICAL PERSPECTIVE

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Background: In Polycythemia vera (PV) and essential thrombocythemia (ET) morbidity relates to thrombotic events. The JAK2 V617F mutation alters both the cellular and plasma compartments of hemostasis favoring a hypercoagulable state. Compared to a matched control population, PV/ET pts have a significantly increased rate of thrombotic events and this risk remains independent of gender and across all age groups. Conventional cardiovascular risk factors (CRF) add to the risk of acute coronary syndrome (ACS).
Aims: Since ACS can occur either as first clinical manifestation of PV/ET or it may complicate its course, we explored the possibility that differences may exist between these two settings.
Methods: Retrospective cohort study of 1,413 consecutive ACS performed at ASST Niguarda Hospital between Jan 2014 and Dec 2019. Patients were divided into 3 groups: *group 1*: patients diagnosed with JAK2+ PV/ET during the index hospitalization; *group 2:* patients with a known diagnosis of JAK2+ PV/ET; *group 3*: control group = ACS in myeloproliferative neoplasm (MPN) negative pts. Clinical and angiography data and outcome events were compared among the 3 groups.
Results: Data are summarized in the Table. Overall, MPN patients differed from MPN negative patients in terms of CRF and extension of coronary artery disease. These differences were even more prominent between MPN group 1 and group 2 patients. Specifically, incidence of CRF was lower and single-vessel disease was more prevalent among group 1 patients. Interestingly, a decreased incidence of long-term adverse cardiovascular events was observed in group 1 MPN patients. At a median follow-up of 18 months, the composite of overall mortality, myocardial infarction, stroke and bleeding events occurred in 2 (6.2%) patients in group 1, in 1 patient (7.7%) in group 2 and 188 patients (13.7%) in MPN-negative ACS patients.

	Group 1 (n = 32)	Group 2 (n = 13)	No MPS (n = 1368)	P value
Age, years	64±15	71±12	66±13	0.219
Male sex, n (%)	20 (62.5)	11 (84.6)	1058 (77.3)	0.115
Hypertension, n (%)	14 (43.7)	9 (69.2)	882 (64.5)	0.050
Diabetes mellitus, n (%)	3 (9.4)	6 (46.1)	402 (29.4)	0.019
Dyslipidemia, n (%)	9 (28.1)	3 (23.1)	631 (46.1)	0.034
Current smoker, n (%)	4 (12.5)	1 (7.7)	378 (27.6)	0.027
Family history of CAD, n (%)	7 (21.9)	3 (23.1)	294 (21.5)	0.989
STE-ACS, n (%)	18 (56.2)	3 (23.1)	716 (52.6)	0.096
Hematologic values				
Hemoglobin, (g/dL)	13.8±2.2	12.7±3.5	13.5±1.8	0.247
White-cell count (10^3/L)	12.6±4.9	13.6±8.7	10.5±4.0	0.002
Neutrophil Count (absolute number)	8 (6-12)	8 (6-10)	6 (4-9)	0.389
Platelet count (10^3/L)	526±195	462±195	231±69	<0.0001
Angiographic features				
Coronary artery disease				<0.001
Mono-vessel, n (%)	32 (100)	4 (33.3)	340 (26.9)	
Two-vessel, n (%)	0	4 (13.8)	327 (25.9)	
Three-vessel, n (%)	0	5 (41.7)	553 (43.8)	
Ticagrelor, n (%)	2 (6.2)	1 (7.7)	508 (37.3)	<0.001
Prasugrel, n (%)	2 (6.2)	0	277 (20.3)	0.028
Clopidogrel, n (%)	19 (59.4)	7 (53.8)	364 (26.7)	<0.001
Acetylsalicylic acid, n (%)	28 (87.5)	10 (76.9)	1254 (92.1)	0.089
Statin, n (%)	26 (81.2)	6 (46.1)	1182 (86.8)	<0.001
ACE-inhibitor/ARB, n (%)	23 (71.9)	9 (69.2)	889 (65.3)	0.713

Summary/Conclusion: ACS is a known complication of JAK2+ PV/ET. In this setting it displays peculiar angiography features according to time of clinical presentation with newly diagnosed PV/ET patients more often showing single-vessel involvement compared to patients with known PV/ET who have angiography features similar to the control group. CRF were also not significantly represented among these patients. It is tempting to hypothesize that mechanisms other than atherosclerotic plaque rupture may be relevant to ACS development when JAK2+ PV/ET occur. Considering the anatomical sites involved, it may be speculated that endothelial dysfunction associated with elevated shear stress may be the main inciting factor leading to thrombosis. In the setting of shear-induced endothelial dysfunction, the overall pro-coagulant features of circulating cells may give rise to thrombus formation even in the absence of underlying plaques. Recognition by the cardiologists of the peculiar angiography features associated with ACS as initial presentation of PV/ET should prompt hematologic counseling aimed at a tailored treatment strategy. Dual anti-platelet therapy alone may not protect from further thrombotic events and a more comprehensive therapeutic strategy, comprising hydroxycarbamide/phlebotomy, is be advisable in these patients.

EP1114 IPSS, DIPSS AND DIPSS-PLUS: PREDICTIVE VALUE FOR SURVIVAL IN PRIMARY MYELOFIBROSIS STAGES

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Background: In the recent years, prognostic models have been validated for primary myelofibrosis (PMF), initially based exclusively on clinical variables, namely the *International Prognostic Scoring System-(IPSS)* and the *Dynamic IPSS-(DIPSS)*. Cytogenetics was incorporated in the most recent scores such as the DIPSS-plus. However, the applicability of PMF scoring systems in the recently recognized pre-fibrotic PMF (pre-PMF) has not been validated.
Aims: To assess the prognostic value of IPSS, DIPSS and DIPSS-plus in PMF stages: pre-PMF and overt-PMF.
Methods: Retrospective and unicentric analysis of records from patients (pts) diagnosed with PMF between January 2010 and December 2019. The diagnoses of pre-PMF and overt-PMF were reviewed according to WHO 2016 criteria. Prognostic scores were calculated considering clinical and laboratory information at diagnosis. Kaplan-Meier method were used for the analysis of progression free survival (PFS) and overall survival (OS). For multivariate analysis were included the variables with p<0.05 in the univariate analysis.
Results: We studied a total of 90 pts, with a median age of 68 years (range, 24-92 years old), 63.3% males. Forty-three (47.8%) pts were at pre-PMF stage.
The overall PFS in our cohort was 101.7 months. In addition to the variables included in the IPSS and DIPSS-plus, histological stage (HR 4.1; p=0.002), increased lactate dehydrogenase (LDH) (HR 9.7; p=0.026) and splenomegaly (HR 2.2; p=0.013) were predictors of PFS. In multivariate analysis, IPSS (HR 5.7; p<0.001), DIPSS (HR 4.5; p<0.001) and DIPSS-plus (HR 4.1; p=0.009) remained predictors of PFS. However, after sub-analysis for the histological stage, all the three scores were predictors of PFS in overt-PMF (HR 7.4, p=0.001; HR 6.8, p<0.001; HR 3.4, p=0.022, respectively) but not in pre-PMF (HR 3.1, p=0.202; HR 6.7, p=0.132; HR 2.5, p=0.237, respectively).
The overall OS was estimated in 124.6 months. Again, beyond the variables included in IPSS and DIPSS-plus, the histological stage (HR 6.2; p=0.001), elevated LDH (HR 8.8; p=0.033) and splenomegaly (HR 3.3 p=0.010) were also predictors of OS. In multivariate analysis, IPSS (HR 6.2; p<0.001), DIPSS (HR 4.5; p<0.001) and DIPSS-plus (HR 4.1; p=0.009) persisted as predictors of OS. However, upon sub-analysis for the histological stage, the aforementioned scores kept as predictors of OS in overt-PMF (HR 7.6, p=0.001; HR 6.1, p<0.001; HR 4.1, p=0.019, respectively) but not in pre-PMF (HR 3.1, p=0.200; HR 3.4, p=0.382; HR 7.9, p=0.988, respectively).
Summary/Conclusion: In our cohort, IPSS, DIPSS and DIPSS-plus were independent predictors of PFS and OS in overt-PMF, but did not in pre-PMF. These findings identify a flaw in prognostic stratification applying the available scoring systems and alarms for the need of validated scores specifically for pre-PMF pts.

EP1115 A POSSIBLE SYNERGISTIC EFFECT OF P SELECTIN GLYCOPROTEIN LIGAND 1 POLYMORPHISM AND ANTIPHOSHOLIPID ANTIBODIES ON THROMBOSIS IN MYELOPROLIFERATIVE NEOPLASIA PATIENTS

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Background: The morbidity and mortality of BCR-ABL negative myeloproliferative neoplasms (polycythaemia vera, essential thrombocyhaemia and primary myelofibrosis) is highly dependent on thrombotic complications. In myeloproliferative neoplasia patients circulating platelets are already activated and they secrets higher levels of surface P-selectin and tissue factor. Anti-β2 glycoprotein 1 antibodies (β2GP1) bind to the β2GP1 receptors on the platelet surface, activating them that is important for thrombus formation. Antiphospholipid antibodies activates endothelial cells, whose dysfunction also plays an important role in the pathogenesis of thrombosis in BCR-ABL negative myeloproliferative neoplasia.
Aims: To evalute the antiphospholipid antibodies in relationship P Selectin Glycoprotein Ligand 1 (PSGL1) polymorphism on the development of thrombosis with other risk factors in patients with MPN.
Methods: A total of 105 MPN patients were included in this retrospective study. 58 of the MPN patients were diagnosed with essential thrombocythemia (ET), 41 with polycythemia vera (PV), 6 with myelofibrosis (MF). Clinical data about the development of thrombosis was collected. PSGL1 polymorphisms was determined from peripheral blood samples using PCR method. In electrophoresis the size of A allele was 558 bp, B allele – 528 bp. Data analysis was performed using "IBM SPSS Statistics 23". There were two different selective and one confirmatory test for the LA determination. The detection of antibodies against β2-glycoprotein-1 (β2GP1) was performed using a chemiluminescent method. The detection of antibodies against cardiolipin (aCL) was performed by ELISA using commercial Aeskulisa Cardiolipin-GM (AESKU.DIAGNOSTICS, Germany).The interdependence of qualitative attributes was evaluated by the criterion of the chi square ($\chi 2$), and the Stjudent t-test or the Mann-Whitney U test was used to compare the quantitative characteristics. The data was statistically reliable when $P<0.05$.
Results: Arterial thrombotic complications were present in 38 (42.2%) of those with MPN. These patients were diagnosed with transient ischaemic attack (TIA), ischaemic stroke or myocardial infarction. aPL together with PSGL1 polymorphism were significant more frequently found in arterial thrombosis MPN patients compared with MPN patients who didn't experienced thrombosis (21.1% and 5.8%; $p< 0.029$).
Summary/Conclusion: Myeloproliferative neoplasm´s patients with antiphospholipid antibodies and PSGL1 polymorphism may have the increased risk of thrombosis development.

EP1116 CHARACTERIZATION OF MYELOID MUTATIONS IN 21 PATIENTS WITH COEXISTING MYELOPROLIFERATIVE AND LYMPHOPROLIFERATIVE SYNDROMES

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Background: The coexistence of myeloproliferative neoplasms (MPN) and lymphoproliferative neoplasms (LPN) is a rare finding. However, studies have demonstrated that patients with MPN have approximately a 3-fold higher risk of developing an LPN than the general population. The clonal origin of these diseases has yet to be elucidated, although there are suggestions that their origin may lie in multipotent hematopoietic stem cells.
Aims: Use of next-generation sequencing (NGS) to identify myeloid mutations in separated cellular populations associated with the development of coexisting MPN/LPN syndromes.
Methods: All patients with a MPN or LPN diagnosis (dx) between 1997 and 2020 were retrospectively analyzed for concomitant MPN/LPN according to the WHO 2016 criteria. Of the 21 patients identified, informed consent was obtained from the live patients (n=13) for peripheral blood (PB) extraction. CD34+ (progenitor cells), CD15+ (granulocytes), and CD19+ (B lymphocytes) cell populations were separated using an autoMACS Pro. So far, genomic DNA of 5 patients has been analyzed by NGS with the MiSeq (Illumina) platform using the targeted panel Myeloid Solution™ (SOPHiA GENETICS). Only variants with VAF ≥1%, MAF<1% and described as having a pathogenic or probably pathogenic effect were considered.
Results: We report a series of 21 patients: 57% received an MPN dx first (average age at dx 66.4 years) then LPN, 28.5% received an LPN dx first (average age at dx 68.1 years) then MPN, while 14.5% had a concomitant dx (average age at dx 64.3 years). The most frequent LPN dx was chronic lymphocytic leukemia (CLL, 33%); the most frequent MPN dx was essential thrombocythemia (ET, 48%). Coexisting syndromes with the highest incidence were CLL-ET (28.6%) and PV-MGUS (14.3%). Patient characteristics are shown in Table 1.
Mutated MPN driver genes were *JAK2* and *CALR* for 81% (n=3, all V617F) and 10% (n=2, 1 Type 1, 1 Type 2), respectively; 10% of patients were triple negative (n=2). The MPN driver mutation was always detected in the CD34+ population, although the allelic frequency (VAF) was slightly inferior compared to PB in 2 cases. In 1 TN patient no mutation was found in PB but the *JAK2* mutation was detected in CD34+ cells (VAF 2.7%). In the CD19+ population, the MPN driver gene mutation was undetectable except for 1 patient who had a high VAF (*CALR* Type 1) in all cell populations and developed the LPN just one year after the initial MPN diagnosis. In the other 3 MPN-first cases, the LPN developed after 3-12 years.
With regard to other myeloid genes, *TET2* was mutated in 2 patients in SP and CD34+ cells, while 1 patient was mutated in both *DNMT3A* and *PTPN11*. None of these variants were detected in the CD19+ populations. The only alteration observed in CD19+ cells was a chromosome 21 deletion (also present in the CD34+ population but not in PB).

Table 1. Patient characteristics.

Patient	Age	Sex	LPN-MPN type	MPN driver mutation	Time between dx (years)	LPN treatment type	MPN treatment type	Treatment response LPN	Treatment response MPN	Concomitant follow up (years)
LPN first, n=6										
1	69	F	CLL-ET	*JAK2* V617F	11	OBS	OBS	SD	SD	13
2*	67	M	SMZL-ET	*JAK2* V617F	3	R-CHOP	HU	ND	SD	2
3	75	F	MALT- PMF	*JAK2* V617F	5	RT	RUX	CR	SD	9
4	51	M	DLBCL-PV	*JAK2* V617F	3	R-CHOP	HU/ RUX	CR	SD	18
5	77	F	CLL-PV	*JAK2* V617F	2	OBS	HU		SD	5
6*	75	M	NHLB-PMF	*CALR*	5.5	RIT	Other*	PR	Progression	3
MPN first, n=12										
7	56	M	ET-CLL	*JAK2* V617F	3	OBS	HU	SD	SD	5
8	47	M	ET-BL	*JAK2* V617F	1	Burkimab-BB	HU	SD	CR	11
9	72	F	ET-AITL/NHL-B	*JAK2* V617F	4	R-CHOEP	HU	SD	ND	0.25
10	46	F	ET-MM	TN	10	VDR	OBS	SD	ND	5
11	63	F	PMF-AITL	*JAK2* V617F	7	R-CHOEP	HU/ RUX	ND	ND	2
12	71	M	ET-CLL	TN	5	OBS	HU	SD	SD	3
13*		M	ET-CLL	*JAK2* V617F	2	OBS	HU	SD	SD	0
14*	61	M	ET-CLL	*JAK2* V617F	5	OBS	HU	SD	SD	15
15	71	F	ET-NHLB	*JAK2* V617F	0.33	OBS	OBS	SD	SD	11
16	67	M	ET-CLL	*JAK2* V617F	12	OBS	Anagrelide	SD	SD	4
17*	63	F	PV-SMZL	*JAK2* V617F	7	HU	R-CHOP	SD	CR	4
18*	74	M	PV-MGUS	*JAK2* V617F	13	HU	OBS	Progression	SD	0.33
Concomitant, n=3										
19	63	M	PV-MGUS	*JAK2* V617F	-	HU	OBS	Progression	SD	10
20	50	M	PV-HL	*JAK2* V617F	-	HU	ABVD	SD	CR	6
21	80	F	PV-MGUS	*JAK2* V617F	-	HU+ Anagrelide	OBS	SD	SD	3

*: patient deceased; *Danatrol + erythropoetin

F: female, M: male, TN: triple negative, LPN: lymphoproliferative neoplasm, MPN: myeloproliferative neoplasm, ET: essential thrombocythemia, PV: polycythemia vera, PMF: primary myelofibrosis, CLL: chronic lymphocytic leukemia, BL: Burkitt lymphoma, AITL: angioimmunoblastic T-cell lymphoma, MALT: mucosa-associated lymphoid tissue, MGUS: monoclonal gammopathy of undetermined significance, HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma, NHLB: B-cell non-Hodgkin lymphoma, SMZL: splenic marginal zone lymphoma, OBS: observation, HU: hydroxyurea, RIT: rituximab, RUX: ruxolitinib, R-CHOP: rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine sulphate,prednisone, R-CHOEP: rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine sulphate-etoposide-prednisone, ABVD: adriamycin-bleomycin-vinblastine-dacarbazine, SD: stable disease, CR: complete response, ND: not determined.

Summary/Conclusion: In 1 patient the MPN driver mutation was present in the CD19+ population and the LPN debuted only one year after the MPN dx. In this case, the mutation was developed in an immature cell preceding myeloid/lymphoid differentiation and could have had a role in the development of LPN. In the rest of the patients, LPN development seemed to be independent of the *JAK2/CALR* driver gene mutation. Our results show that the genetic analysis of CD34+ cells could help reveal the driver gene mutation in triple negative cases. The study of

myeloid and lymphoid separated populations gives us a better understanding of the mechanisms of concomitant MPN/LPN development.

EP1117 PULMONARY MANIFESTATIONS OF ERDHEIM-CHESTER DISEASE : CLINICAL CHARACTERISTICS, OUTCOMES AND COMPARISON WITH LANGERHANS CELL HISTIOCYTOSIS

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Background: Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis that typically affect many organs including lung and pleura. However, studies concerning pulmonary involvement are limited in ECD patients.
Aims: The aim of the study is to describe the clinical manifestations, radiological findings and treatment outcomes of ECD pulmonary involvement, explore its prognostic value, as well as compare the pulmonary involvement of our ECD cohort with the adult LCH patients in our center.
Methods: We performed a retrospective study of the clinical features, radiological characteristics and treatment outcomes of 54 consecutive ECD patients at Peking Union Medical College Hospital between January 2013 and October 2020. Data of adult Langerhans cell histiocytosis (LCH) patients with pulmonary involvement diagnosed from January 1990 to November 2019 in our center were also retrospectively analyzed. Clinical and radiological characteristics between these two cohorts were compared.
Results: The median age of diagnosis was 48 years (range 9-66 years) for the 54 ECD patients. 49 patients (91%) had pulmonary involvement, while 14 (25.9%) had respiratory symptoms. Chest computed tomography (CT) scans revealed lung involvement in 49 (91%) patients and pleura involvement in 34 (63%). 33 (61%) patients had interstitial lung disease (ILD) with varying degrees of interlobular septal thickening (57.4%), micronodules (55.6%), and ground-glass opacities (48.1%). Diffusion dysfunction was the most frequent pattern in pulmonary function test and the median diffusion lung capacity for carbon monoxide was 65.1% predicted (37.5-111% predicted). Patients with pulmonary involvement between ECD and LCH show significant differences in smoking status (10.3% VS 59.3%, P<0.001), respiratory symptoms (28.6% VS 57.5%, P=0.001) like cough, pneumothorax (0 VS 23.9%, P<0.001), and the radiological findings, including cysts (P<0.001), opacities (P<0.001), and pleural thickening (P<0.001). With the median follow-up duration of 24 months (range, 1–84 months), the estimated 3-year OS of this cohort were 90.2%. Patients with ILD tended to have worse PFS than those with no ILD (P = 0.29).
Summary/Conclusion: Pulmonary involvement is usually asymptomatic and therefore underestimated among ECD patients. Typical findings on CT scans include interlobular septal thickening, micronodules, ground-glass opacities, and pleural thickening. The pulmonary involvement of ECD is quite different from LCH in clinical and radiological manifestations.

EP1118 THE ROLE OF NEUTROPHIL LYMPHOCYTE RATIO AND PLATELET LYMPHOCYTE RATIO AS AN INDICATOR TO THROMBOSIS IN PHILADELPHIA NEGATIVE MYELOPROLIFERATIVE NEOPLASMS: PRELIMINARY DATA OF PROSPECTIVE COHORT

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Background: Major thrombotic events are devastating complications in the Philadelphia negative myeloproliferative diseases. The neutrophil-lymphocyte ratio (NLR) and the platelet- lymphocyte ratio (PLR) were found to be associated with the burden of thrombotic events.
Aims: Our objective is to determine the role of NLR, and PLR ratios detected at the diagnosis of the MPN diseases as an indicator to thrombosis in conjugation with the other risk factors and to illustrate the difference between the patients developed thrombosis at the diagnosis of MPN disease and patients who develop the thrombosis after the diagnosis.
Methods: The current study is a single-center observational prospective cohort (NCT03599700, Clinical Trials.gov) conducted in a university-affiliated hospital (Assiut University Hospital, Assiut, Egypt).
Subjects were enrolled if BCR-ABL negative myeloproliferative neoplasms e.g.: Polycythemia vera, Essential thrombocythemia, and Primary myelofibrosis and the age was more than 18 years.
Clinical and demographic data were collected. Laboratory assessment included complete blood count (CBC). Follow up for thrombotic events were planned for three years from the start of the study. The patients were divided to three groups according to the incidence of thrombosis either no thrombosis or thrombosis at diagnosis of the MPN or thrombosis after the diagnosis of the disease.
Results: Within 15 months of the study, we recruited 204 patients with 142 patients (69.6%) of whom showed no thrombosis and 42 patients (20.6%) of the patients affected by thrombosis at the diagnosis and 20 patients (9.8%) of the patients developed thrombosis during their follow up.
We found that thrombosis at and after diagnosis occurred in 42 patients (27%) at age <65 years while it occurred in 20 patients (40.8%) at age ≥ 65 years group (P=0.05).
PLR showed a significant difference between Patients without thrombosis group and both Patients with thrombosis at diagnosis and after diagnosis groups (P= 0.002).
NLR showed a significant difference between Patients without thrombosis group and the group of Patients with thrombosis at diagnosis and after diagnosis groups (P= 0.03).
Univariate analysis was done for the thrombosis risk factors: sex, BMI, diagnosis subclassification, presence of constitutional symptoms, JAK mutation, PLR, NLR, age ≥65 years and smoking status.
PLR, constitutional symptoms, smoking status, JAK mutation and MPN subclassification were the significant factors and incorporated into multivariate analysis.

	P -value	Odds ratio	95% CI: lower limit	95% CI: upper limit
PLR	0.032	1.002	1.001	1.004
constitutional symptoms	0.073	7.437	0.832	66.509
Smoking	0.006	3.323	1.410	7.831
JAK mutation	0.009	2.843	1.299	6.225
ET versus PMF	0.020	4.338	1.259	14.943
PRV versus PMF	0.015	3.917	1.306	11.746

Summary/Conclusion: In conclusion, PLR is a strong predictor for thrombosis in patients of MPNs while NLR appears to be higher in the group of patient suffering from thrombosis but not efficiently predict future events. This effect appears independently from other well known risk factors. JAK2 mutation, MPN sub classification and smoking are significantly associated to the burden of thrombotic risk.

EP1119 RUXOLITINIB-ASSOCIATED TUBERCULOSIS IN MYELOPROLIFERATIVE NEOPLASMS (MPN): SYSTEMATIC REVIEW AND META-ANALYSIS OF 26 CASE REPORTS

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Background: Despite significant benefits of ruxolitinib (RUX) in MPN management, e.g. primary (PMF) or secondary myelofibrosis and polycythemia vera (PV), the reports of opportunistic infections occurring during RUX treatment, particularly pulmonary (PTB) or disseminated tuberculosis (DTB), are increasing worldwide.

Aims: To identify PTB/DTB cases in RUX-treated MPN and report on epidemiology, clinical manifestations, RUX associations, outcomes.
Methods: Systematic search computed in PubMed/Medline, Web of Science, ScienceDirect, SCOPUS, from the inception of these databases until 15.11.2020. Relevant English-written articles were identified based on the Eligibility criteria: 1. Confirmed MPN diagnosis, 2. Confirmed diagnosis of PTB/DTB caused by *Mycobacterium tuberculosis*, 3. MPN managed with RUX. Exclusion criteria: reports of other mycobacteria apart from *M. tuberculosis*, RUX used in other disorders, *in vitro studies*, animal studies. The initial search identified 156 publications, of which 22 were selected based on title/abstract screening. Following full-text review, 20 publications depicting 26 distinct case reports were included in the systematic review and meta-analysis.
Results: 26 case reports were identified: 69.2% females, mean age 65.6 years, 80.8% PMF. JAK2V617F mutation was detected in 65.4% of cases. RUX mean dose was 35 mg/day (40.74% received 40 mg/day) and the average time from RUX initiation to TB diagnosis was 7 months. TB screening was performed only in 19.2% of subjects. DTB was more frequent *versus* PTB (65.4% versus 34.6%). PTB and DTP were observed primarily in PMF (80.8%) and less frequently in post-PV-MF (7.7%) or PV (3.85%). The most common presentations were fever (80.7%), peripheral lymphadenopathy (38.5%), night sweats (23.1%), fatigue/tiredness (19.2%), weight loss (15.4%), cough (11.54%) and shortness of breath (7.7%). All patients received 6, 9 or 12 months of antitubercular treatment (ATT), i.e. HRZE (isoniazid + rifampicin + pyrazinamide + ethambutol) or variants. RUX was discontinued in 69.2% of cases and maintained in 11.5% of cases in combination with ATT. RUX re-initiation was decided in 23.1% of patients. TB-related death occurred in 23.1% of the subjects involved. Most case reports did not report on follow-up visits, thus assessing TB resolution or relapse is difficult to pursue. The attached table details the case reports of RUX-associated TB included in our analysis (+ = Yes; – = No;? = Unknown/Unspecified/Unavailable; P-pulmonary, D-disseminated TB).

	Ref./Year	Age	Sex	PMF	JAK2 V617F	RUX dose mg/d	Δt [months]	TB	ATT, ΔATT [months]	RUX discontinuation	TB resolution	RUX reintroduction	TB relapse	Outcome
1	Abidi/2016	69	M	+	+	40	1	P	6 HRZE + 3 MR	+	+	+, after 6 months of ATT	–	Alive
2	Branco/2015	78	F	+	+	30	19	D	2 HRZE + 10 MR	–	?	Not discontinued	?	Alive
3	Chen/2015	82	M	+	+	40	2	P	HRZE	+	?		?	Alive
4	Colombo/2018	?	M	+	?	?	?	D	HRZE	?	?	?	?	Alive
5	He/2017	60	M	+	?	?	4	P	HRZE	+	?		?	Alive
6	Hopman/2014	62	M	+	+	40	1.75	D	9 HRZE	+	?	+, 20 mg/d, then 40 mg/d	?	Alive
7	Keiner/2015	72	M	+	+	?	5	D	+	?	?	?	?	Died
8	Keiner/2015	68	M	+	+	?	1	P	+	?	?	?	?	Died
9	Khaldi/2016	78	F	+	+	40	36	P	+	+	?	?	?	Died
10	Khaldi/2015	62	M	+	+	20	13	P	+, 10	+	+	+, after 1 month of ATT	–	Alive
11	Khaldi/2015	54	M	+	+	40	?	P	HRZE	+	+	–	–	Alive
12	Kim/2013	?	F	PMF	?	?	1	D	+	+	?	–	?	Died
13	Kim/2013	?	M	PMF	?	?	2	D	+	–	–	Not discontinued	–	Alive
14	Lescoute/2010	73	M	+	+	30	6	D	+	–	–	–	–	Died
15	Mekkis/2015	64	M	PV, MF	+	40	9	D	–	?	–	–	–	Died
16	Neelis/2015	67	M	+	?	40	10	P	HRZE	+	?	–	?	Alive
17	Neelis/2015	67	F	+	+	?	6	D	6 HRZE	+	?	+	?	Alive
18	Rhinehart/2014	65	F	PV, MF	+	?	6	D	6 HRZE	+	–	+, + H prophylaxis	Yes	Alive
19	Tzanis/2016	35	M	+	+	?	1.5	D	9 HRZE	+	+	+, 20 mg/d	–	Alive
20	Zaimenias/2018	69	F	+	?	30	?	D	Yes	?	?	?	?	Alive
21	Feng/2020	41	M	+	+	40	4	P	12 HRZE-Levofloxacin	+	+	+, 20 mg/d	?	Alive
22	Feng/2020	66	M	+	+	40	2	D	12 HR, levofloxacin, cefuroxime, moxifloxacin	–	?	Not discontinued	?	Alive
23	Repelaer/2018	52	F	+	?	40	8	D	6 HRZE	+	+	+	?	Alive
24	Sakiyama/2020	76	M	PV	+	20	6	D	6 HRZE	+	+	–	–	Alive
25	Shamil/2015	78	F	+	?	?	?	D	12 HRZE	+	+	?	?	Alive
26	Tsukamoto/2020	73	M	+	+	40	6	D	HRZE	+	+	–	–	Alive

Summary/Conclusion: Opportunistic infections, including PTB/DTB, can develop during RUX treatment due to its immunosuppressive effects. Screening for TB is advised prior to RUX prescription by skin tests, IFN-γ releasing assays and (or) chest X-rays. Prophylaxis can be considered in TB-endemic areas.

EP1120 VARIABLES ASSOCIATED WITH PATIENT-REPORTED OUTCOMES IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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Background: The Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are characterized by clonal proliferation of myeloid–derived hematopoietic stem cells. Patient-reported outcomes (PROs) are an assessment of health outcomes including symptom status, physical function, mental health, social function, and well-being from the patients' perspective. Besides the life-threatening complications, patients with MPN also suffer from substantial symptom burden, which has aroused great attention in recent years. PROs other than symptom burden such as the impact on work productivity and daily living, satisfaction level with therapy, and health-related quality of life (HRQoL) were also studied in patients with MPN. However, there were limited data of PROs and their associated variables in MPN patients in the developing countries, as most of the published data were from western developed countries, and variables associated with PROs were not fully explored in those studies using multivariate analyses. With different socio-demographic status, financial status, health insurance policy, humanistic philosophy, and treatment pattern, MPN patients in the developing countries might have distinct PROs and different variables associated with them.
Aims: To explore PROs including symptom burden, impact on daily life and work, obstacles during therapy, satisfaction level with therapy, and HRQoL in patients with MPN in China, a representative of developing countries, and to identify variables associated with those PROs.
Methods: A multi-center, cross-sectional study was conducted in patients with MPN across China.
Results: Data from 1,500 respondents including ET (n = 707), PV (n = 316) and MF (n = 477) were analyzed. In multivariate analyses, *CALR* mutation [HR =0.4 (0.2-0.9); $P = 0.020$] was significantly-associated with lower MPN-10 scores in respondents with MF. Higher MPN-10 scores were significantly-associated with negative impact on daily life and work as well as lower satisfaction level in those with ET [HR = 3.9 (2.3-6.5); $P < 0.001$ and HR = 2.1 (1.2-3.9); $P = 0.016$], PV [HR = 3.2 (1.6-6.5); $P = 0.001$ and HR = 3.5 (1.4-8.5); $P = 0.007$] and MF [HR = 2.4 (1.4-4.2); $P = 0.002$ and HR = 3.9 (2.1-7.5); $P < 0.001$]. Receiving ruxolitinib was significantly-associated with high satisfaction and satisfaction in respondents with MF [HR = 0.09 (0.03-0.3); $P < 0.001$]. In addition, demographics and clinical variables including age, gender, household registration, marital status, education level, comorbidity burden, concomitant medication, splenomegaly, complete blood count and annual *out-of-pocket* costs were also impacting PROs.
Summary/Conclusion: Socio-demographic and clinical variables were significantly-associated with PROs in respondents with MPNs.

EP1121 USE OF RUXOLITINIB IN ELDERLY PATIENTS WITH PRIMARY MYELOFIBROSIS

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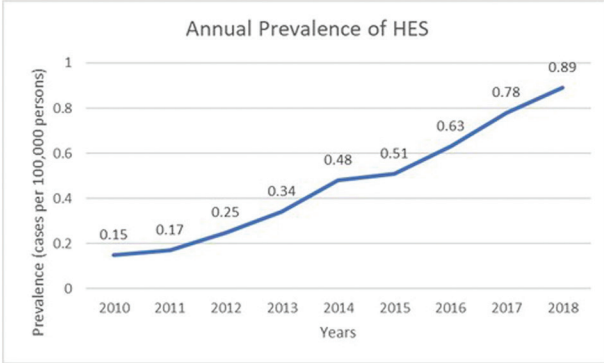
Background: Ruxolitinib (Rx) is a Janus kinase (JAK) 1/JAK2 inhibitor with established efficacy in improving primary myelofibrosis (PMF)-related symptoms and survival. However, while aging is known to correlate with worse prognosis in PMF, real-life studies become essential to demonstrate the efficacy and safety of Rx in older populations.
Aims: To compare survival of elderly patients treated (Rx-t) *versus* non-treated (Rx-nt) with Rx.
Methods: Retrospective and unicentric analysis of records from elderly patients (age ≥65 years) diagnosed with PMF (WHO 2016) between January 2010 and December 2019.The Cox regression model and Kaplan-Meier method were used for the analysis of progression free survival (PFS) and overall survival (OS).
Results: We analysed a cohort of 70 patients, 70% males and with a median age of 74 years old (range, 65-92 years old). Thirteen patients (16.6%) had post-polycythemia vera (PV)/post-essential thrombocythemia (TE) MF. *JAK2V617F* mutation was identified in 71,4% of the patients, while 7,1% and 14.3% harboured a mutation in the *MPL* and *CALR* genes, respectively. Five patients (7.1%) were triple negative for those mutations.
About 87% of the patients required treatment in the course of the disease, 20% with ≥2 lines of therapy. Seventeen-percent were Rx-t. Rx-t patients were younger (69 *versus* 75 years old; p=0,011) and showed a higher incidence of MF post-PV/TE (50 *versus* 12%, p=0,002), compared to Rx-nt. The frequency of *JAK2V617F* mutation was equivalent in both groups (83 *versus* 69%; p=NS), however, the allele burden was higher in Rx-t patients (VAF 73 *versus* 33%; p=0,029). All Rx-t patients were at overt fibrotic stage (p=0,006). Blood tests at diagnosis demonstrated that the majority of the Rx-t presented with anaemia (Hb<12g/dL; p=0,034), however no significant differences were observed in leucocyte counts, LDH, circulating blasts or constitutional symptoms (CS), compared to Rx-nt. With no surprise, most patients selected for treatment with Rx presented with splenomegaly (92 *versus* 50%; p=0,008). There was no significant difference in the distribution through International Prognostic Scoring System (IPSS), dynamic IPSS (DIPSS) or DIPSS-*plus,* between Rx-t *versus* Rx-nt patients. PFS and OS in our cohort was estimated in 62,7 and 101,8 months, respectively.
In the univariate analysis, the variables age, anaemia, CS, circulating blasts, splenomegaly, IPSS and DIPSS intermediate-2/high-risk, were significantly associated with PFS; the same variables in addition to fibrosis grade ≥2, were related to OS. After Cox multivariate analysis and after adjusting for variables with impact on PFS and OS in the univariate analysis, we found that treatment with Rx improves PFS (HR 0,28, p=NS, IC95% 0,05-1,52) and OS (HR 0,05, p=0,009; IC95% 0,01-0,48).
Summary/Conclusion: In our cohort, Rx showed to have an independent beneficial impact in mortality of elderly patients with PMF, including patients with high risk IPSS and DIPSS score, therefore demonstrating that advanced age does not stand as a limitation for treatment with Rx.

EP1122 THE INCREASING INCIDENCE AND PREVALENCE OF HYPEREOSINOPHILIC SYNDROME (HES) IN THE UK

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Background: Hypereosinophilic syndrome (HES) is a group of rare hematologic disorders of unknown etiology defined by sustained eosinophilia associated with organ damage. The burden of this rare condition is not yet well characterized. Reliable estimates of the incidence and/or prevalence of the disease are not readily available, since most publications are case reports without clear details of the population from which they are drawn.
Aims: To explore the incidence and prevalence of HES using UK real-world primary care data.
Methods: Primary care data from the UK Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases, were analyzed. Patients of interest were identified using medical codes specific for HES and for chronic eosinophilic leukemia not otherwise specified (CEL-NOS) as a subtype. Annual incidence rates and prevalence were estimated for the years 2010 to 2018 (inclusive) based on the assumption that patients with diagnosed HES would be identified if they were followed for at least 365 days within CPRD. For calculations of incidence, patients with no records of HES within the first 365 days of observation were considered disease-free and hence "at risk" of developing HES in the future. For calculations of prevalence, HES patients were identified from the population of patients who were continually registered for the full calendar year of interest; their HES diagnosis could occur either during or at any time before the calendar year of interest. The impact of this assumption was tested in additional sensitivity analyses applying a minimum observation period of 730 days (two years) or 1035 days (three years) to identify existing prevalent cases.
Results: During the study period, 93 patients were identified with a first diagnosis of HES, 57% were male, with a mean (SD) age of 57.0 (19.3) years. Of these, 12 patients had a diagnosis of CEL-NOS; they were slightly older (average age of 67 years) and predominantly male (92%). From 2010 to 2018, the overall annual incidence rate of patients diagnosed with HES ranged from <0.04 to 0.17 per 100,000 person-years and the overall annual prevalence ranged from 0.15 to 0.89 cases per 100,000 persons (Figure 1). Sensitivity analyses based on minimum observation periods of two and three years gave similar results.



Summary/Conclusion: These results provide estimates of the burden of HES in the UK and indicate that whilst HES is a very rare disease, there is evidence that it is increasingly being recorded in UK primary care. We discuss potential explanations for the patterns seen.
Funding: [GSK 208701][DG1] This study was reviewed and approved by ISAC (protocol number 18_242).

EP1123 INTERLEUKIN-6 AND ITS RELATION TO CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH MYELOFIBROSIS

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Background: Myelofibrosis (MF) is a myeloproliferative disease, characterized by a heterogeneous clinical picture due to bone marrow fibrosis, ineffective extramedullary hematopoiesis and excessive splenomegaly. The pathogenesis of MF is multifactorial, determined by genetic profile of the patient, bone marrow microenvironment, response to inflammatory (cytokine) stimuli and age. Inflammatory cytokines are key mediators in the pathological relation between tumor microenvironment and the clonal hematopoiesis in MF. Interleukin-6 (IL-6) is a multifunctional, pleotropic, pro-inflammatory cytokine that is released by immune-competent cells as a result of infection and/or challenge to the immune system. It's a key participator in the tumor genesis of oncological and hematological neoplasms. IL-6 is involved in a number of pathophysiological mechanisms in MF development and is of major importance for the clinical manifestation, prognosis and progression of the disease.

Aims: The aim of the study is to analyze serum IL-6 levels in patients with MF and its relation to clinical and laboratory characteristics of patients.
Methods: We analyze 68 patients with MF (overt MF -27 patients, prefibrotic MF – 25 patients, post-polycythemia vera (post-PV) MF -9 patients and post-essential thrombocytemia (ET) MF- 7 patients) and 12 healthy controls. The mean age of the patients' group is 67,7 years; male: female ratio - 1,7:1. According to the Dynamic International Prognostic Scoring System (DIPSS) 6 patients are high risk; 35 patients are intermediate 2 risk; 22 patients are intermediate 1 risk and 5 patients are low risk. According to the number of transfusions that patients receive per month: 40 patients are transfusion-independent and patients, receiving an average of 1 blood unit/month (BU/m) are 5; 2 BUs/m – 7 patients; 3 BUs/m – 4 patients; 4 BUs/m - 7 patients; 5 BUs/m - 4 patients and > 6 BUs/m- 1 patient. Regarding treatment 26 patients are on best supportive therapy (BST); 26 patients are treated with cytoreductive treatment (Hydroxyurea-23 patients; Interferon α -3 patients) and 16 patients are treated with target therapy (Ruxolitinib). Degree of fibrosis in the bone marrow (grade 0-3), carrier of Jak2 V617F mutation, spleen size by ultrasound examination and peripheral blood count parameters (hemoglobin, leukocytes, platelets, MCV) are analyzed in all patients. We measure serum IL-6 levels by ELISA in all patients and healthy controls according to the manufacturer's operating instructions. Statistical analysis is performed with SPSS version 20.
Results: Levels of IL-6 are significantly higher in patients with MF compared to healthy controls (26.96 ± 46.73 pg/ml; -0.03 ± 1.68pg/ml; t = 1.99; p = 0.05). A significant difference is found between healthy controls, patients with overt MF (p = 0.036) and patients with post-PV MF (p = 0.028). IL-6 levels are significantly higher in patients with grade 3 fibrosis in comparison to the other grades (60.4 ± 77.3 pg /ml; p = 0.025). There is a strong significant correlation between IL-6 and the number of blood transfusions per month (r = 0.488; p <0.001). No correlation is found with hemoglobin, leukocyte count, MCV, spleen size, Jak2 mutation, DIPSS, symptomatic disease and treatment.
Summary/Conclusion: IL-6 is a key mediator in the pathogenesis and clinical evolution of MF. Its involvement in the establishment of a cytokine risk model of MF, makes it a potential target for therapeutic response, control and monitoring of the disease.

Platelets disorders

EP1124 THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RA) INCREASE T REGULATORY AND T HELPER CELLS IN SPLEENS OF PRIMARY IMMUNE THROMBOCYTOPENIA

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Background: Primary Immune Thrombocytopenia (ITP) is an autoimmune disorder, characterized by low platelets counts due to immune-mediated platelet destruction. The spleen plays a central role in the pathogenesis of ITP, as it is the main site of anti-platelet immune responses and platelet destruction. Thrombopoietin receptor agonists (TPO-RA) are a valid second-line therapy for ITP, being associated with increased platelet production and immune modulatory effects. Such immunological mechanisms are poorly characterized and nothing is known on the splenic effects of TPO-RA administration.
Aims: This study aimed at assessing: (i) the immunological effects of TPO-RA on ITP spleens; and (ii) the effects of TPO-RA administration on splenectomy outcome.
Methods: A clinically annotated series of 35 ITP spleens removed from therapeutic purposes was histologically assessed for the following parameters: (i) white pulp features (lymphoid follicle density and marginal zone width); (iii) subset of CD207/PD1 positive T-cells(which include T follicular helper (Tfh) cells; (iv) cytotoxic T cell density (as assessed by CD8 immunostain); (v) Th1 cell density (as assessed by tBet immunostain); (vi) Th2 cell density (as assessed by GATA3 immunostain); (vii) Treg cell density (as assessed by FOXP3 immunostain). Ten non-ITP spleens were used as controls. ITP patients were stratified into responders and non-responders to splenectomy, based on IWG consensus criteria. Statistical analysis was performed by non-parametric tests for quantitative (Mann-Whitney-Wilcoxon test) and qualitative (Fisher's exact test). Kaplan-Meyer and log rank methods were used for survival analyses. Differences between groups were considered statistically significant for *p*-values <0.05.
Results: The study population included 12/35 (34.3%) males and 23/35 (65.7%) females (M:F ratio: 0.5) with mean age at splenectomy of 41.0 years (range: 16.8 – 68.2 years). TPO-RAs were administered in 13/35 (37.1%) cases. The spleens of TPO-RA treated patients had higher Treg, Th1 and Th2 densities compared to TPO-RA untreated patients (Treg density: 73.7 cells/HPF *vs* 49.4 cells; Th1 density: 79.8 cells/HPF *vs* 49.8 cells/HPF; Th2 density: 281.6 cells/HPF *vs* 185.9 cells/HPF; p< 0.05; Figure 1A). No other differences were noted between TPO-RA treated and untreated cases. Splenic Treg, Th1 and Th2 densities of TPO-RA treated ITP were similar to those of non-ITP controls (p> 0.05). In ITP patients, the outcome of splenectomy was not influenced by prior TPO-RA treatment and/or splenic T cell patterns (Figure 1B).

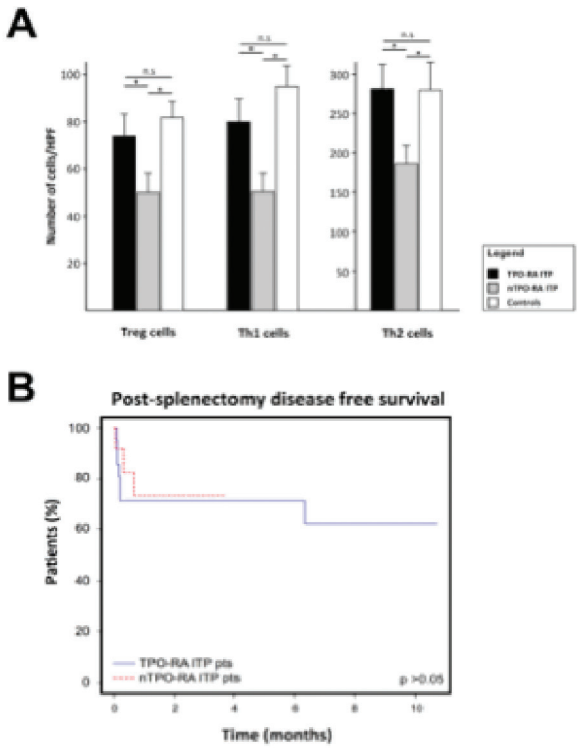


Figure 1. Effects of TPO-RA on ITP spleens.
A. TPO-RA treatment is associated with higher Treg, Th1 and Th2 cell density in ITP spleens. T cell density values are comparable with those of control spleens.
B. Disease free survival following splenectomy was not influenced by prior TPO-RA therapy (TPO-RA ITP pts= patients treated with TPO-RA; nTPO-RA ITP pts= patients not treated with

Summary/Conclusion: Treatment with TPO-RAs in ITP is associated with increased splenic Treg, Th1 and Th2 cells, at values comparable to those of healthy controls. TPO-RA does not influence the outcome of splenectomy in primary ITP.

EP1125 OFF-LABEL USE OF ELTROMBOPAG IN ADULT PATIENTS WITH IMMUNE THROMBOCYTOPENIA BEFORE SIX MONTHS OF DISEASE DURATION IN THE REAL-WORLD IN FRANCE. RESULTS OF THE ELEXTRA STUDY.

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Background: Eltrombopag, a thrombopoietin receptor agonist (TPO-RA), has been available in Europe for the treatment of chronic primary immune thrombocytopenia (ITP) since 2010. Since 2019, it has been indicated in patients with primary ITP, lasting 6 months or longer from diagnosis and who are refractory to other treatments, aged 1 year and above. However, French ITP management guidelines published in 2017, as well as international guidelines updated in 2019 consider the use of second-line treatments earlier in the disease course, including TPO-RAs.
Aims: The ELEXTRA study has been designed to assess the use, the efficacy and the safety of eltrombopag in adult patients with ITP in the real world in France. The present study focused on patients treated with eltrombopag off label before 6 months of ITP duration.
Methods: The source of study population was the multicenter CARMEN-France registry, aimed at the prospective follow-up of adults with incident ITP in France. Patients included in the registry between 2013 and 2019 who were exposed to eltrombopag during the first 6 months of ITP course were selected. Efficacy was assessed in patients who had a platelet count <30 x 10^9/L at eltrombopag initiation. Overall and complete responses were defined by platelet counts ≥30 x 10^9/L and ≥100 x 10^9/L, respectively. Adverse drug reactions (ADRs) with a World Health Organization causality score at least as *"possible"* were described.
Results: Out of 799 patients included in the registry, 156 (19.5%) had been exposed to eltrombopag. Among them, 95 (60.9%) were treated off-label with eltrombopag during the first 6 months of ITP duration. Mean age was 60.5 years; 50 (52.6%) were men; 33 (34.7%) had at least one comorbidity of the Charlson Comorbidity Index; 56 (58.9%) had at least one cardiovascular risk factor (not including age and sex). At ITP diagnosis, the median platelet count was 7 x 10^9/L and 76 (80.0%) patients had bleeding. Median time from ITP onset to eltrombopag exposure was 1.6 months: 74 (77.9%) patients were exposed before 3 months and 21 (22.1%) between 3 and 6 months. Treatments before eltrombopag were: corticosteroids in 91 (95.8%) patients, intravenous immunoglobulin (IVIg) in 66 (69.5%), dapsone in 11 (11.6%), hydroxychloroquine in 6 (6.3%), rituximab in 5 (5.3%), romiplostim in 5 (5.3%), vinblastine in 5 (5.3%), danazol in 2 (2.1%); no patient was splenectomized. Eltrombopag was used as second-line and third-line agent in 41 (43.2%) and 32 (33.7%) patients, respectively. Among the 95 patients, 48 had a platelet count <30 x 10^9/L at eltrombopag initiation; among them, 39 (81.3%) achieved overall response and 35 (79.2%) complete response. Among the 39 patients who achieved overall response, 25 (64.1%) had a concomitant exposure to another ITP treatment at eltrombopag initiation (including steroids, IVIg in the past month or rituximab in the past 6 months). At last follow-up, 57 had stopped eltrombopag, including 17 for absence or loss of response, 15 for ADR and 9 for sustained complete response. Overall, 17 ADRs were reported in 16 (16.8%) patients: thrombocytosis (n=5), venous thrombosis (n=6: 4 pulmonary embolism, 1 deep vein thrombosis, 1 soleal vein thrombosis), rash (n=3), hepatitis, gastrointestinal discomfort, and diarrhea (n=1 each).
Summary/Conclusion: Eltrombopag was mostly used off-label before 6 months of ITP duration in the French real-world practice. Efficacy was similar to that observed in ITP lasting >6 months. The pattern of ADRs was in accordance with previous reports.

EP1126 EFFECTIVENESS OF ROMIPLOSTIM ON PLATELET ENDPOINTS AMONG PATIENTS WITH NEWLY DIAGNOSED, PERSISTENT AND CHRONIC IMMUNE THROMBOCYTOPENIA IN ROUTINE CLINICAL PRACTICE IN DENMARK, SWEDEN, AND NORWAY

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Background: Romiplostim is approved for the treatment of chronic immune thrombocytopenia (ITP for ≥12 months) in adults who are refractory to other treatments such as steroids and intravenous immunoglobulin. In 2021, the romiplostim indication was expanded to also cover adult patients with ITP for <12 months duration.
Aims: To examine baseline characteristics, dosage, and platelet endpoints after initiation of romiplostim in newly diagnosed (ITP duration <3 months), persistent (ITP duration 3-12 months) and chronic (ITP duration >12 months) ITP patients treated in routine clinical practice in Denmark, Sweden and Norway.
Methods: From the population-based Nordic Country Patient Registry for Romiplostim, we included all adult (≥18 years) romiplostim-exposed patients with ITP for at least 6 months between 1 April 2009 and 31 December 2018. We disaggregated the cohort according to time from ITP diagnosis to romiplostim initiation into newly diagnosed, persistent, and chronic ITP. For each exposure group, we described patient characteristics at romiplostim initiation, romiplostim dosage, duration of romiplostim treatment, platelet count during and after romiplostim treatment, and durable platelet response (defined as ≥75% of all recorded platelet count measurements ≥50 x 10^9/L during weeks 14 through 24 after date of first romiplostim administration).
Results: Among the 262 patients initiating romiplostim, 77 had newly diagnosed, 41 had persistent, and 144 had chronic ITP. The proportions aged 70+ years were 26%, 42% and 29% in the three groups, and 13%, 15%, and 16% had Charlson Comorbidity Index Score ≥3, respectively. The three groups had similar proportions of patients with a platelet count <50x10^9/L within 90 days before romiplostim initiation (91%, 88%, and 90%, respectively). The proportions of patients with <2 recorded ITP medication within 6 months prior to romiplostim were 33%, 37%, and 43% in the three groups, respectively. The median of first romiplostim doses were also similar (1.1, 1.1, 1.1 µg/kg, respectively), while there were slight differences in last maintenance romiplostim doses (3.6, 2.5, 2.9 µg/kg, respectively). The median [quartile (Q) Q1,Q3] duration of romiplostim exposure was 19 [3,59], 17 [7,59], and 35 [8,125] weeks, respectively.
The median [Q1, Q3] time to first recorded platelet count ≥50x10^9/L within 2 to 24 weeks after romiplostim initiation was 24 [19,34] days for newly diagnosed ITP and 21 [19,34] days for persistent or chronic ITP. The median [Q1,Q3] platelet count (x10^9/L) during romiplostim treatment was 71 [23,154] in newly diagnosed, 75 [41,133] in persistent, and 76 [33,153] in chronic ITP. The median [Q1, Q3] of the last platelet count within 31-100 days after discontinuing romiplostim among 47, 16, and 51 in patients not receiving any ITP treatment in the period was 171 [107,297], 120 [59,259], and 120 [47,249), respectively. Durable platelet response was achieved in 66%, 53%, and 54% of patients with newly diagnosed, persistent, and chronic ITP, respectively.
Summary/Conclusion: Baseline characteristics and platelet-based outcomes were comparable among newly diagnosed, persistent, and chronic ITP groups treated with romiplostim in routine clinical care of patients with at least six months history of ITP. This suggests that initiation of romiplostim is not guided by ITP duration but rather by patient and disease characteristics.

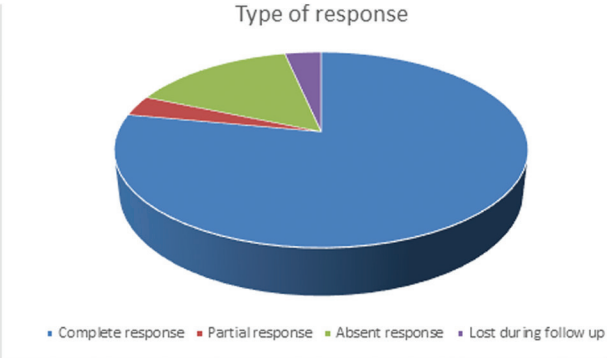
EP1127 OFF-LABEL USE OF ELTROMBOPAG IN A PEDIATRIC POPULATION WITH NEWLY-DIAGNOSED/PERSISTENT IMMUNE THROMBOCYTOPENIC PURPURA

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Background: Immune Thrombocytopenic Purpura (ITP) is an immune mediated disorder characterized by an isolated decrease of the platelet count. Symptoms are usually mild, with cutaneous and/or mucosal bleeding, rarely serious symptoms occur, such as intracranial hemorrhage. ITP is classified into 3 groups: newly diagnosed (within 3 months from the onset), persistent (3 to 12 months from the onset), chronic (after 12 months from the onset). Infusion of immunoglobulin or steroid therapy are the first line of treatment. Current guidelines suggest the use of thrombopoietin receptor agonists (TPO-RAs), such as Eltrombopag (EPAG), in patients with persistent thrombocytopenia. They stimulate thrombopoiesis through the activation of the thrombopoietin receptors, furthermore TPO-RAs can influence platelet antibody production and T regulatory cell count. EPAG is an effective and safe therapy, although its

use is currently approved in patients with ITP after at least 6 months from the diagnosis. Some studies, in the adult setting, have already described the safety and efficacy of EPAG in patients before the 6th month from the onset (off label use).Currently there are no studies on the use of EPAG in the same setting in a cohort of pediatric patients with ITP.
Aims: Evaluate the safety and efficacy of the use of EPAG within 6 months from the onset on a cohort of pediatric patients with ITP.
Methods: *Study population:* 59 patients aged between 1 and 18 years were enrolled from February 2013 and December 2020.
Response evaluation: We evaluated the type of response based on the platelet count: complete if the platelet count was at least > 100.000 in one determination, partial if the platelet count was at least once between 30.000 and 100.000, absent if the platelet count never overcame 30.000. We also defined the persistent response as a platelet count constantly over 30.000, in the absence of symptoms nor rescue therapies over a follow-up of at least 1 year.
Results: We enrolled 59 patients, 39 with newly diagnosed ITP and 20 with persistent ITP. 46 patients had a complete response (80,7%), 2 patients (3,5%) had a partial response, 9 patients did not respond to EPAG. 2 patients were lost at follow-up. 39 of the 49 patients who responded to the treatment with EPAG had a follow-up longer than 1 year, allowing the evaluation of the persistence of the response. 29 patients (74,4%) had a persistent response, with no differences between the group with newly diagnosed ITP and persistent ITP. 14 patients (23,7%) had at least one adverse event. 3 patients presented with significant thrombocytosis (over 1.000.000) that promptly resolved after a temporary, brief suspension of the treatment. Other adverse events were hypertransaminasemia, nausea, hypoferritinemia with or without anemia. In one patient who had grade 3 hypertransaminasemia and acydosis EPAG was suspended.



Summary/Conclusion: This study is, to the best of our knowledge, the first reporting on the use of EPAG in a pediatric population with newly diagnosed or persistent (3-6 months) ITP. Our data highlight the efficacy of this therapy and its safety, with only a small proportion of patients reporting reversible adverse events. Therefore, given the difficulties to treat patients who do not respond to the first line therapy or who have an early relapse, EPAG could be an option.
We believe further studies are needed to explore the use of EPAG in these contexts.

EP1129 CLINICAL-PATHOLOGICAL PREDICTORS OF SPLENECTOMY RESPONSE IN PRIMARY IMMUNE THROMBOCYTOPENIA: A MULTI-CENTER ITALIAN STUDY.

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Background: Splenectomy is a valuable second-line therapy for primary Immune Thrombocytopenia (ITP), with response rates exceeding 60% of cases. It is nonetheless an invasive procedure with potentially severe side effects (thrombotic events, major bleeding and life-threatening infections). At present, there are no validated predictors of splenectomy response in ITP. Their identification may nonetheless help identify ITP patients with the highest chances of benefitting from this procedure.
Aims: This study was aimed at identifying possible clinical-pathological predictors of splenectomy outcome in primary adult ITP.
Methods: A discovery set of 27 clinically-annotated ITP spleens from Padua University Hospital (Padua – Italy) was histologically assessed for the following parameters: (i) density of lymphoid follicles; (ii) width of peri-follicular marginal zones; (iii) density of T regulatory, Th1, Th2, cytotoxic T cells and Cd207/PD1-positive T-cells (which include T follicular helper cells; (iv) width of perivascular T cell sheaths; and (v) red pulp features (plasma cell, histiocyte and sinusoid density). Splenectomized ITP patients were stratified into responder and non-responder subgroups based on IWG consensus criteria and clinical-pathological data were matched to identify possible predictors of surgical outcome. The obtained results were validated in an additional set of 31 ITP patients from Sant'Orsola University Hospital (Bologna – Italy) and San Bortolo Hospital (Vicenza - Italy). Statistical analysis was performed by non-parametric tests for quantitative (Mann-Whitney-Wilcoxon test) and qualitative (Fisher's exact test) variables. Kaplan-Meyer and log rank methods were used for survival analyses. Differences between groups were considered statistically significant for *p*-values <0.05.
Results: The discovery set consisted of 9/27 (33.3%) males and 18/27 (66.7%) females with mean age at surgery of 36 years (range: 18-67 years). Histological evaluation of ITP spleens documented heterogeneous morphology, spanning from white pulp hyperplasia to marked lymphoid atrophy. No single clinical-pathological parameter predicted splenectomy outcome. However, the combination of multiple variables (*i.e.* age at surgery >45 years; concurrent autoimmune diseases and/or high ANA counts; low splenic Cd207/PD1-positive T-cell density (which include T follicular helper cells); low splenic marginal zone width) efficiently stratified patients into splenectomy response groups. Indeed, the occurrence of ≥2 clinical-pathological (left upper panel) or ≥1 clinical risk factors (left lower panel) was associated with significantly worse splenectomy outcome (p <0.05;). These results were confirmed in a validation set of 31 ITP cases, which included 14/31 (45.2) males and 17/31 (54.8%) females with mean age at surgery 33 years (range: 19-69 years) (Right panels). Splenectomy response did not correlate with prior medical therapies.

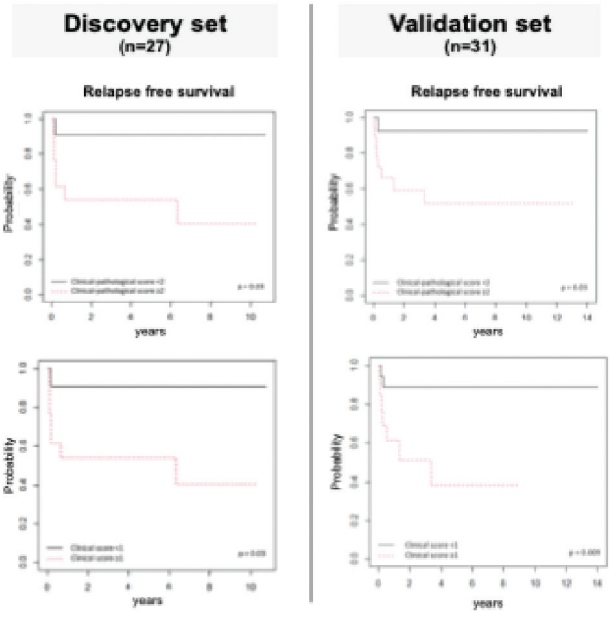


Figure 1. Disease free survival curves of the discovery set and validation set.
The curves stratifying patients according to clinical-pathological risk factors (*upper panels*) included the following variables: (i) age at surgery >45 years; (ii) concurrent autoimmune diseases and/or high ANA counts; (iii) low splenic T follicular help cell density; (iv) low splenic marginal zone width. The curves stratifying patients based on clinical risk factors only (*lower panels*) included: (i) age at surgery >45 years; (ii) concurrent autoimmune diseases and/or high ANA counts.

Summary/Conclusion: The integration of clinical-pathological parameters may predict splenectomy outcome, contributing to the management of ITP patients.

EP1130 TREATMENT OF IMMUNE THROMBOCYTOPENIA IN THE COVID-19 ERA: FOSTAMATINIB, AN ORAL SPLEEN TYROSINE KINASE INHIBITOR

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ITP is an autoimmune disease primarily mediated by spleen tyrosine kinase (SYK) signaling-dependent phagocytosis of autoantibody-bound platelets by macrophages. Fostamatinib is a potent SYK inhibitor, is approved for ITP in the US, Canada, and Europe, and has been shown to elevate platelet counts and decrease bleeding. Fostamatinib may also abrogate thrombosis by mitigating SYK signaling in platelets. Furthermore, preclinical studies in rodents showed that R406 (the active metabolite of fostamatinib) is not immunosuppressive, preserving both the innate and humoral responses to immune challenges.[1]

Background: Management of immune thrombocytopenia (ITP) has become increasingly challenging during the COVID-19 pandemic. Immunosuppressive treatments used to treat ITP can increase the susceptibility of patients to develop COVID-19. Additionally, therapies which increase the risk of thrombosis may not be optimal due to the hypercoagulable state also observed in patients with COVID-19 infection. The need to minimize office visits, to limit potential exposure to the virus, renders therapies requiring intravenous administration or injections as well as treatments requiring frequent titration less suitable. Consequently, ITP management requires careful patient-centric consideration during the pandemic.
Aims: To evaluate fostamatinib as an ITP treatment during the COVID-19 era
Methods: Review of the safety data from the phase 3 studies for fostamatinib in ITP as well as titration and mode of administration.
Results: Patients (n=146) in the trials had a median age of 53 years (range 20-88), a median of 5 prior ITP treatments, and 229 years of fostamatinib exposure. An increase in platelet count ≥50,000/μL was observed in 54% of patients on fostamatinib treatment. These patients maintained their response to treatment for 86% of treatment days. In the placebo-controlled phase, there was a 2.4-fold difference in duration of exposure to fostamatinib vs. placebo (29 vs. 12 patient-exposure years, respectively). Consequently, the incidence of infections with fostamatinib was somewhat higher than with placebo (27% vs. 21%). The incidence of overall adverse events was similarly higher with fostamatinib vs placebo (83% vs 75%). No patients had opportunistic infections.
Office visits can be minimized due to oral administration of fostamatinib and simplified titration. Fostamatinib dosing is initiated at 100mg BID in patients and increased to 150mg BID after 4 weeks if needed. Titration visits are also minimized due to the low incidence of thrombocytosis (1.4% over 5 years).
ITP patients have an increased risk of thrombotic events, which may be due to SYK-dependent platelet activation in patients with ITP.[2] In the randomized fostamatinib studies, 87% of patients had at least one risk factor for thrombosis, and 58% had multiple risk factors. Over the 62-month study, one (0.7%) thrombotic event was reported: a patient with pre-existing atherosclerosis had a mild transient ischemic attack, which resolved spontaneously. This rate is lower than seen in long-term ITP clinical trials (2-8 years duration), which ranged from 2.6% to 8.9%.
Summary/Conclusion: Fostamatinib is an immunomodulatory treatment that elevates platelet counts and may lower the risk of thrombosis in ITP. There is also a reduced need for office visits due to oral administration, simplified titration, and infrequency of thrombocytosis. Fostamatinib is an appropriate therapeutic option for the treatment of ITP in the COVID-19 era.
1. Zhu Y, et al. Toxicol Appl Pharmacol. 2007;**221**(3):268-77
2. Manne BK, et al. J Biol Chem. 2015; 290: 11557-11568

EP1131 APPLICATION OF HIGH-THROUGHPUT SEQUENCING TO IDENTIFY COPY NUMBER VARIATIONS IN INHERITED PLATELET DISORDERS

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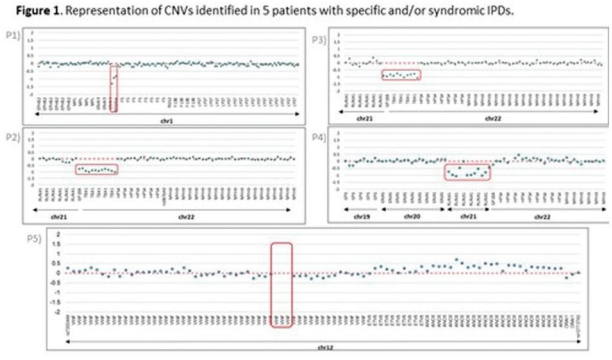
Background: Inherited platelet disorders (IPD) are a heterogeneous group of rare diseases, whose functional and molecular diagnosis has traditionally been complex. Although, high-throughput sequencing (HTS) has allowed us to increase the number of patients with an accurate genetic diagnosis, there are many specific and/or syndromic IPD patients with unknown underlying molecular variations. So, it is probably challenging by the limitation to identify large and complex deletions or amplifications of DNA segments between 50bp and 1kb, called Copy Number Variations (CNV). Comparative Genetic Hybridization array (aCGH) or Multiplex Ligation-dependent Probe Amplification (MLPA) has become the gold standard for constitutional genetic diagnosis of CNV and big structural chromosomal variants, translocations and aneuploidy. The application of HTS to detect CNV is being studied in IPD.
Aims: To identify CNVs using a custom HTS panel in patients with specific and/or syndromic IPDs.
Methods: Custom HTS panel was designed using the SureDesign Studio (Agilent Technologies, Santa Clara, CA, USA) with 57,070 probes, including coding regions for 108 genes with relevance in inherited bleeding disorders, which also allowed to detect CNVs. Regions of interest were enriched for each library following the SureSelectQXT-Target-Enrichment protocol (Agilent), and finally were sequenced on an Illumina NextSeq platform, with a read length of 2x150 nucleotides. Data were processed using an in-house pipeline. CNV analysis were made using depth-of-coverage method, which assumes a linear correlation between the coverage depth and the number of copies. Lower reading depth than expected represented losses or deletions, while higher depth represented gains or amplifications.
Results: CNVs were detected in 5 patients whose, clinical and laboratory phenotypes were included in Table 1. For CNV analysis an average of $1{,}8x10^6$ reads per sample was obtained with a minimum mean coverage of 300X that allowed detecting deletions in the following genes: *RBM8A, GP1BB, TBX1, RUNX1 and VWF*. In patient 1 (P1), thrombocytopenia-absent radius syndrome was previously diagnosed and HTS allowed us to identify a low frequency SNP which affects the 5'UTR region of RBM8A (c.-21 G>A; rs139428292) and a deletion on chromosome 1q. The latter was validated with aCGH showing a microdeletion at chromosome band 1q21.1. In P2, Di George syndrome (DGS) was diagnosed and deletion of *GP1BB* and *TBX1* confirmed a del22q. Additionally, in P3, a syndromic thrombocytopenia (table 1) was suspected and a deletion of *GP1BB* and *TBX1* was detected related to incomplete DGS. In these 2 patients, deletions were validated with MLPA and aCGH, respectively. A deletion on chromosome 21q which involved *RUNX1* was identified in P4 with syndromic thrombocytopenia. Finally, a homozygous deletion of 3 exons (14-16) of *VWF*, was detected in P5 (von Willebrand disease type 3) (Figure 1).

Table 1. Clinical and biological phenotype of patients with IPD in whom CNVs have been analyzed.

Case	Age / gender / BS	Clinical symptoms	Laboratory phenotype	Suspected / final IPD	CNVs
1	45 y, female / 2; heavy menstrual bleeding	Bicuspid aortic valve and cow's milk intolerance, bilateral radioulnar agenesis, hip dysplasia, other skeletal and facial malformations	P=84x10³/mm³ MPV=13,8 fl. BF: large platelets	Thrombocytopenia with absent radius syndrome	*RBM8A* deletion, del1q, and SNP which affects 5'UTR region
2	13 y, male / 0	Hypertelorism, prognathism, dental mal-occlusion, short stature, psychomotor retardation, bicuspid aortic valve, umbilical hernia	P=135x10³/mm³ VPM=13.7 fl. BF: large platelets	DiGeorge syndrome	*GP1BB* and *TBX1* deletion, del22q
3	14 y, male / 0	Hypertelorism, short stature, learning difficulties, hearing loss, infections, situs solitus	P=79x10³/mm³ MPV=12.8 fl. BF: large platelets	Syndromic thrombocytopenia / incomplete DGS	*GP1BB* and *TBX1* deletion, del22q
4	1 y, male / 2; epistaxis and ecchymosis	Bilateral sensorineural deafness, corpus callosum hypoplasia, cardiac and facial malformations	P=35x10³/mm³ MPV=8 fl. BF: dysmorphic cells	Syndromic thrombocytopenia	*RUNX1* deletion del21q
5	5 y, male / 9	Consanguinity, epistaxis, ecchimosis, bleeding after dental extraction, hemartroses	Normal platelet count Severely reduced VWF:Rco and Ag	VWD type 3	Homozygous deletion *VWF* (exons 14-16)

Abbreviations: P: platelet counts; MPV: mean platelet volume; BF: blood film; DGS: DiGeorge syndrome; VWD: von Willebrand disease ; BS: bleeding score according to ISTH-BAT.

Figure 1. Representation of CNVs identified in 5 patients with specific and/or syndromic IPDs.



Summary/Conclusion: Our custom HTS panel has allowed us not only identify single-nucleotide variants but also CNVs. CNV analysis is particularly useful in IPDs patients with specific phenotype with unknow underlying genetic variants and/or a syndromic thrombocytopenias.

EP1132 CLINICAL APPLICATION OF GENETIC TESTING IN PATIENTS WITH NOT ACQUIRED THROMBOCYTOPENIA: ONE CENTER EXPERIENCE

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Background: Misdiagnosed thrombocytopenia, mainly autoimmune forms, could lead to inadequate treatments with eventual development of side effects. Recently, the knowledge about inherited thrombocytopenia has expanded offering a new field of research and a new diagnostic, prognostic and therapeutic approach for these patients.
Aims: To evaluate the applicability and utility of a next generation sequencing (NGS) based gene panel in the diagnostic of suspected inherited thrombocytopenia in the clinical practice.
Methods: This prospective descriptive study included patients with a previous diagnosis of not specified thrombocytopenia who fulfilled inclusion criteria: not acquired thrombocytopenia (no previous normal range platelets count) and not known secondary causes of thrombocytopenia. A family history of thrombocytopenia and lack of response to immunosuppressive treatment were also recorded.
All participants underwent a complete medical and family history, a physical examination and several laboratory tests including a complete blood count, blood chemistry and a peripheral blood smear. A total of 200 platelets were evaluated in every blood smear and platelet size, granulation and vacuolization were described. Platelets larger than half a red blood cell were considered large forms. Bone marrow was recorded if it was previously studied. The NGS gene panel was performed to all the patients. Data are presented as medians, maximum, minimum and percentages. Informed consents were required for all patients.
Results: Thirty patients were included in the study. They were 51 (22-86) year old by median and showed a median platelet count of 76000/µl (10000 to 120000) and a median platelet volume of 11.7fl (8.3-13.9) at the time of the inclusion. Almost half of subjects (47%) had family history of thrombocytopenia and only 1 patients (3%) had family history of hematologic malignancy: one brother with an unknown type of acute leukaemia. None of the patients presented known syndromic disorder. Nine patients (30%) referred previous haemorrhagic complications, in most cases with mild symptoms. Ten (33%) participants received previous treatment for immune thrombocytopenia without response. Six (20%), 3 (10%) and 5 (17%) of the peripheral blood smear samples showed large, hypogranular and vacuolated platelets respectively. The NGS panel proved that 12 out of the 30 patients (40%) presented some genetic mutation related to inherited thrombocytopenia (see table 1). In total, 15 gene alterations were identified. It is remarkable that all the patients who showed large platelets in blood smear matched with some type of gene mutation.

Patients (n = 30)	
Age, years	51 (22-86)
Sex (number, %)	
- Male	13 (43%)
- Female	17 (57%)
Family background (number, %)	
Thrombocytopenia	14 (47%)
Hematologic malignancy	1 (3%)
Haemorrhagic symptoms (number, %)	9 (30%)
Platelet count (platelet/µL)	76000 (10000-126000)
Platelet volume (fl)	11,7 (8,3-13,9)
Previous treatment (number, %)	
- Yes	10 (33%)
- No	20 (67%)
Type of treatment (number, %)	10 (33%)
Glucocorticoids	20 (67%)
Intravenous Immunoglobulins	5 (17%)
Splenectomy	0 (0%)
Rituximab	3 (10%)
Thrombopoietin analogs	1 (3%)
Others	3 (10%)
Peripheral blood smear (number, %)	
- Large/giant platelets	6 (20%)
- Hypogranular platelets	3 (10%)
- Vacuolated platelets	5 (17%)
Patients with NGS gene mutation (number, %)	12 (40%)
Gene alterations (number, %)	15
- ITGA2B/ITGB3	4 (27%)
- RUNX1	2 (13%)
- MYH9	2 (13%)
- GFI1B	2 (13%)
- NBEAL2	2 (13%)
- GP1BA	1 (7%)
- TUBB1	1 (7%)
- ADAMST13	1 (7%)

Summary/Conclusion: In this one center experience, the application of a NGS based gene panel allowed to diagnose a considerable amount of patients with suspected inherited thrombocytopenia. Identifying these patients is important to avoid useless treatments (up 33% in our series) and to recognize some forms that can develop secondary diseases requiring follow-up in clinical practice.

EP1133 COGNITIVE IMPAIRMENT IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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Background: Immune thrombocytopenia (ITP) is an autoimmune condition characterised by a low platelet count (<100 x 10^9/L). Patients with ITP have an increased risk of bruising and bleeding. However, a few studies have shown that they also suffer from other symptoms (e.g. memory and concentration problems) that are not related to bleeding, suggesting that ITP patients might suffer from cognitive impairment.
Aims: The study hypothesis was that patients with ITP suffer from cognitive impairment. The aims were to establish what cognitive domains are impaired and what the prevalence of cognitive impairment in this population is. The secondary objective was to investigate the link between ITP disease parameters and cognitive impairment.
Methods: Seventy patients with ITP and a nadir platelet count ≤ 30 x 10^9/L were recruited to the study and were then invited to Hammersmith Hospital, London, for the following procedures: cognitive testing using an automated neuropsychological test battery (CANTAB), completion of SMOG bleeding questionnaire and full blood count. CANTAB is a validated automated software used in clinical practice and research to assess cognitive impairment. Five key cognitive domains (episodic memory, executive function, processing speed, working memory and attention) were assessed using different CANTAB tasks. The scores for each test were automatically processed by the software, and z-scores standardized for age, sex and education level were generated. Based on the z-scores, the patients' cognitive performance was categorised as impaired or not impaired. The patients' clinical metadata (including date of diagnosis, lowest platelet count recorded during the course of the disease, number of types of ITP treatments received and co-morbidities) was collected from paper and electronic medical records.
Results: The summary of the patients' demographics and clinical characteristics is presented in Table 1.

Table 1. Demographics and clinical characteristics of the population studied

	Median (range)
Age at the time of cognitive test, years	40 (19, 88)
Age at the time of ITP diagnosis, years	40 (4, 83)
Female, n (%)	46 (65.7)
Duration of disease, months	67.5 (1, 535)
Nadir platelet count, x 10^9/L	5 (0, 30)
Number of types of ITP treatments received during the course of the disease	4 (0, 14)
Platelet count at the time of test, x 10^9/L	93 (4, 653)
Patients receiving ITP treatment at the time of cognitive test, n (%)	36 (51)
Patients with co-morbidities, n (%)	46 (65.7)

Of the 70 patients tested, 50% (95 % CI [37.8%, 63.2%]) had at least one impaired cognitive domain: 30% had impairment in one domain, 17% in two domains and 3% in three domains. The frequency of cognitive impairment per domain is illustrated in Figure 1.
Organ bleeding was found to be associated with impaired episodic memory (p = 0.017). No other disease parameters were associated with impaired cognition.

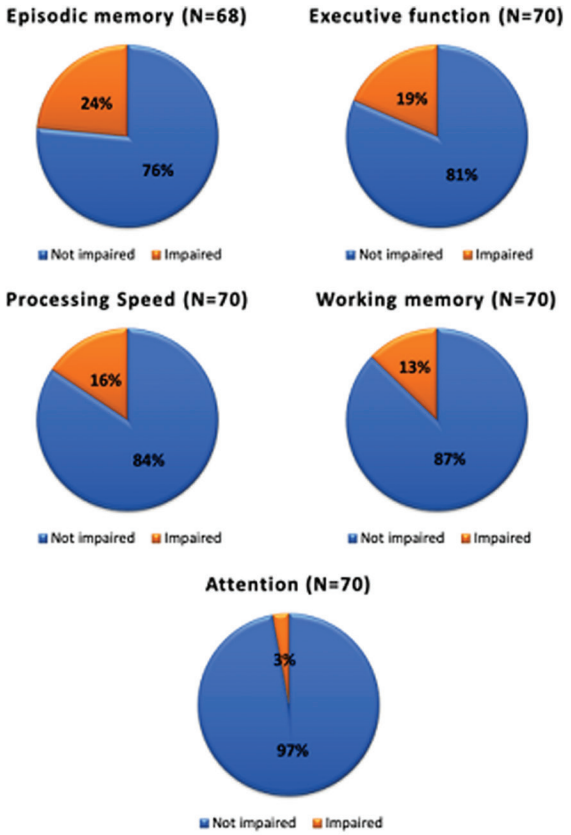


Figure 1. Pie charts showing the percentage of patients with cognitive impairment per domain
Episodic memory 95% CI [14.1, 35.4]; Executive function 95 %CI [10.3,29.7]; Processing speed 95 %CI [8.1, 26.4]; Working memory 95 %CI [6.1, 23]; Attention 95% CI [0.3,9.9].

Summary/Conclusion: Fifty percent of patients with ITP were found to have impaired cognition. Patients with higher organ bleeding scores were more likely to have impaired episodic memory. No other disease parameters, including duration of disease, or platelet count were associated with impaired cognition. These results suggest that ITP is not just a 'low platelet' disease.

EP1134 EFFECTIVENESS AND SAFETY OF ROMIPLOSTIM AMONG PATIENTS WITH NEWLY DIAGNOSED, PERSISTENT AND CHRONIC ITP IN ROUTINE CENTRAL AND EASTERN EUROPEAN CLINICAL PRACTICE: AN ANALYSIS OF THE PLATON STUDY

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Background: Immune thrombocytopenia (ITP) is a rare immune-related condition characterized by low platelet counts and an increased haemorrhagic tendency. Romiplostim is a thrombopoietin receptor agonist (TPO-RA) used to treat ITP. Recent guidelines have recommended the earlier use of TPO-RAs following first-line therapy with corticosteroids, including in patients with ITP <1 year since diagnosis. However, outcomes of romiplostim treatment by ITP duration at initiation in real-world practice are required to strengthen the evidence in this setting.
Aims: We assessed effectiveness and safety of romiplostim within 24 weeks after initiation by duration of ITP: <3 ("newly diagnosed"), 3-12 ("persistent"), and >12 ("chronic") months according to the updated product label. Real-world data collected between December 2010 and July 2017 in five Central and Eastern European countries were analysed.
Methods: This was a post-hoc analysis of the PLATON single arm, observational cohort study of adults receiving ≥1 dose of romiplostim within the indication approved at the time of study conduct (i.e. as second-line therapy after failure of other interventions, or where surgery was contraindicated). The planned observation period was 24 months. Durable platelet response was achieved if ≥75% of platelet count measurements during weeks 14-24 after romiplostim initiation were ≥50 x 10^9/L and no rescue therapy was administered. Overall platelet response was defined as at least one platelet measurement ≥50x10^9/L during weeks 2-24 after romiplostim initiation. Other outcomes included rescue therapy, bleeding, discontinuation of other ITP medications and adverse drug reactions (ADR). Patient and disease history were retrospectively collected at enrolment, prospective follow-up began at the first romiplostim dose and ended at the earliest of 24 months, loss to follow-up, censoring, or death.
Results: Of 100 patients, 22 (22%) were classified as newly diagnosed, 17 (17%) as persistent, and 61 (61%) as chronic at romiplostim initiation. The proportion of patients with splenectomy at initiation was highest in chronic patients (33%). Durable platelet response was achieved in 50% (CI: 28-72%) of newly diagnosed patients, 35% (CI: 14-62%) of patients with persistent ITP, and 31% (CI: 20-44%) of those with chronic ITP. Overall platelet response was achieved in >80% of patients across all strata. More newly diagnosed than persistent or chronic ITP patients discontinued all other concomitant ITP medications. Safety was comparable across ITP strata; the incidence of thrombotic ADRs was low and no occurrences of bone marrow ADRs were reported (Table).

Table. Characteristics of patients initiating romiplostim (2010-2017) and effectiveness and safety endpoints in routine clinical practice

	Duration of ITP		
	<3 months (N=22)	3–12 months (N=17)	>12 months (N=61)
Patient characteristics			
Median (IQR) ITP duration, years	0.1 (0.1, 0.1)	0.5 (0.3, 0.7)	4.7 (2.5, 14.0)
Median (IQR) platelet count, 10^9 cells/L	8 (4, 16)	19 (7, 45)	26 (14, 42)
Prior splenectomy, n (%)	1 (5)	2 (12)	20 (33)
Number of prior ITP therapies[a], n (%)			
0	1 (5)	0	1 (2)
1	9 (41)	5 (29)	18 (30)
2	4 (18)	2 (12)	11 (18)
≥3	8 (36)	10 (59)	31 (51)
Prior bleeding events[b], n (%)	15 (68.2)	7 (41.2)	18 (29.5)
Duration of romiplostim exposure, months			
Mean (SD)	14.13 (10.27)	17.31 (9.26)	17.62 (8.59)
Median (range)	18.60 (0.5, 24.4)	23.92 (0.7, 24.4)	23.69 (0.9, 24.4)
Efficacy outcomes, estimates [95% CI]			
Overall platelet response, %	82 [60, 95]	88 [64, 99]	85 [74, 93]
Durable platelet response, %	50 [28, 72]	35 [14, 62]	31 [20, 44]
KM median time to first platelet response (after day 7)[c], days	27 [15, 86]	15 [15, 57]	22 [15, 22]
Discontinuation of all non-romiplostim ITP treatments, %	32 [14, 55]	18 [4, 43]	16 [8, 28]
Any rescue therapy, %	14 [3, 35]	12 [2, 36]	10 [4, 20]
Specific types of bleeding[d], %	5 [0, 23]	0	3 [0, 11]
Bleeding requiring emergency treatment, %	14 [3, 35]	6 [0, 29]	5 [1, 14]
Incidence of ADR[e] [95% CI]			
Any adverse drug reaction	15.4 [4.2, 39.5]	32.6 [14.1, 64.3]	4.5 [1.2, 11.4]
Thrombotic adverse drug reaction	0	0	1.1 [0.0, 6.2]
Bone marrow fibrosis	0	0	0

CI, confidence interval of percentage; IQR, interquartile range; ITP, immune thrombocytopenia; KM, Kaplan-Meier estimates
[a]Prior medications include those that have ended prior to initiation of romiplostim.
[b]Patients experiencing bleeding events within 6 months prior to romiplostim initiation.
[c]Time to first platelet count ≥ 50 x 10^9/L during weeks 2 through 24 after index date, in the absence of rescue therapy.
[d]Abnormal vaginal bleeding, central nervous system bleeding with neurologic symptoms, hematemesis, haematuria, and/or melena.
[e]Exposure-adjusted incidence of adverse drug reactions per 100 patient years.

Summary/Conclusion: In this real-world study in Central and Eastern Europe, platelet response to romiplostim was consistent between the early (newly diagnosed / persistent) and chronic ITP settings. ADRs were infrequent and similar across strata of ITP duration. These findings support the utilisation of romiplostim in patients with newly diagnosed and persistent ITP in accordance with recent guidelines and according to the romiplostim label extension for these patients.

EP1135 UNUSUAL LABORATORY FEATURES AND CLINICAL COURSE OF HEPARIN INDUCED THROMBOCYTOPENIA IN CARDIOPULMONARY PATIENTS.

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Background: Heparin induced thrombocytopenia (HIT) is characterised by a rapid fall in the platelet count normally 5-10 days after starting

heparin therapy with or without thromboembolic complications and commonly seen in the cardiac population. For laboratory diagnosis of HIT antibodies, both antigen assays and platelet activation (functional) assays are available. Both tests are very sensitive (high negative predictive value) but specificity is problematic, especially for the antigen assays, which also detect non-pathogenic immunoglobulins. Functional tests including the Serotonin release assay (SRA) and heparin induced platelet activation (HIPA) are more specific but only available in specialised laboratories.
Aims: 1. To assess the laboratory diagnosis for detecting anti-PF4/heparin antibodies and assays in cardiopulmonary bypass (CPB) cardio thoracic intensive care unit (ICU) patients. **2**.To evaluates the positive and negative predictive value of various HIT laboratory tests and assess any correlation between HIT, the underlying diagnosis, underlying procedure, valve replacement and cardiac devices.
Methods: This is a retrospective 1-year study in CPB patients from a single cardiothoracic ICU centre. The '4 T's' (*T*hrombocytopenia, *T*iming of platelet count fall, *T*hrombosis and exclude other causes for *T*hrombocytopenia,) was used for the clinical diagnosis of HIT. Two laboratory diagnostic tests were performed, the pan specific screening test which includes pan specific antibodies IgG, IgA and IgM, followed by confirmatory HIT specific IgG ELISA. Functional assays, the SRA and HIPA were not available in our laboratories. Clinical details were obtained from ICU-ICCA[7*] system.
Results: Total N=80 patients (F:23, M:57) had HIT probability "4 T" score >4. Total N=38 patients (48%) were HiT screen pan specific IgGAM negative and n=40 (50%) were HIT pan specific positive. Only n=14 patients (17%) were panspecific and HIT IgG ELISA positive and 2 cases were inconclusive. All HIT positive acute patients received Argatroban except one who received Fondaparinux. There were 5 unusual cases. One patient had Eosinophilic myocarditis and was HIT ELISA IgG neg but the 4-T score was >6 and patient received Argatroban and responded with platelet recovery and no further thrombosis. One patient with Sarcoidosis had aggressive course and received IV IG but succumbed secondary to bleeding. One patient progressed to gut ischemia and had surgical intervention but perished. Two patients with mechanical valves were on Argatroban/Warfarin but relapsed during ICU stepdown stage and received and responded to IV immunoglobulin. It is observed that 9/16 (>50%) HIT+patients had valve replacement or cardiac devices.

Table 1. Details of Cardiothoracic diagnosis of HIT-Positive patients

Pt no:	Age/sex	Diagnosis
1	54/M	Cardiomyopathy
2	63/M	t-MVR+AVR
3	67/M	m-MVR/AVR
4	57/M	VAD
6	30/M	VAD
7	53/M	t-MVR
8	67/M	Bilateral lung transplant
9	45/M	m-AVR
9	66/M	Late presentation STEMI, PCI, not suitable for heart transplant/for alternative treatment
10	75/F	Type A aortic dissection, ascending aorta (28mmHaemashield graft) and re-suspension of the Aortic Valve
11	74/M	Aortic+mitral+tricuspid repair and CABG
12	56/M	t-MVR
13	55/M	Sarcoidosis-cardiac transplant
14	56/F	Eosinophilic Myocarditis
15	56/F	Aortic intramural haematoma repair and m-AVR
16	55/M	t-AVR and CABG

1. HIT=Heparin Induced thrombocytopenia/thrombosis (HITT).
2. VAD= ventricular assisted device, MVR=mitral valve replacement.
3. AVR=Aortic valve replacement, t=tissue and m=mechanical.
4. CABG=Coronary artery bypass graft, STEMI=ST elevation myocardial infarction.
5. ECMO= Extracorporeal Membrane Oxygenation.
6. PCI=Percutaneous coronary intervention.
7. *ICCA=IntelliSpace Critical Care and Anaesthesia, Critical care information system.

Summary/Conclusion: 1. 80% of thrombocytopenia in ICU patients was secondary and not HIT related. 2. Pan specific HIT antibody test had positive predictive value of only 35% and Argatroban treatment based on pan specific antibody positivity may be uncertain and may lead to complications. 3.The autoimmune diseases patients like sarcoidosis and eosinophilic myocardits course varies in pathogenic and non-pathogenic HIT antibody production and clinical severity. The functional assays SRA or HIPA would be more useful in these cases. 4. Patients underlying diagnosis as well as underlying surgical procedures do play a key role in the incidence and severity of HIT and thrombosis 5. It may simply be a selected patients caseload surgery practice or an indication that patients with valve replacement and cardiac devices showed relatively higher HIT incidence and this requires larger studies and further investigations.

EP1136 CAPLACIZUMAB FOR ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: A SINGLE-INSTITUTION EXPERIENCE

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Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is caused by a deficiency in a von Willebrand factor (vWF) cleaving protease called ADAMTS13. Caplacizumab (C) is a monoclonal antibody that targets the A1 domain of vWF preventing platelet adhesion. The clinical trials that lead to the approval of C in aTTP have demonstrated improved outcomes. Experience outside clinical trials has been limited as many centers have never used this agent.
Aims: We report our single institution experience with C since it became commercially available. The aim of this study was to examine the efficacy and toxicity of C in patients with aTTP in standard practice.
Methods: This retrospective study included all patients admitted at our institution that were diagnosed with aTTP and received C since its approval. We used the following definitions through our data collection and analysis. Response: platelet count (PC) more than 150,000/uL and LDH less than 2 times the upper limit of normal (ULN). Exacerbation: aTTP event occurring within 30 days after end of plasma exchange (PLEX). Complete Response (CR): response without exacerbation. Relapse: aTTP event occurring more than 30 days after the end of PLEX. Day 1 was the first day of PLEX.
Results: Patient characteristics: Ten patients with aTTP received C at our institution in 2019-2020. The median age of diagnosis was 52 years. Five (50%) patients were white, 3 (30%) were African American and 2 (20%) were Hispanic. Nobody had fever. Five (50%) subjects had neurologic symptoms (weakness, numbness, and altered mental status). Six (60%) patients had refractory aTTP while 4 (40%) had newly diagnosed aTTP at the time of starting C. Prior to receiving PLEX and C, 2 (20%) patients had bleeding events, one in the form of hematuria and another with severe anemia with a drop in hemoglobin of 2.0 g/dL in 24 hours requiring blood transfusion post thoracic aortic aneurysm repair. Two (20%) patients had a thrombotic stroke. Median (range) laboratory values prior to PLEX and C demonstrated: PC 29/uL (9-61), LDH 518 U/L (182-1850), ADAMTS13 activity 3.0% (3.0-82.0) and ADAMTS13 inhibitor 1.4 BU (0.5-32.0).
Treatments: All subjects received glucocorticoids, rituximab, PLEX and C. The median number of PLEX was 12 (1-33) days. C was started at a median of 5 (2-34) days after the start of PLEX and continued for median treatment duration of 33 (8-108) days with 3 patients still on C. Two patients received vincristine.
Efficacy: Time to normalized PC, LDH and ADAMTS13 activity in days were 5 (3-50), 3.5 (0-146), and 32.5 (0-89), respectively. The median event free survival from the start of PLEX was 75.5 (16-576) days. Six (60%) patients achieved CR, 3 (30%) had refractory disease and 1 (10%) had relapsed aTTP. No one had a major bleeding or major thrombotic event while taking C and no one died. The reason for C discontinuation was normalization of ADAMTS13 in 1 patient and completion of the prescribed course in the rest of our cohort.

Table 1. Labs and Treatment Outcomes

Treatment Response	Patient Cohort (N=10) Median (Range) Count (%)
Baseline Labs before PLEX	
Platelet (/uL) [N=10]	29.0 (9.0-61.0)
LDH (U/L) [N=9]	518 (182-1850)
AST (U/L) [N=9]	26 (3-111)
ALT (U/L) [N=9]	20 (17-33)
Bilirubin (mg/dL) [N=9]	1.8 (0.70-4.0)
Creatinine (mg/dL) [N=10]	1.0 (0.70-2.5)
ADAMTS13 Inhibitor (IU) [N=7]	1.40 (0.50-32.0)
ADAMTS13 Activity (%) [N=9]	3.0(3.0-82.0)
Baseline Labs before Caplacizumab	
Platelet (/uL) [N=10]	95.5 (7.0-314.0)
LDH (U/L) [N=9]	255 (182-562)
AST (U/L) [N=9]	20 (11-36)
ALT (U/L) [N=9]	19 (13-49)
Bilirubin (mg/dL) [N=9]	0.70 (0.30-4.70)
Creatinine (mg/dL) [N=10]	0.9 (0.70-2.5)
ADAMTS13 Inhibitor (IU) [N=7]	4.30 (1.90-32.0)
ADAMTS13 Activity (%) [N=9]	3.0 (3.0-82.0)
Complete Remission	6 (60%)
Refractory	3 (30%)
Relapse	1 (10%)
Event Free Survival from Initiation of PLEX in days (N=10)	75.5 (16-578)
Event Free Survival from the End of Caplacizumab in Days (N=5)	433 (9.0-541)
Event Free Survival from the Start of PLEX in Days (N=10)	433 (9-541)
Number of Patients Hospitalized	10 (100%)
Duration of Hospitalization in Days	10.5 (4.0-37.0)
Number of Patients with an ICU Stay	2 (20%)
Duration of ICU Stay in Days	6.5 (3.0-10.0)
Adverse Events while on Caplacizumab	
Thrombotic Event	0 (0%)
Bleeding Event	0 (0%)
Other	0 (0%)
Reason for Drug Discontinuation (N=10)	
Normalization of ADAMTS13	1(10%)
Completion of Prescribed Course	6 (60%)
Patients still on Caplacizumab (N=10)	3 (30%)

Summary/Conclusion: Our study demonstrates that C is safe and effective at treating aTTP. C was associated with a short time to platelet normalization and number of PLEX days. No patient had a major bleeding event. While our population is small due to the rarity of aTTP, our data is important since it was derived from real-world experience and included all unselected patients. Finally, our data is consistent with clinical trial findings reported in the literature.

EP1138 BICYTOPENIA AND PANCYTOPENIA IN NEONATES: PREVALENCE, RISK FACTORS, AND OUTCOME

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Background: Neonatal anemia, neutropenia, and thrombocytopenia are common hematological problems in neonatal intensive care units. In the literature, there are studies evaluating neonatal anemia, thrombocytopenia, and neutropenia; but to date, no study has investigated the prevalance, risk factors, and outcome of neonatal bicytopenia and pancytopenia.
Aims: In our study, we aimed to evaluate the prevalence, risk factors, and outcome of bicytopenia and pancytopenia in neonates.
Methods: A retrospective analysis was conducted on the medical records of 2672 neonates hospitalized at neonatal intensive care unit between January 1, 2015 and January 1, 2019 and those with bicytopenia or pancytopenia were enrolled. Hemoglobin, neutrophil, and platelet counts were obtained from a whole blood EDTA sample taken from newborns for routine medical treatment. A hemoglobin concentration <7 gr/dL was accepted as severe anemia. Platelet count <50,000/mm^3 was accepted as severe thrombocytopenia. An absolute neutrophil count of <500/μL was accepted as severe neutropenia. The study was approved by the local ethics committee.
Results: Bicytopenia or pancytopenia was detected in 103 (3.8%) of 2672 newborns. The prevalence of bicytopenia and pancytopenia was 3.4% and 0.4%, respectively. The most common clinical findings in both pancytopenic and bicytopenic patients were pallor (63.6% and 53%, respectively) and bleeding (45.4% and 35%, respectively). Anemia and thrombocytopenia were found in 69.6% of bicytopenic patients, neutropenia and thrombocytopenia in 25%, and anemia and neutropenia in 5.4%. When prenatal risk factors were investigated, it was observed that bicytopenia and pancytopenia were more common in preterm babies compared to term babies (p<0.0001, p=0.02, respectively) and preterm infants with very low birth weight had increased risk for development of bicytopenia and pancytopenia (p=0.008, p=0.046, respectively). Asphytic delivery and gestational hypertension were found to be significant risk factors for development of bicytopenia (p<0.0001, p<0.0001). Sepsis (42.2%) and congenital heart anomaly (21.5%) were the two most common underlying diseases in neonates with bicytopenia; sepsis was also found to be the most common underlying disease in neonates with pancytopenia. Mean postnatal age of detection of bicytopenia was 8±7.3 days, nadir was 9±7.6 days, and resolving day was 5±4.6 days. Mean postnatal age of detection of pancytopenia was 7±6.4 days, nadir was 9±7.2 days, and resolving day was 7±6.4 days. Blood product transfusion was given to 76% of bicytopenic patients and 100% of pancytopenic patients. Bicytopenia or pancytopenia recurred in 4.9% of the patients within the first month. Among newborns with bicytopenia or pancytopenia, 4.8% had severe anemia and 32% had severe thrombocytopenia. The presence of severe anemia, severe thrombocytopenia, and the need for mechanical ventilation were found to be poor prognostic factors leading to a prolonged recovery period. Death occurred in 15.2% of bicytopenic patients and 27.3% of pancytopenic patients. Sepsis was the most common cause of death in these patients.
Summary/Conclusion: This study showed that prematurity, asphytic delivery, and gestational hypertension are important prenatal risk factors for development of neonatal bicytopenia and pancytopenia. Sepsis was the most common underlying disease and cause of death in these newborns. Poor outcome due to neonatal bicytopenia and pancytopenia may be improved by eliminating preventable risk factors.

EP1139 IMMUNE THROMBOCYTOPENIA AND COVID-19: A SINGLE CENTRE EXPERIENCE

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Background: Immune thrombocytopenia (ITP) is an acquired autoimmune disorder defined by a platelet count <100×10^9/L without explanation. This laboratory parameter has emerged as an important complication and have been shown to correlate with severe course in the coronavirus disease (COVID-19) caused by novel coronavirus SARS-CoV-2.
Aims: To analyze the clinical characteristics, diagnostic, blood count parameters, therapeutic strategies and outcomes in patients admitted with COVID-19 infection with acquired ITP.
Methods: An observational, longitudinal, descriptive and retrospective study was performed on all patients who were COVID-19 positive and platelet count < 100×10^9/L admitted to hospital between March 1 2020 and January 31 2021 at our centre. All patients were laboratory confirmed COVID-19 positive with a positive nasopharyngeal swab. Clinical and demographic data were collected for each patient, including age, gender, nadir platelet count, bleeding symptoms, time to recovery from start of treatment and clinical outcomes. Patients with previous hematological pathologies or thrombocytopenia were excluded. Mild COVID-19 disease was defined by presence of fever and cough only. Moderate disease was defined by presence of unilateral pneumonia by radiological evidence and/or clinical worsening. Severe disease was defined by presence of bilateral pneumonia by radiological evidence, admission to intensive care unit (ICU) during admission or met criteria for ARDS. Response to treatment was defined by documentation of platelet doubling or platelet count reaching at least > 30 × 10^9 /L (partial response-PR) or level reached > 100 × 10^9 /L or up to baseline count of that patient (complete response-CR). The results are expressed in percentages for qualitative variables, and in means and interquartilic ranges for continuous variables. The data were included in an Excel database

(Microsoft®) and the IBM SPSS Statistics® 20 program was used for their analysis.
Results: A total of 27 patients were identified, 17 males (62.96%) and 10 females (37.03%). The mean age at the time of the event was 78 years old (interquartile range-IQR-: 28 years). Attending to severity, 15 had severe disease (55.5%), 9 moderate and only 3 patients (11%) had a mild presentation.
The mean time from first COVID-19 manifestations to first ITP expression was 5 days (0–23). and in most of our patients was an incidental finding, presenting only 22% haemorragic clinic associated.
The majority of patients in our study did not receive a specific treatment for suspected ITP (e.g. only 6 were treated with intravenous immunoglobulins which were needed due to bleeding). But most patients were already treated with low doses of steroids as part of their treatment for COVID-19. The response rate was about 63% (PR and CR), with a mean of response of six days (IQR of 6.5 days).
Patients with severe disease and those who died at the end of the study, had lower platelet count than survivors and patients with moderate disease. However, our differences were not statisticaly significant.

			Average (%)
N		27	100
Gender	Male	17	63
	Female	10	37
Defeated		11	40.7
Severity	Sever	15	55.5
	Moderate	9	33.3
	Mild	3	11.11
Response	Complete response	12	44.4
	Partial response	5	18.6
	No response	10	37
Haemorrage		6	22.2

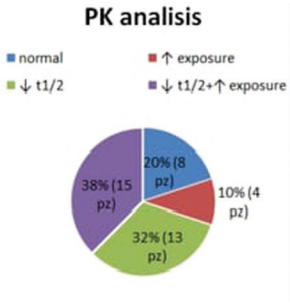
Summary/Conclusion: In our study, ITP was more frequent in severe COVID-19, with lower nadir platelet count, as described in literature. Bleeding events were infrequent. Glucocorticoids were used as a treatment for COVID-19 disease, only used in few patients as ITP specific treatment. The results should be confirmed with prospective randomized controlled studies.

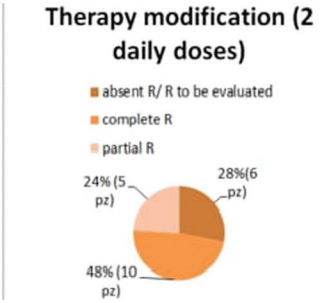
EP1140 PHARMACOKINETIC EVALUATION OF ELTROMBOPAG IN A COHORT OF PEDIATRIC PATIENTS WITH IMMUNE THROMBOCYTOPENIC PURPURA

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Background: Immune thrombocytopenic purpura (ITP) is an immune mediated acquired disorder characterized by decreased platelet count and increased risk of bleeding. The disease is classified into 3 categories according to the time from diagnosis: newly-diagnosed (within 3 months of onset), persistent (between 3 and 12 months), chronic (beyond 12 months). Eltrombopag (EPAG) is an orally TPO-RA (Thrombopoietin-Receptor Agonist), approved for patients with pediatric chronic ITP older than 1 year, refractory to first line therapy. In two Randomized Controlled Trials conducted in pediatric age, EPAG led to an improvement of platelet counts and a reduction in bleeding severity. In addition, in some studies conducted on adults with newly-diagnosed ITP the use off-label of EPAG has also shown good results. However, there is still a significant proportion (about 20%) of pediatric patients who do not show a response to EPAG. Scarce data are currently available regarding the pharmacokinetics of EPAG in children: the estimated median plasma EPAG time to maximum plasma concentration (Tmax) and geometric mean plasma EPAG half-life (t1/2) values are consistent with the adult values, respectively 4 hours and 47-51 hours. The area under plasma concentration-time curve over a dosing interval at steady-state (AUC(0-t)) and maximum plasma concentration (Cmax) values were similar between adolescents and adults while children have higher dose normalized AUC(0-t) and Cmax.
Aims: Explore potential variability of EPAG pharmacokinetic in a cohort of pediatric patients affected by refractory ITP with no or variable response to EPAG or who experienced significant side effects.
Methods: Subjects aged 0 to 18 years were enrolled for pharmacokinetic assessment. Blood samples were obtained at 0, 2, 4 and 8 hours after the administration. Patients had started EPAG at least since 2 weeks. Analysis of EPAG plasma concentration was performed by mass spectrometry coupled with UHPLC (Ultra High Performance Liquid Chromatography) platform.
Results: We performed 40 PK analysis (24 Females, 16 Males). Patients who started therapy at different stages of the disease were considered (16 newly diagnosed, 12 persistent, 12 chronic). The median dose of EPAG given once daily was 50 mg, ranging from 12.5 mg (n subjects=3) to 150 mg (n subject=1). Overall, EPAG peak (Tmax) occured between 2 and 4 hours with a population Cmax of 50 ug/mL and t1/2 of 25 hours. Our cohort of patients therefore showed a Tmax consistent with the literature values, on the other hand, t1/2 appeared to be reduced when compared to known data. Moreover, 32% (13 patients) of our population had an extremely short half-life with values below 12 hours. With regard to exposure, 47.5% of patients (19 patients) have higher Cmax and AUC(0-t) values compared to literature. Based on these results, we tried to change the time of administration of EPAG in about 21 patients, who had shortened t1/2 and/or increased exposure, dividing the daily dose into 2 administrations. 15 patients showed a response, 10 showed a complete response (PLTs >100.000), 5 a partial response (PLTs 30.000-100.000), although 2 patients did not maintain the response in the follow-up and 1 had a fluctuating response.





Summary/Conclusion: These data highlight the need to further explore variability of EPAG exposure and its pharmacokinetic/pharmacodynamic profile in the pediatric population. Our results also suggest the possibility of improving the response to EPAG by modifying the administration although further studies are needed.

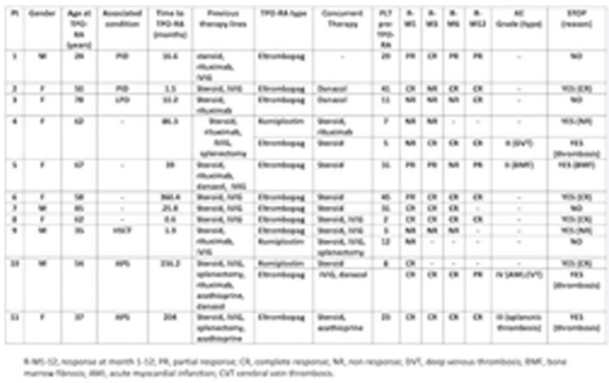
EP1141 EFFICACY OF THROMBOPOIETIN RECEPTOR AGONISTS IN EVANS SYNDROME: A SINGLE CENTER SERIES

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Background: Evans syndrome (ES) is a rare condition, defined as the presence of two autoimmune cytopenias (AIC), more frequently autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), and rarely autoimmune neutropenia (AIN). ES can be classified as primary or secondary to various conditions, including lymphoproliferative disease (LPD), primary immune deficiencies (PID) or other systemic autoimmune diseases (AID). ES onset may be acute and life-threatening, whilst its clinical course is usually chronic and marked by several relapses of AIHA, ITP or both. First line therapy is based on steroids +/- intravenous immunoglobulins (IVIG), followed by rituximab and splenectomy in refractory/relapsing cases. Concerning ITP, splenectomy is not always feasible, and rituximab is poorly effective on the long term. Thrombopoietin receptors agonists (TPO-RA), such as romiplostim

(ROMI) and eltrombopag (EPAG), are highly effective in primary ITP, whilst their use in ES has never been systematically studied.
Aims: to evaluate the efficacy and safety of TPO-RA in a cohort of patients with ES.
Methods: ES patients treated with TPO-RA out of a cohort of 46 cases followed at a tertiary hematologic hospital were retrospectively evaluated. Baseline hematologic parameters, associated conditions, previous/concomitant treatments were assessed. The time from diagnosis to first TPO-RA was collected. Response rates were evaluated at 1, 3, 6, and 12 months, and classified as partial (PR) or complete (CR), for platelets >30x10^9/L or >100x10^9/L, respectively. Treatment emergent adverse events (TEAEs) were registered and graded according to CTCAE.
Results: As shown in Table 1, 11 patients have been evaluated: 4 males and 6 females, with a median age at the start of TPO-RA of 55.6 years (24-85). Six patients suffered from secondary ES: 2 PID, 2 antiphospholipid syndrome (APS), 1 post allogenic stem cells transplant (SCT), and 1 LPD. All patients had received steroids +/- IVIG, and the majority at least one further line including rituximab (N=6), splenectomy (N=3), azathioprine (N=2), and danazol (N=1). The median time from diagnosis to TPO-RA was 25.8 months (0.6-360.4). Response rates to the first TPO-RA (9 EPAG and 2 ROMI) were: 72% at month 1 (45% CR, 27% PR, N=11), 60% at month 3 (50% CR, 10% PR, N=10); 66% at month 6 (55% CR 11% PR, N=9); 100% at 12 months (71% CR, 28% PR, N=7). Of note, 91% of patients required concomitant therapies, including steroids +/- IVIG (N=10), danazol (N=3), rituximab, splenectomy and azathioprine (N=1 each). Interestingly, 3 patients switched to the alternative TPO-RA (2 ROMI to EPAG and 1 vice versa) mainly because of no response (NR); two out of 3 responded. Four out of 11 (36%) patients developed at least one TEAE: 3 venous thromboses (1 deep venous thrombosis, 1 cerebral vein thrombosis CVT, and 1 splanchnic thrombosis) and 1 acute myocardial infarction (in the same APS patient experiencing CVT). Four patients are still receiving TPO-RA, whilst the other stopped because of persistent CR (N=3), thrombosis (N=3), or increase in bone marrow reticulin fibrosis (N=1).



Summary/Conclusion: TPO-RA were effective in about 70% of ES patients, even heavily pre-treated, but required a concomitant therapy in the majority of them. Moreover, TPO-RA use was complicated by a high occurrence of thrombotic events that may be also favored by underlying conditions. These findings highlight that ES is sustained by a profound immune dysregulation where autoimmune platelet destruction cannot be completely overcome by bone marrow stimulation.

EP1142 ELTROMBOPAG PLUS RHTPO VERSUS ELTROMBOPAG FOR ITP DURING THE COVID-19 PANDEMIC (ELABORATE-19)

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Background: Immune thrombocytopenia (ITP) is an acquired thrombocytopenia caused by immune-mediated platelet destruction and impaired platelet production. Recombinant human thrombopoietin (rhTPO) and Eltrombopag, a small molecule agonist of thrombopoietin receptor (TPO-RA), are both recommended as the subsequent treatment for ITP patients, which also already showed robust efficacy. They increase the number of platelets through different mechanisms, and previous studies demonstrated that they might exert synergic effect. During the COVID-19 pandemic, the classical subsequent treatment regimen for ITP of immunosuppressants and/or steroids might increase patients' susceptibility of virus infections. The investigators hypothesized that the combination of these two agents could be a promising option for ITP treatment during the COVID-19 pandemic. To minimize ITP patients' risk during the COVID-19 global crisis and to improve treatment efficacy, this treatment regimen of Eltrombopag plus rhTPO should be investigated. This trial is registered with ClinicalTrials.gov, number NCT01667263.
Aims: This study aimed to evaluate the sustained responses at 6 months and safety of Eltrombopag plus rhTPO as treatment for corticosteroid-resistant or relapsed ITP patients during the COVID-19 pandemic.
Methods: In this open-label, randomized, phase 2 trial, we enrolled confirmed corticosteroid-resistant or relapsed adult ITP patients from 5 different tertiary medical centers in China. They were randomly assigned 1:1 with an interactive web-based response system to receive either Eltrombopag 25-75 mg oral daily according to platelet response plus rh-TPO 300U/kg subcutaneous injection once daily for 7 consecutive days, followed by a tapering dose in maintenance therapy or Eltrombopag monotherapy for 12 weeks (Figure 1). The primary endpoint was 6-month sustained response (SR) defined as platelet counts maintained > 30×10^9/L and at least a doubling of baseline platelet count. Key secondary endpoints were initial response by day 14, duration of response (DOR), TTR, bleeding scores, and adverse events (AEs).
Results: Between August 2020, and March 2021, 60 patients were randomly allocated into either rh-TPO plus Eltrombopag (n=30) or Eltrombopag monotherapy (n=30). At the 6-month follow-up, the proportion of patients with SR was significantly higher in the rh-TPO plus Eltrombopag group than in the Eltrombopag monotherapy group (66.7% vs 36.7%, p= 0.020). The combination of rh-TPO and Eltrombopag resulted in a higher incidence of initial response by day 14 compared with Eltrombopag monotherapy (76.7% vs 60%, p= 0.165). Throughout the follow-up period, overall DOR was greater in the combination group, estimated by the Kaplan-Meier analysis. Bleeding was more effectively controlled in the rh-TPO plus Eltrombopag arm, with fewer bleeding events and lower bleeding scores. There was no difference between the 2 groups in terms of rescue treatments. All subjects tolerated the treatment well, and no grade 4 adverse events or treatment-related death were reported. No statistically significant differences were observed in the incidence of treatment-related AEs between the two groups.
Summary/Conclusion: Rh-TPO plus Eltrombopag is an effective and safe treatment for corticosteroid-resistant or relapsed ITP patients during the COVID-19 pandemic. (NCT04516837)

EP1143 IMMUNE THROMBOCYTOPENIA ASSOCIATED WITH LYMPHOID MALIGNANCIES: REPORT FROM A FRENCH PROSPECTIVE REGISTER.

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Background: The incidence of immune thrombocytopenia (ITP) is around 3/100,000 person-years. ITP is associated to another disease in 15-20% of the cases, mostly systemic auto-immune diseases, or hematological malignancies. For the latter, the association is principally reported with chronic lymphoid leukemia (CLL), large granular leukemia (LGL) and Hodgkin lymphoma (HL). As data have been derived from cohorts from tertiary centers with a possible selection bias, the accurate incidence rate of lymphoid malignancies (LM)-related ITP remains elusive.
Aims: Determination of the frequency, clinical characteristics and evolution of LM-related ITP based on the prospective data collected in the register of hematological malignancies of Côte d'Or (RHEMCO), a population-based register recording all incident hematological malignancies occurring in a restricted geographical area of 532,886 inhabitants.
Methods: Patients included in RHEMCO between January 1995 and December 2015 (n=3499) were analyzed to calculate incidences. The medical records of ITP patients referred to our tertiary hospital during the same period were also considered for the clinical description and the evolution of LM-related ITP. ITP was defined as a thrombocytopenia

<100 G/L after exclusion of other causes. Response was defined as a platelet count >30 G/L with at least a 2-fold increase of baseline level.
Results: Based on RHEMCO, the frequency of ITP during LM was 1.06% (n=37/3499): 3.46% for T cell lymphoma, 1.21% for CLL, 0.82% for B cell lymphoma and 0.36% for HL. The frequency of Evans' syndrome (ES) was 0.29% (n=10/3499) in the whole cohort: 0.44% during CLL, 0.43% for T cell lymphoma, and 0.24% for B cell lymphoma.
From RHEMCO and medical records, 76 patients with secondary ITP were identified, among which 17 with ES. For ITP, the median age at diagnosis was 69.5 [interquartile range (IQR): 19-94] years and 59% were male. For ES, the median age was 62 [IQR: 29-85] and 76% were male. Among all LM-related ITP, CLL and indolent B cell lymphoma were the most represented (29% each), followed by T cell lymphoma (20%), aggressive B cell lymphoma (18.5%) and HL (3.5%). ES was mostly associated with indolent B cell lymphoma (47%) or CLL (41%), T cell lymphoma or HL representing only 6% each. LM occurred before ITP in 46% of the cases, with a median delay of 3 [IQR: 0.5-18.4] years and in 65% for ES with a delay of 5.1 [IQR: 0.3-10.1] years. LM and ITP were simultaneous (≤ 3 months) in 44% for ITP and 29% for ES. Bleedings were reported in 45% and splenomegaly in 29% of the cases. The median platelet count at diagnosis was 30 [IQR: 1-96] G/L.
All the patients were treated: 84% received specific medications for ITP and 91.5% for LM. Responses to ITP treatments were 63% for steroids and IVIg, 79% for rituximab and 80% for thrombopoietin receptor agonists. After 4.4-year follow-up, ITP was considered in remission in 53%.
Summary/Conclusion: LM-related ITP is a rare condition, with an incidence of 0.073/100,000 person-years for CLL, 0.072/100,000 for B cell lymphoma and 0.059/100,000 for T cell lymphoma. The diagnosis of LM precedes or is concomitant of ITP in most of the cases (90%). Responses rates to usual ITP therapies seem to be lower than in primary ITP, with a remission rate of 50%.

EP1144 A MULTICENTER U.S. STUDY OF AVATROMBOPAG SWITCH THERAPY FOLLOWING PRIOR ELTROMBOPAG OR ROMIPLOSTIM

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Background: Avatrombopag (AVA) is an oral thrombopoietin receptor agonist (TPO-RA) approved for treatment of chronic immune thrombocytopenia (ITP). Data describing effectiveness of AVA following treatment with other TPO-RAs is limited.
Aims: Evaluate ITP treatment outcomes in patients who switched from romiplostim or eltrombopag (ROMI/ELT) to AVA.
Methods: We retrospectively evaluated all adults with ITP switched from ROMI/ELT to AVA at four U.S. tertiary ITP referral centers from July 2019 through December 2020 who were treated with AVA for at least two months by the data cutoff date.
Results: *Patient Characteristics:* 45 patients were included, with a median (range) age of 60 (21-87) years; 53% were female. Mean treatment duration with ROMI/ELT prior to switch was 26.4 months and mean AVA treatment duration was 9 months. At AVA initiation, patients had ITP for a mean of 8.3 years with a mean (range) of 4.8 (2-10) unique prior ITP treatments. The reason for switching to AVA was convenience in 23 patients (51%), ineffectiveness of ROMI/ELT in 14 (31%), and adverse event on ROMI/ELT in 8 (18%). The TPO-RA prior to switch was ROMI in 33 patients (73%), ELT in 11 (24%) and both simultaneously in 1 (2%).
Platelet Outcomes: In all patients, the median platelet count (Plt) on ROMI/ELT was 45×10^9/L vs. 114×10^9/L on AVA ($P<0.0001$); in patients switched for ineffectiveness of ROMI/ELT, it was 28×10^9/L on ROMI/ELT vs. 88×10^9/L on AVA ($P=0.025$), **FIGURE**. On AVA, in the absence of rescue therapy (>8 weeks from rescue corticosteroids or >4 weeks from rescue IVIG), Plt ≥50×10^9/L was achieved by 42/45 patients (93%), including 12/14 (86%) switched due to ineffectiveness of ROMI/ELT; Plt ≥100×10^9/L (complete response) was achieved by 39/45 patients (87%), including 10/14 (71%) switched due to ineffectiveness of ROMI/ELT.
AVA Dosing: The median total weekly AVA dose was 140 mg (20 mg daily) in all patients and 280 mg (40 mg daily) in patients switching due to ROMI/ELT ineffectiveness.
Concomitant Medications/Rescue Therapy: Of the 19 patients who required concomitant corticosteroids while on ROMI/ELT, 12 (63%) were able to discontinue steroids, 6 (32%) reduced steroid dose, and none increased steroid dose after switching to AVA. 15 patients (33%) required rescue in the year prior to switching versus 9 (20%) following the switch; this included 4 patients who had also required rescue on ROMI/ELT and 5 who had not previously required rescue. 11 patients requiring rescue on ROMI/ELT did not require rescue after the switch to AVA.
AVA Discontinuation: 7 patients (16%) discontinued AVA, including 2 patients (4%) for adverse events (headache, portal vein thrombosis), 1 (2%) for lack of response, 1 for patient preference, 1 for achievement of remission, 1 for transition to rituximab to treat concomitant hemolytic anemia (patient with Evans syndrome), and 1 due to lack of the medication on a formulary.

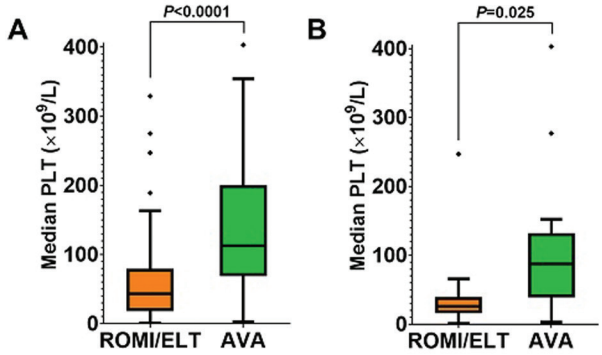


Figure. Median platelet counts for each patient prior to switch (during treatment with romiplostim or eltrombopag) vs. following the switch to avatrombopag. For each patient, the median platelet count is the median of the most recent 3 platelet counts measured while receiving that agent. **(A)** All patients (N=45). **(B)** Patients switched due to ineffectiveness of romiplostim or eltrombopag (N=14). One patient with median Plt 585×10^9/L on avatrombopag omitted from both graphs to preserve graph resolution.

Summary/Conclusion: In a heavily pretreated chronic ITP population, AVA was effective following therapy with ROMI/ELT, with high response rates even in patients with inadequate response to a prior TPO-RA.

EP1145 EPIDEMIOLOGY, TREATMENT PATTERNS, AND CLINICAL OUTCOMES AMONG PATIENTS WITH ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA (ATTP) IN THE UNITED STATES: AN ELECTRONIC HEALTH RECORDS ANALYSIS

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Background: aTTP is an ultra-rare and potentially life-threatening thrombotic microangiopathy (TMA). Owing to the rarity of the disease, data on epidemiology, disease management, and clinical outcomes are scarce and often heterogeneous.
Aims: To assess the epidemiology, disease management, and clinical outcomes in patients with aTTP.
Methods: A longitudinal, retrospective observational study identified patients with an aTTP diagnosis from October 2015 to December 2019 in the Optum-Humedica database. Patients were eligible if they had ≥1 documented ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) test result <10% or ≥1 aTTP episode, defined as having ≥1 inpatient stay with an International Classification of Diseases (ICD) diagnosis of TMA (ICD, Ninth Revision [ICD-9], dx: 446.6; ICD, Tenth Revision [ICD-10], dx: M31.1) and ≥1 therapeutic plasma exchange (TPE) procedure (Current Procedural Terminology-4 code: 36514; ICD-10: 6A551Z3) during the same

inpatient stay. Patients with a diagnosis of hemolytic uremic syndrome, *Escherichia coli* infection, human immunodeficiency virus, organ/stem cell transplant, systemic infection, and malignancy ≤6 months before or at index date were excluded. Index date was defined as the date of the earliest occurrence of an ADAMTS13 test result <10% or first TMA+TPE-related hospitalization during the study period. Index aTTP episode was defined as the first occurrence of TMA+TPE-related hospitalization. Patients were followed from the index date until the loss to follow-up, end of study period, or death, whichever occurred first. Incidence of aTTP, demographic, and clinical characteristics of patients, treatment patterns, and clinical outcomes were descriptively analyzed.

Results: A total of 666 patients met inclusion criteria for aTTP diagnosis. Among these, 302 (45%) patients had ≥1 reported aTTP episode (TMA+TPE-related hospitalization). Patient demographics are summarized in the **Table**. The annual proportion of patients with documented aTTP (ADAMTS13 <10% or an aTTP episode) was 3.43/million, while the annual incidence of ≥1 aTTP episode was 1.81/million (averaged over 2016–2019).

Patients with ≥1 aTTP episode received a mean of 16.7 TPE sessions (standard deviation, 22.3); 86%, 59%, and 7% of patients received corticosteroids, rituximab, and other immunosuppressant treatments, respectively. The therapies received among all patients with aTTP diagnosis are summarized in the **Table**.

Exacerbations (rehospitalizations for TPE within the first 30 days following discharge for any aTTP episode) occurred in 17% (52/302) of patients with ≥1 episode. Relapse (new aTTP episode >30 days after discharge for the index episode) was reported in 11% (34/302) of these patients.

Mortality rate during follow-up among all patients with aTTP diagnosis was 25% (167/666), with 77% (129/167) of deaths occurring within 6 months of the index date. For patients with ≥1 aTTP episode, 14% (41/302) died, with 51% (21/41) of deaths occurring within 45 days of the index episode. Among all patients with aTTP diagnosis, 21% (139/666) of patients had ≥1 thromboembolic event (TE); of 193 total TEs reported, the most common were cerebral infarction (CI [55%]) and myocardial infarction (MI [19%]). For patients with ≥1 aTTP episode, 34% (103/302) had ≥1 TE; of the 152 TEs reported, CI (51%) and MI (21%) were the most common (**Table**).

Table. Demographics, treatment patterns, and clinical outcomes of patients with aTTP in the post-index period

	All patients with aTTP diagnosis (n=666)	Patients with ≥1 aTTP episode (n=302)
Demographic characteristics		
Mean (SD) age, years	49.2 (18.7)	46.2 (16.2)
Females, n (%)	421 (63)	219 (73)
Race, n (%)		
Caucasian	380 (57)	150 (50)
African American	214 (32)	116 (38)
Asian	10 (2)	5 (2)
Other or unknown	62 (9)	31 (10)
Mean (SD) BMI, kg/m^2	29.1 (7.0)	30.2 (6.7)
Treatments received		
TPE, n (%)	329 (49)	302 (100)
Mean (SD) number of TPE per patient	15.9 (21.7)	16.7 (22.3)
Corticosteroids, n (%)	406 (61)	260 (86)
Rituximab, n (%)	210 (32)	178 (59)
Other immunosuppressant medications, n (%)	14 (2)	10 (3)
Outcomes		
Exacerbation, n (%)	N/A	52 (17)
Relapse, n (%)	N/A	34 (11)
Number of patients with ≥1 TE event, %	139 (21)	103 (34)
Total number of TEs, %	193	152
TE type, n (%; of total number of TEs)		
Arterial embolism	7 (4)	7 (5)
Cerebral infarction	106 (55)	77 (51)
Deep vein thrombosis	2 (1)	2 (1)
Mesenteric vein embolism	1 (1)	1 (1)
Myocardial infarction	37 (19)	32 (21)
Portal vein obstruction	5 (3)	4 (3)
Pulmonary embolism	15 (8)	12 (8)
Vascular syndromes	20 (10)	17 (11)
Number of deaths (%)	167 (25)	41 (14)
Time of death, n (%; of total number of deaths)		
Within 45 days of index aTTP episode	21 (13)	21 (51)
0–6 months from the index date	129 (77)	29 (71)

aTTP, acquired thrombotic thrombocytopenic purpura; BMI, body mass index; N/A, not applicable; TE, thromboembolic event; TPE, therapeutic plasma exchange.

Summary/Conclusion: Despite treatment with TPE and immunosuppressants, the high mortality and morbidity observed in this patient population demonstrates the need for more effective therapies to improve clinical outcomes.

EP1146 STYDY OF FAS, CASPASE-8 (CASP8) AND -10 (CASP10) POLYMORPHISMS IN CHILDREN AND ADOLESCENTS WITH IMMUNE THROMBOCYTOPENIA

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Background: Immune thrombocytopenia (ITP) is a relatively common acquired bleeding disorder in childhood. ITP is characterized by a low circulating platelet count due to the production of autoantibodies against platelet glycoproteins, followed by their destruction via the reticuloendothelial system. Apoptosis is a physiologic mechanism of programmed cell death, crucial for controlling the cell number during development and for the entire lifespan of an organism. Deregulation of the apoptosis signalling may compromise the homeostasis of an organism and cause a wide range of diseases. Fas is a transmembrane molecule belonging to the tumor necrosis factor (TNF) receptor superfamily. Fas ligation by FasL induces programmed cell death in several lymphoid cell lines and may play a role in immune response control, lymphocyte life span regulation and induction of peripheral tolerance. Caspases are cysteine proteases that play a central role in apoptosis. Caspase-8 and caspase-10 are the first enzymes in the proteolytic cascade that are activated by Fas ligand and TNF. According to the literature, mutations in either CASP8 or CASP10 influence immune surveillance of malignancies and cause lymphoproliferation (ALPS).

Aims: The aim of this study was to identify whether polymorphisms of FAS, CASP8 and CASP10 play a role in the pathophysiology of ITP in children and adolescents.

Methods: In this study 30 children and adolescents with ITP and 60 healthy individuals as control group were included. At first, extraction of the DNA from peripheral blood cells was performed and then analysed by PCR. The PCR was followed by digestion using selected restricted enzymes in order to genotype individuals for the SNPs under study. For the *FAS* (rs2234767) and *CASP8* (rs1045485), the restriction enzyme *BstU*I was applied while for the *CASP10* (rs13006529), the enzyme *Ssp*I. Digestion products were analysed by agarose gel electrophoresis and statistical analysis was performed using the GraphPad Prism (GraphPad Software, San Diego, CA, USA) program.

Results: Statistical analysis of data showed that allele T of *CASP10* rs13006529 SNP was associated with the diagnosis of ITP. However, no association for the studied SNPs of *FAS* and *CASP8* genes was detected.

Summary/Conclusion: Allele T of *CASP10* rs13006529 SNP appeared has a statistically significant difference between patients and controls, thus suggesting its role in the development of ITP. Its effect may be related to the role of caspase 10 in the endogenous pathway of apoptosis as well as its involvement in the process of autophagy. As regards with the *FAS* (rs2234767) and *CASP8* (rs1045485) SNPs no association with ITP was observed. However, these results are considered as early due to the small number of samples examined. Further analysis of a higher number of samples is needed in order to clarify the role of the SNPs under study in children and adolescents with ITP.

EP1147 DARATUMUMAB, AN ORIGINAL APPROACH FOR TREATING REFRACTORY AUTOIMMUNE CYTOPENIA

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Background: Patients with autoimmune cytopenias failing first- or second-line treatments have an increased morbidity and mortality, and therapeutic alternatives are needed. Daratumumab, an anti-CD38 monoclonal antibody developed for multiple myeloma, could target long-lived autoreactive plasma cells.
Aims: The aim of the study was to assess safety and efficacy of daratumumab given for refractory autoimmune cytopenias.
Methods: We conducted an observational, retrospective, multicenter study throughout the network of the French reference center for adult' immune cytopenias including patients receiving compassionate off-label treatment by daratumumab for either refractory immune thrombocytopenia (ITP) or warm autoimmune hemolytic anemia (wAIHA) between 2020 and 2021. Response was assessed according to international criteria. Patients who required any other treatment more than six weeks after first daratumumab infusion were considered non-responders.
Results: Eight patients (5 female) with a median age of 45 years [range 34-70] were included in the study. Treatment by daratumumab was given for ITP (5 patients), wAIHA (2 patients), and acquired Glanzmann thrombastenia complicating ITP (1 patient) with a median disease duration of 84.5 months [range 18-174]. Five patients had underlying Evans syndrome and one patient had ITP secondary to antiphospholipid syndrome. Five patients were splenectomized and all 8 patients failed to respond to rituximab (median time from last infusion of 11 months [3-98]). Patients received a median number of 6 [range 4-11] weekly infusions of daratumumab at 16mg/kg of body weight with dexamethasone premedication.
Median follow up after daratumumab was 6 months [range 3-9]. Three patients had a minor reaction at first daratumumab infusion. Two patients had infectious events during follow up (one bacterial pneumonia and one COVID-19 pneumonia). After exclusion of 2 patients who received regular intravenous immunoglobulin, hypogammaglobulinemia (i.e., gammaglobulins <6g/L) was observed in 5/6 patients. Median concentration of gammaglobulins was 7.1 g/L [4.8-16.2] before treatment, versus 4.2 g/L [3.5-7.6] at 3 months and 6.1g/L [6-15.5] at 9 months.
Five patients were given daratumumab for ITP with low platelet counts (median 11 x10^9/L, [range 0-21]). Two achieved a CR after respectively 3 and 4 infusions, including one of who relapsed after 3 months. Anti-β2GP1 antibodies and lupus anticoagulant disappeared upon treatment in the patient with antiphospholipid syndrome. Another steroid dependent patient required a transient increase in corticosteroid doses one month after daratumumab, but with a definite weaning at 6 months. The remaining 2 patients had no response.
Two patients had wAIHA and a positive IgG DAT (no C3). One patient received 4 daratumumab infusions associated with corticosteroids tapered during 6 weeks, resulting in a CR that lasted 9 months. The other patient had no response. Daratumumab had no clinical efficacy in the patient with an ITP that had acquired Glanzmann thrombastenia with bleeding symptoms despite normal platelet counts.
Summary/Conclusion: Overall, these data suggest that daratumumab may be effective in a subset of patients with autoimmune cytopenia refractory to standard therapy. The response appears transient as some patients with CR eventually relapsed during the follow-up. As most patients experienced transient hypogammaglobulinemia, the risk of infection should be weighted in the therapeutic decision. Prospective studies are needed to confirm these preliminary data.

EP1148 DURABILITY OF PLATELET COUNT RESPONSE IN PATIENTS TREATED WITH AVATROMBOPAG FOR IMMUNE THROMBOCYTOPENIA (ITP): POST-HOC RESULTS FROM THE PHASE 3 CORE AND OPEN-LABEL EXTENSION STUDY

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Background: The clinical management of ITP has been evolving. Thrombopoietin receptor agonists (TPO-RAs) have become widely utilized as second-line treatments, and the 2019 ASH guidelines recommend their use over rituximab to achieve a durable response. Avatrombopag (AVA) is an oral TPO-RA approved in 2019 for patients (Pts) with ITP. A high proportion of Pts (~90%) respond to AVA; but limited information is available regarding the durability of response over time utilizing clinically relevant loss of response (LOR) definitions.
Aims: To understand the time it took Pts to experience their first LOR and the overall percent of treatment days a response level platelet (PC) was achieved.
Methods: A Phase 3 study (NCT01438840) enrolled 32 AVA and 17 placebo-treated (PBO) Pts with ITP. The core study design included a 6-week study drug titration period, 12-week concomitant ITP medication reduction period, and an 8-week maintenance period. Subjects who completed the maintenance phase of the core or discontinued early because of lack of treatment effect were eligible for the Extension Phase. These Pts all received open-label 20 mg AVA once daily and underwent a 6-week conversion period, and a 90-week maintenance period.
For this post-hoc analysis, we assessed how many days it took for Pts randomized to AVA who responded in the Core and continued into the extension to experience their first LOR or reach study conclusion. After the initial PC ≥50,000/μL was noted, we also examined the percentage of remaining treatment time that initial response was maintained.
Response was defined as the first time achieving a PC ≥50,000/μL. LOR was defined as a Pt experiencing a PC <30,000/μL for 4 consecutive weeks (LOR-4wk), or in a more conservative manner, Pts experiencing a PC <30,000/μL on 2 consecutive scheduled visits (LOR-2vis). During the Core, visits were weekly or biweekly depending on the phase of the study with 21 visits occurring over 26 weeks. In the Extension, visits were every 3-4 days, weekly, bi-weekly, or monthly depending on the phase with 31 planned over 96 weeks. The protocol was amended to end the study on 3/10/2014 when the last patient exited the Core Study.
When a LOR was observed, the date of the first PC <30,000/μL was used for subsequent calculations with a return of response defined as a PC exceeding ≥30,000/μL again. Pts who required rescue therapy (n=4) were included in the analyses and the first date of administration was used for the LOR date. Pts requiring corticosteroids (n=3) as rescue therapy were considered non-responders for a minimum of 8 weeks and Pts receiving a platelet transfusion (n=1) for a minimum of 1 week.
Results: 32 Pts were randomized to AVA, 29 responded, and 21 continued into the Extension Phase and were evaluated here.
61.9% (13/21) and 42.9% (9/21) of AVA-responsive Pts never experienced a LOR-4wk or LOR-2vis, respectively. The average number of months until all Pts experienced their first LOR-4wk, discontinued, or completed the study was 8.2 months (median 9.4) and 6.9 months (median 4.8) for the LOR-2vis analysis. Pts maintained their initial response on average for 83.5% (median 100%) of their remaining time in the study for LOR-4wk and for 79.3% (median 100%) in the LOR-2vis analyses (Table 1).

Table 1: Durability of Initial Avatrombopag Response

	Months Patient in Core + Extension From 1st PC ≥ 50	Months Until 1st Loss of Response	% of Time with Response
4 Consecutive Weeks <30 = Loss of Response			
ALL PATIENTS (n=21)			
Mean (SD)	11.2 (2.9)	8.2 (5.0)	83.5% (26.7)
Median (min, max)	10.8 (6.2, 16.8)	9.4 (0.5, 16.8)	100% (11.0, 100)
NO RESCUE ONLY (n=17)			
Mean (SD)	11.2 (2.8)	9.6 (4.5)	90.8% (20.1%)
Median (min, max)	10.8 (6.2, 16.8)	10.4 (0.5, 16.8)	100% (31.4, 100)
RESCUE ONLY (n=4)			
Mean (SD)	11.1 (3.3)	2.2 (1.7)	52.6% (29.0)
Median (min, max)	11.3 (7.1, 14.7)	1.6 (0.5, 5.1)	57.0% (11.0, 85.3)
2 Consecutive Scheduled Visits <30 = Loss of Response			
ALL PATIENTS (n=21)			
Mean (SD)	11.2 (2.9)	6.9 (5.5)	79.3% (27.5)
Median (min, max)	10.8 (6.2, 16.8)	4.8 (0.5, 16.8)	93.6% (11.0, 100)
NO RESCUE ONLY (n=17)			
Mean (SD)	11.2 (2.8)	8.0 (5.5)	86.6% (22.5%)
Median (min, max)	10.8 (6.2, 16.8)	10.4 (0.5, 16.8)	100% (18.6, 100)
RESCUE ONLY (n=4)			
Mean (SD)	11.1 (3.3)	2.0 (1.4)	48.4% (25.1)
Median (min, max)	11.3 (7.1, 14.7)	1.6 (0.5, 4.4)	52.8% (11.0, 76.9)

Summary/Conclusion: These data suggest that the initial response to AVA is durable, with up to 62% of Pts never experiencing a LOR in the core or extension, and stable with Pts maintaining a response on average for up to 84% of the time despite the planned objective of reducing concomitant medications and required AVA starting dose in the extension.

EP1149 SERUM COMPLEMENT LEVELS IN IMMUNE THROMBOCYTOPENIA: RELATION WITH CLINICAL PRESENTATION AND TREATMENT RESPONSE.

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Background: The complement system activation is one of the mechanisms behind platelet destruction in immune thrombocytopenia, but its role in the clinical setting is still limited.
Aims: Characterized C3, C4, and CH50 levels from ITP patients and its relation with the clinical presentation and treatment response.
Methods: A retrospective observational study in a teaching hospital with specific ITP outpatient consults. Complement levels were measured in any moment of the disease course through turbidimetric immunoassays. The relations between complements levels and characteristics of the disease and the response to treatments were evaluated with regression analysis
Results: Forty-three ITP patients with complement C3, C4, CH50 were included. Medium age was 44 years (16.99). In the moment when complement levels were measured 70% of patients were not receiving any treatment. There were 16% of previously splenectomized patients. Medium C3: 103,5 (34-28), medium C4: 14,5 (4-171), with 75% of the patients with levels of C4 below the normal range. Medium CH50 49 (12-95). Not responders to first line treatment had lower C3 levels (p: 0,018). Patients receiving treatment had lower mean C4 (p: 0,039) and lower C3 (p: 0,065). In multivariable analyses patients receiving TPO agonist had lower levels of C3, C4, and CH50 (p: 0,024; 0,019 y 0,054). There were no relation between complement level and severity of bleeding, refractory disease or splenectomy status.
Summary/Conclusion: ITP patients had lower levels of C4, especially those on active treatment. Patients not responders to first line treatments had lower levels of C3. Those on treatment with thrombopoietin receptor agonists had lower levels of C3,C4, y CH50. Further prospective studies are needed to evaluate the role of complement in the current clinical practice and with the emergent complement- directed therapies.

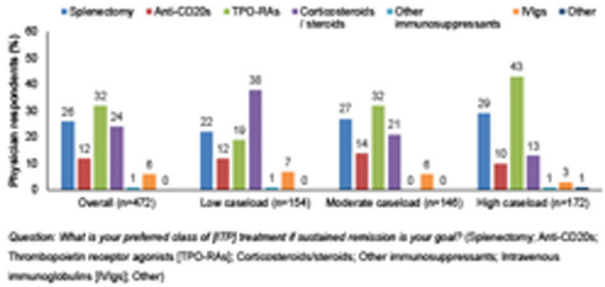
EP1150 GEOGRAPHIC DISTRIBUTION OF PATIENT AND PHYSICIAN ITP TREATMENT PREFERENCES AND EFFECT OF PHYSICIAN CASELOAD ON TREATMENT PRACTICES: RESULTS FROM THE ITP WORLD IMPACT SURVEY (I-WISH)

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Background: American Society of Hematology 2019 guidelines for immune thrombocytopenia (ITP) recommend considering individual patient (pt) preference when selecting second-line therapy in adults with ITP. We previously reported pts' and physicians' (MDs') perspectives on ITP treatments (txs) across all countries included in the ITP World Impact Survey (I-WISh), which examined ITP's burden and impact on quality of life (QoL). A better understanding of the geographic differences in pts' and MDs' tx preferences and the effects of MD caseload may reveal areas in which additional discussion and education might be beneficial.
Aims: Using I-WISh data, define the geographic distribution of pt and MD tx preferences and the effect of MDs' ITP caseload on their tx practices and attitudes.
Methods: I-WISh was an exploratory, cross-sectional 30-minute survey of 1507 pts with ITP and 472 ITP-treating MDs conducted in 13 countries (Dec 2017-Aug 2018). Pts were recruited via MDs and pt advocacy groups (PAGs). A steering group of expert ITP clinicians and PAG leads developed the survey. Pts' and MDs' preferences on tx modalities were evaluated through responses to specific questions. MD caseload was defined as 'low' (≤10 pts currently treated), 'medium' (11-29), or 'high' (≥30). Differences in responses between 'low' and 'high' caseload status were considered meaningful if they differed by >10 percentage points.
Results: Mean pt age was 47 years; 65% were female. MDs had a mean caseload of 34 current pts with ITP; MDs with 'low', 'moderate', and 'high' caseload status had mean caseloads of 7, 19, and 70 current pts with ITP, respectively.
Most pts (90%; n=1360/1507) had a preference for orally administered ITP txs (once [83%] or twice [7%] daily) over an injection; pt preference for oral ITP tx was >85% in countries excluding France (80%), Turkey (77%), and Germany (70%). MDs' (first-choice) preference for orally administered ITP txs (versus subcutaneous [SC] or intravenous [IV] tx) was broadly aligned with that of pts, and was selected by 77% of all MDs (n=365/472).
There were distinct geographical differences in MDs' preferred ITP txs when pursuing a tx goal of 'sustained remission': splenectomy was the preferred tx class in Canada (70%), Colombia (48%), and the USA (36%); corticosteroids (CSs) in China (56%) and India (33%); and thrombopoietin-receptor agonists (TPO-RAs) in Egypt (70%), Turkey (57%), the UK (55%), Spain (48%), Italy (43%), France (41%), Japan (39%), and Germany (27%).
For pts with persistent/chronic/recurrent ITP, MDs' first-choice preference for oral (vs SC or IV) ITP tx appeared to increase with rising caseload ('low', 'moderate', and 'high' caseload: 68%, 77%, and 87%, respectively). As MDs' caseload increased, shifts in the preferred tx class for the goal of 'sustained remission' were also seen; preference for TPO-RAs increased (19%→43%) whereas CSs decreased (38%→13%).TPO-RAs were the overall preferred tx class (Fig. 1).

Figure 1. Physicians' preferred immune thrombocytopenia (ITP) treatment class if 'sustained remission' is the goal (overall and by caseload status)



Question: What is your preferred class of [ITP] treatment if sustained remission is your goal? (Splenectomy; Anti-CD20s; Thrombopoietin receptor agonists [TPO-RAs]; Corticosteroids/steroids; Other immunosuppressants; Intravenous immunoglobulins [IVIgs]; Other)

Summary/Conclusion: Both pts and MDs appeared to demonstrate a preference for oral ITP txs over an injection (SC/IV) option, with some geographic differences in preferences. There were also apparent shifts in MD tx preferences with changes in ITP caseload in approaching sustained clinical remission. An important limitation was question phraseology, which did not include factors such as substantial dietary restrictions for oral medications. Also, country sample sizes varied, and data were collected prior to the COVID-19 pandemic: tx preferences may have changed subsequently. Nonetheless, these findings warrant confirmation.

EP1151 LENGTH OF THROMBOPOIETIN RECEPTOR AGONIST (TPO-RA) TREATMENT AND PERSISTENCE IN IMMUNE THROMBOCYTOPENIA (ITP): REAL WORLD UNITED STATES CLAIMS ANALYSES

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Background: The recent ASH Guidelines[1] and International Consensus Report[2] for the management of ITP suggest consideration of TPO-RAs as subsequent therapy following an insufficient response to first-line treatments, especially if seeking a durable platelet response. Avatrombopag (AVA), a TPO-RA which was FDA approved in 2019, also recently received EMA approval for adults suffering with chronic ITP. AVA is orally-administered, does not have food type restrictions, nor carry a boxed warning for hepatoxicity or requires liver function monitoring.
Aims: To understand length of therapy (LOT) and persistence (PER) of treatment in adult ITP patients in US, treated with an FDA-approved TPO-RA (AVA, eltrombopag (ELT) or romiplostim (ROMI).
Methods: The Symphony Health Claims Database[3] was used to understand LOT and PER for ELT and ROMI in US adult ITP patients. Claims data were evaluated and inclusion in the analyses required a D69.3 or D69.49 ICD-10 diagnostic code for ITP, and ≥ 1 first-initiated claim for ELT or ROMI during the 2019 calendar year. Due to AVA claims not being available in the Symphony Database, data from a closed system of specialty pharmacies (CVS, Accredo, Biologics, Kroger, PharmaCord, Panther) accounting for ~78% of AVA prescriptions were used. Adult patients with a D69.3 or D69.49 diagnostic code, receiving ≥ 1 initial shipment of AVA from August 2019 through December 2019 were included in the evaluation, with LOT and PER calculated over the first 365 days following initial shipment of AVA from the specialty pharmacy. Days of supply were considered to be 7 days per administration for ROMI and were provided specifically in each claim for ELT, with no cap on supply. Days of supply for AVA were provided by the pharmacy with a maximum of 90 days per shipment.
LOT for each TPO-RA was determined by calculating the time between the first claim/shipment date and the last claim/shipment date, while adding on the number of days of supply provided in the last claim/shipment (e.g. 30 day supply).
PER for each TPO-RA were determined by claims occurring in specific months (e.g. a patient with a claim on January 31st and another on February 1st would have 2 months of persistence). For each therapy, gaps in claims/shipments were allowed, with no max duration between data points. Unlike LOT, PER did not add the number of days of supply to the last evaluable claim/shipment.
Results: LOT and PER for AVA, ELT and ROMI are shown below (Table 1). 171 unique AVA patients were captured via specialty pharmacy data, while 1,400 ELT and 1,283 ROMI patients had evaluable claims. LOT was highest in AVA patients, regardless of whether a conservative single claim/shipment, or ≥ 2 claims/shipments were used for inclusion, with a max of 9.3 months of therapy administered over a potential max 12-month time frame. PER for each individual month reached was highest for AVA, with the median AVA patient reaching 10 months of treatment.

Table 1: Length of Therapy (LOT) and Persistence of Treatment (PER) for TPO-RAs in Adult ITP

Length of Therapy (LOT)		
TPO-RA	Months of Therapy (1 claim/shipment)	Months of Therapy (2+ claims/shipments)
AVA (n=171)	7.7	9.3
ELT (n=1,400)	6.5	8.2
ROMI (n=1,283)	5.5	6.4

Persistence of Treatment (PER)												
	Proportion (%) of Patients by Month Reached											
TPO-RA	1	2	3	4	5	6	7	8	9	10	11	12
AVA (n=171)	100	80	71	66	63	60	57	56	52	51	47	43
ELT (n=1,400)	100	75	66	60	55	50	47	43	40	37	34	29
ROMI (n=1,283)	100	78	63	55	51	46	42	38	35	32	30	28

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3. Symphony Health, PatientSource®, January 2018 – December 2020.

Summary/Conclusion: These data suggest that AVA has greater length of treatment and higher rates of persistence than other TPO-RAs, which may be due to a variety of variables including 1) route of administration, 2) convenience, 3) patient preference, 4) efficacy, 5) side effects, 6) insurance coverage. These results should be interpreted with caution. Claims data using matched methodologies were utilized to calculate LOT and PER for each TPO-RA, however due to AVA's commercial availability occurring in July 2019, slightly different time frames were evaluated. Also, different sources of data capture were necessary due to lack of a consistent source.

EP1152 IMMUNE THROMBOCYTOPENIA DURING COVID-19 PANDEMIC: AN ITALIAN MONOCENTRIC EXPERIENCE

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Background: Immune thrombocytopenia (ITP) is an acquired immune disorder characterised by a platelet count < $100x10^9$/L, leading to an increased bleeding risk. Infectious diseases, especially from viral agents, may potentially cause ITP. Since the novel pandemic caused by severe acute respiratory syndrome coronavirus-2(SARS-CoV2), known as COVID-19, has started in February 2020, different cases of ITP in patients affected by SARS-CoV2 have been reported. The management of COVID-19 in patients with simultaneous or previous ITP can be challenging because of the great involvement of the haemostatic system in this viral infection.
Aims: To describe the management and outcome of patients with newly diagnosed (ND), chronic and previous ITP, infected by COVID-19.
Methods: Data were collected from clinical charts and updated through telephone contacts. All patients expressed their agreement to participate to the study.
Results: Seventeen patients had RT-PCR confirmed SARS-CoV2 infection on a nasopharyngeal swab (October 2020-January 2021). Six patients were male (35.3%) and 11 female (64.7%). The median age was 57 years (range 30-90). At the time of the COVID-19 infection, as regards ITP, patients were grouped as follows: 3 had simultaneous ND ITP (17.6%) and 1 experienced a relapse (5.8%) (median platelet count $5.5x10^9$/L; range 2-$30x10^9$/L); 7 had chronic ITP on treatment (41.2%) (eltrombopag, n=5; romiplostim, n=1; prednisone, n=1) and 2 patients had stable chronic ITP off-therapy (11.8%) (median platelet count $63x10^9$/L; range 30-$100x10^9$/L); 4 patients had a previous ITP on follow-up (FU) (23.6%) (platelet count >$100x10^9$/L). Fever, anosmia, dysgeusia, articular pain and mild-to-moderate respiratory distress were considered typically COVID19-related symptoms. Overall, 15 patients were symptomatic: 11 had only COVID19-related symptoms (64.8%), 1 presented with isolated mucocutaneous bleeding (5.8%) and 3 reported both (17.6%). Two patients did not refer any symptoms throughout the course of the infection (11.8%). Six cases required hospitalization (35.3%): 3 for acute decrease of platelet count and bleeding symptoms (17.6%) (ND ITP=2; ITP relapse=1); 3 for pneumonia (17.6%) (ND ITP=1; chronic ITP on treatment=1; ITP on FU=1). Patients with bleeding symptoms were responsive to dexamethasone (40 mg/day, days 1-4) and immunoglobulins (1 g/kg). Patients with pneumonia were successfully treated with antibiotics and oral corticosteroids. The median duration of stay in the hospital was 10.5 days (range 3-20). Eleven patients recovered at home without any bleeding; they did not show any significant change in the platelet count at the first evaluation after quarantine (64.7%). Twelve patients had previously received either steroids (n=8) or steroid+splenectomy (n=4) (70.5%). Serious respiratory distress, requiring mechanic ventilation, was not recorded. Anti-thrombotic prophylaxis of COVID-related thromboembolism was not used and no cases of thrombosis were observed. The viral seroconversion was observed in all patients and no death occurred.
Summary/Conclusion: In our experience, ND ITP triggered by COVID-19 has been responsive to immunoglobulins and steroids. Overall outcome has been favourable also for COVID-19 patients with a stable off-therapy or on treatment ITP.

EP1153 IMPACT OF AUTOIMMUNE ANTIBODIES IN PATIENTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA: REAL WORLD RETROSPECTIVE STUDY FROM THE ITP REGISTRY OF THE HELLENIC SOCIETY OF HEMATOLOGY

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Background: Background: Previous reports have suggested an increased frequency of autoantibodies (AutoAbs) in patients (pts) with ITP. However, the features of those ITP pts bearing AutoAbs have not been fully elucidated thus far.
Aims: Aims: To describe real world characteristics at diagnosis and evaluate disease outcome in pts with primary ITP and elevated at least one of antinuclear antibodies (ANA), rheumatoid factor (RF), antiphospholipid (APL) Abs or antithyroid Abs. Data from the national database (ITP registry) operated under the auspices of the Hellenic Society of Hematology was used.
Methods: Methods: The Greek ITP registry recruits pts (n=1514, to date) nationally through a network of 26 sites. In the present study we retrospectively analyzed data from pts with primary ITP aged over 18 years, who were diagnosed from 1979 to 2020
Results: Results: The total number of evaluable pts was 554. Pts were excluded from the study if they had a diagnosis of systemic lupus erythematosus, rheumatoid arthritis, thyroid disorder or antiphospholipid syndrome at the time of ITP initial presentation Of the 420 pts tested for ANA, 94 (22.4%) were positive with a titer of ≥ 1/160. There was no difference in age, sex or frequency of concurrently used medications between ANA^+ and ANA^- pts. However, the median platelet count at diagnosis was significantly lower in ANA^+ pts ($21.8x10^9$/L, interquartile range: 5.7-30.5x10^9/L; P=0.048) than in ANA^- pts ($28.2x10^9$/L, interquartile range: 8-43.3x10^9/L; P=0.048). Furthermore in ANA^+ pts epistaxis and oral cavity bleeding were more frequently observed than in ANA^- pts (P=0.0477 and P=0.0008; respectively). Of the 416 pts tested for RF, 20 (4.9%) were positive. RF^+ and RF^- pts had similar age and sex distribution as well as frequency of concurrently used medications and platelet counts at diagnosis. However, epistaxis and oral cavity bleeding were more frequently observed in RF^+ pts than in RF^- ones (P=0.021 and P=0.0445; respectively). Of the 208 pts tested for APL antibodies and of the 75 pts tested for antithyroid Abs, 24 (11.5%) and 19 (25%) were positive, respectively. Neither APL Ab^+ nor antithyroid Ab^+ pts had distinctive features in terms of age, sex, frequency of concurrently used medications platelet count at diagnosis or location of bleeding, as compared to APL Ab^- and antithyroid Ab^- pts, respectively. The frequency of antiplatelet Ab positivity, the overall response to treatment and the frequency of chronic ITP development did differ between positive and negative patients for any of the aforementioned autoimmune markers.
Summary/Conclusion: Summary/Conclusion: The presence of elevated ANA or RF characterizes ITP patients with distinct presentation. However neither response to treatment nor the development of chronic disease seems to be influenced by these autoAbs. On the other hand neither the presence of APL Abs nor antithyroid Abs did seems to affect the clinical profile of the pts. Additional studies are warranted to confirm our results and probe more deeply in the significance of autoimmune markers in ITP

EP1154 SLEEP HEALTH IN ADULTS WITH IMMUNE THROMBOCYTOPENIA: QUALITY OF LIFE DATA FROM THE PLATELET DISORDER SUPPORT ASSOCIATION (PDSA) PATIENT REGISTRY

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Background: While poor sleep health has been documented in several autoimmune diseases, it's never been evaluated in patients with immune thrombocytopenia (ITP), an autoimmune bleeding disorder. In this study, sleep health refers to participants' overall satisfaction with their sleep, sleep quality, effort it takes to fall asleep, and problems sleeping.
Aims: We reviewed data from the ITP Natural History Patient Registry on sleep health among adults with ITP to examine the extent of sleep disruption in ITP patients and whether overall sleep health is worse among those receiving treatment, particularly a corticosteroid.
Methods: Adults ≥18 years with ITP completed both a demographic and a Quality of Life (QoL) survey regarding their symptoms within the last seven days.
Results: Within the 310 respondents, 248 were female (80%), 260 from the USA (83%), 180 were employed (58%), 288 insured (93%), and 235 were under the age of 65 (76%, range 18-100 years). Overall, 249 (80%) reported they had problems sleeping, 217 (70%) reported they were not very satisfied with their sleep, 155 (50%) worried about falling asleep, and 180 (58%) reported difficulties falling asleep. When asked about the quality of their sleep, 162 (52%) reported fair/poor sleep quality and 244 (79%) indicated their sleep was restless. Only 100 (32%) respondents indicated their sleep was refreshing.
Of the 310 respondents, 129 (42%) were receiving treatment for ITP. Among those, 102 (79%) reported they had problems sleeping, 92 (71%) were not very satisfied with their sleep, 68 (53%) worried about falling asleep, and 80 (62%) reported difficulties falling asleep. When asked about the quality of their sleep, 72 (56%) reported fair/poor sleep quality and 107 (83%) indicated their sleep was restless. Only 40 (31%) respondents reported their sleep was refreshing. Sleep health was not significantly worse in the treatment group compared to the non-treatment group despite high levels of poor sleep health.
Within the 129 respondents on treatment, 30 (10%) were receiving corticosteroids. Among those, 28 (90%) reported problems sleeping, 25 (84%) were not very satisfied with their sleep, 19 (64%) worried about falling asleep, 22 (74%) reported difficulties falling asleep, 20 (67%) reported fair/poor quality of sleep, 28 (90%) reported restless sleeping, and 16 (53%) reported their sleep was refreshing. Corticosteroid users reported more problems sleeping than those receiving a non-corticosteroid treatment and this difference was significant (p=.033, p<.05). Corticosteroid users also reported more restless sleep compared to the 181 respondents not receiving any treatment and this difference was found to be significant (p=0.044, p<.05). No other significant differences in sleep health were identified between corticosteroid users and non-corticosteroid users, or between corticosteroid-users and those not receiving treatment.
Summary/Conclusion: Overall, adults with ITP reported high levels of poor sleep health above what is expected from general population data, particularly among those receiving corticosteroids. Certain elements of sleep health were significantly worse among corticosteroid users, whereas other elements did not appear to be related to treatment for ITP. These results could be due to the low sample of participants currently taking corticosteroids in the study. Further work is needed to understand

what additional factors aside from corticosteroids may be influencing poor sleep health in this patient population.

EP1155 ASSOCIATION OF IMMUNE THROMBOCYTOPENIA AND INFLAMMATORY BOWEL DISEASE IN CHILDREN

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Background: Many extraintestinal autoimmune manifestations are reported in inflammatory bowel disease (IBD): Immune thrombocytopenia (ITP) can be associated: only a few patients are of pediatric age.
Aims: In this retrospective study we analyzed the largest series of children affected by both ITP and IBD. The coexistence of both diseases was investigated in children diagnosed from January 1th 2000 to December 31th 2019.
Methods: This retrospective study was designed by the Coagulation Defects Study Group of A.I.E.O.P. (Associazione Italiana Emato-Oncologia Pediatrica). Informed consent was obtained from the parents or the legal guardians of all patients. Clinical characteristics of both IBD and ITP, onset of disorders and patient's response to treatment were collected through a structured form sent to 55 Italian pediatric referring centers for hematological disorders. IBDs were classified as Crohn disease (CD), Ulcerative colitis (UC) and Inflammatory bowel *disease unclassified* (IBDU). ITP was defined as *newly diagnosed* (within 3 months from diagnosis), *persistent* (between 3 and 12 months from diagnosis) and *chronic* (cITP, lasting for more than 12 months). The ITP bleeding score was defined as *Type A: asymptomatic-paucisymptomatic ITP*, clinical symptoms ranging from no bleeding to few petechiae and some bruises without mucosal hemorrhages; *type B: intermediate ITP,* clinical picture with more petechiae, bruising and mucosal hemorrhages; *type C: severe ITP,* clinical picture with severe cutaneous and mucosal bleeding symptoms. As timing of diagnosis the patients were classified as: 1) *IBD first*: IBD was diagnosed before ITP; 2) *ITP first*: ITP was diagnosed before IBD; 3) *Simultaneous diagnosis*: the second disease (IBD or ITP) was diagnosed during hospitalization or initial ascertainment for the other disorder.
Results: Centers responded to the survey and reported the coexistence of IBD and ITP in 14 children. The most relevant clinical features of this cohort are shown in table I. The first diagnosis was ITP in 57.1% and IBD in 35.7% of patients: it was simultaneous in 7.1%. IBD was classified as UC (57.1%), CD (35.7%) and *IBDU* (7.1%). The bleeding score was A in 71.4% and B in 28.6% of patients. ITP turned to be persistent in 9/14 patients (64.3%) and chronic in 7/14 (50%). At ITP onset 4/14 of the patients (28.6%) were not treated (wait&see), 8/14 (57.1%) received iv immunoglobulin (IVIG) and 2/14 (14.3%) oral prednisone. Subsequent rescue therapies for ITP were attempted in 7 patients (50.0%). At the last follow up 5/14 patients (35.8%) were still presenting cITP and 3 patients were still on treatment. No therapy for ITP other than steroids had any effect on IBD and vice versa. Colectomy resulted in recovery from ITP in 1 of the 2 patients surgically treated. At the last FUP 35.8% of patients were still presenting cITP and 3 patients were still on treatment (with eltrombopag).

Table 1. Characteristics of study population

Sex (F%)	50%
IBD diagnosis (years, median)	8.4
ITP diagnosis (years, median)	7.6
Platelets (median) at ITP diagnosis	31,500/mmc
Familiarity for autoimmune diseases	28.6%
Extraintestinal disorders	28.6%
IBD type	UC: 57.1% CD: 35.7% IBDU: 7.1%
ITP score bleeding	score A: 71.4% score B: 28.6%
Timing of diagnosis	ITP first: 57.1% IBD first: 35.7% Simultaneous: 7.1%
Persistent ITP at 3 months	64.3%
Chronic ITP at 12 months	50.0%
Chronic ITP at last FUP	35.8%
First line therapy for ITP	IVIG: 57.1% Wait&see: 28.6% Oral prednisone: 14.3%
FUP from ITP diagnosis (median, years)	6.2
FUP from IBD diagnosis (median, years)	3.7

IBD: inflammatory bowel disease; ITP: immune thrombocytopenia; CD: Crohn disease; UC: Ulcerative colitis; IBDU: inflammatory bowel disease unclassified; FUP: Follow Up; IVIG: iv immunoglobulin.

Summary/Conclusion: We present the largest case series reported to date of children affected by both IBD and ITP. In all patients ITP was mild without any evident impact on IBD severity. It seems that UC is the type of IBD more commonly associated to ITP and that incidence of cITP (50%) is higher than what usually reported in pediatric age. Colectomy can occasionally result in ITP recovery and steroids can be effective in both diseases. Finally eltrombopag retains its high efficiency also in pediatric ITPs associated to IBD.

EP1156 DEVELOPMENT AND VALIDATION OF THE C-SCORE, A SCORE OF DIAGNOSIS A SEVERE THROMBOCYTOPENIA OR OTHER CYTOPENIAS IN HEPATIC CIRRHOSIS

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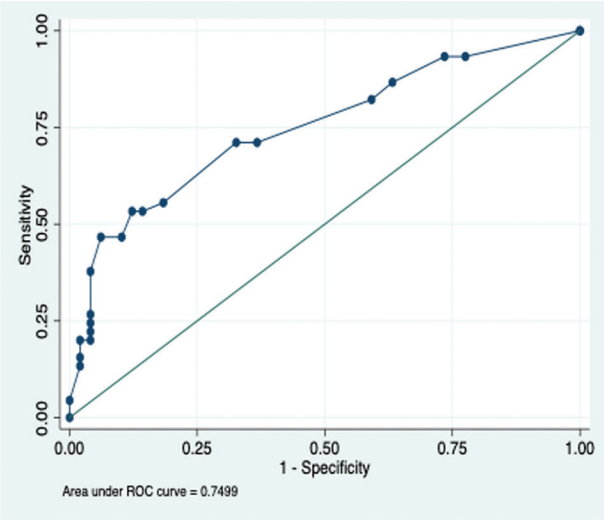
Background: Patient's cirrhosis develops thrombocytopenia or other cytopenias from multiple factors, including hypersplenism, because it has no unique clinical or laboratory features to distinguish cytopenias is due cirrhosis or from other diseases.
Aims: This study was conducted to develop a diagnostic score for severe cytopenias in patients with hepatic cirrhosis.
Methods: In one referral center in Mexico City retrospective cohort of 95 patients with hepatitic cirrhosis of any etiology with thrombocytopenia or other cytopenia, (hematologic disease were excluded in hematologist evaluation and with bone marrow aspiration and biopsy), was used to construct the severe cytopenias in hepatic cirrhosis diagnostic score, called the C-score. We divide two groups according to severity of cytopenias: severe (absolute neutrophil count ≤1000 cells/μL or platelet count ≤ 50X10 /μL) and no severe cytopenias. Six variables were evaluated for their association with diagnosis of cytopenias in hepatic cirrhosis and logistic regression was used to calculate the weight of each criterion included in the score.
Results: The group of severe cytopenias included 45 patients, no difference was observed in patient characteristics, included age, sex, etiology of cirrhosis, Child-Pugh Score, presence of esophageal varices, hemoglobin levels, lactate dehydrogenase, INR, creatinine. Six variables: 2 clinical (ascites and state of cirrhosis), 2 laboratory (lymphocytes and hemoglobin) and one radiological (spleen size, measured by the same radiologist) and one prognostic (MELD-Na), were used in the development the C-score. The possible number of points assigned to each variable ranged from 0 to – 3 for hemoglobin to 0-12 for spleen size and ascites (table 1). The area under the ROC curve for the C-Score was 0.74 (CI 95%, 0.65-0.84, P *0.05*), indicating excellent discrimination

(figure 1). The pseudo R^2 statistic for the model was 0.15. The best cutoff value for de C-Score was ≥15, corresponding to a sensitivity of 71.11%, a specificity of 67.35%, positive predictive value of 66.67%, negative predictive value of 71.74% and accurate classification of 69.15% of the patients. The probability of having severe cytopenias in hepatic cirrhosis ranged from 30.22 % with a score of 5 to 89% with score of 40. We perform internal validation with the area under the ROC curve of 0.752 (min: 0.673, max 0.840).ç

Table 1.The C-Score

Parameter	Points
Spleen Size (cm)	
<14	0
≥14	12
Lymphocytes (cells/µL)	
>800	0
≤800	6
Ascites	
No	0
Mild	1
Moderate/severe	12
Hemoglobin (g/dl)	
≤7	0
>7	-3
MELD-Na	
<14	0
≥14	7
Cirrhosis stage	
Compensated	0
Decompensated	5

Figure 1. Area under the receiver operating characteristic curve for C-Score



Summary/Conclusion: Discussion: Severe cytopenias are frequently in patients with cirrhosis, with multifactorial pathogenesis, difficult diagnosis and many of the times the patient undergoes unnecessary diagnostic workup. The C-Score is the first for the diagnosis of severe cytopenias in patients with cirrhosis, C-Score has limitations, was developed using a retrospective study population and in this initial study we focus on the development of the score, since we do not have a cohort for external validation, we perform internal validation by bootstrap, prospective validation of the score in other samples of patients is needed before it is recommended for widespread use.

Conclusion: The C-Score can be used to estimate the patients risks of having severe cytopenias in hepatic cirrhosis and it can help the clinician to make adequate diagnosis and treatment decisions in clinical practice.

EP1157 EFFECTIVENESS AND SAFETY OF ROMIPLOSTIM IN PATIENTS WITH NEWLY DIAGNOSED, PERSISTENT AND CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA IN GERMAN ROUTINE CLINICAL PRACTICE: THE OBSERVATIONAL PLATEAU STUDY

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Background: Immune thrombocytopenia (ITP) is a rare autoimmune disease characterised by low platelet counts. Romiplostim is a thrombopoietin-receptor agonist (TPO-RA) that increases platelet production and is indicated in Europe for the treatment of primary ITP in adult patients (pts) who are refractory to other treatments (e.g. corticosteroids/immunoglobulins). In 2021, romiplostim was approved for use in all phases of ITP, i.e. newly diagnosed (0–3 months [M]), persistent (>3–12M) and chronic ITP (>12M). This is in line with current European guidelines to switch adult pts earlier from corticosteroids to TPO-RAs. Although romiplostim was previously restricted to chronic ITP, there has been clinical evidence supporting the use of romiplostim in earlier disease phases (Kuter, Br J Haematol 2019; Newland, Br J Haematol 2016). Real-world data on the routine use of romiplostim in pts with ITP duration of ≤12M can help guide current and future clinical practice.
Aims: To assess the effectiveness and safety of romiplostim in adults with primary ITP, according to ITP phase, in routine clinical practice in Germany.
Methods: This was a *post-hoc* analysis of the single-arm, prospective, observational PLATEAU study. Data were collected from adult pts (≥18 years of age) who received ≥1 dose of romiplostim in haemato-oncological centres across Germany during the years 2010–2016. After the first romiplostim dose, follow-up data were collected for up to 2 years or until loss to follow up/death. Retrospective data were collected for bleeding events for up to 6M prior to romiplostim. Overall platelet response was defined as ≥1 platelet count measurement ≥50 x 10^9/L during weeks 2–24 after romiplostim initiation. Durable platelet response was achieved if ≥75% of all platelet count measurements were ≥50 x 10^9/L during weeks 14–24 after romiplostim initiation. Other outcomes included patient demographics, romiplostim use, and adverse drug reactions (ADRs). Subgroup analyses were performed according to ITP phases (time from diagnosis to romiplostim initiation: <3M; 3–12M; >12M).
Results: A total of 96 pts were included in the analysis. At the time of romiplostim initiation, 18 (18.8%) were newly diagnosed, 25 (26.0%) had persistent ITP, and 53 (55.2%) had chronic ITP (**Table**). The median (Q1–Q3) time from ITP diagnosis to romiplostim initiation was 14.9M (4.3–54.2). The proportion of pts who were non-splenectomised at treatment initiation was 87.5%. No newly diagnosed pts were splenectomised (versus 12.0% and 11.3% of pts with persistent or chronic ITP, respectively). Overall platelet response was achieved in 100% of pts with newly diagnosed and persistent ITP, and in 96.2% of pts with chronic ITP. Durable platelet response was achieved in 88.2% of newly diagnosed pts, 65.0% of pts with persistent ITP, and 69.4% of pts with chronic ITP. The median time to first platelet response was 8.5 days (newly diagnosed), and 7 days (for both persistent and chronic ITP). Safety was comparable across all ITP phases; there were two occurrences of bone marrow ADRs, both in pts with chronic ITP, and no thrombotic ADRs.

Table. Characteristics, effectiveness and safety of romiplostim treatment, for patients (N=96) with newly diagnosed, persistent and chronic primary ITP in German routine clinical practice (2010 –2016)

	Phases of ITP (time from ITP diagnosis to romiplostim initiation)		
	Newly diagnosed <3 months n=18 (18.8%)	Persistent 3–12 months n=25 (26.0%)	Chronic >12 months n=53 (55.2%)
Patient characteristics at the time of romiplostim initiation			
Male, n (%)	13 (72.2)	14 (56.0)	23 (43.4)
Age, years*	64 (56–76)	70 (56–79)	67 (55–72)
Time from ITP diagnosis to romiplostim initiation, months*	1.0 (0.5–1.4)	5.8 (4.7–9.0)	51.0 (26.4–100.5)
Platelet count, x10^9/L*	32 (21–50)	28 (19–78)	29 (15–45)
Prior splenectomy, n (%) †	0	3 (12.0)	6 (11.3)
≥1 prior ITP therapies, n (%) ‡	13 (72.2)	23 (92.0)	49 (92.5)
Prior bleeding events§, n (%)	7 (38.9)	10 (40.0)	16 (30.2)
Type III or IV (transfusion required)	*1 (5.6)*	*0*	*0*
Prior bone marrow biopsy, n (%) †	11 (61.1)	18 (72.0)	29 (54.7)
Duration of romiplostim exposure, weeks			
Mean (SD)	82.1 (33.9)	66.3 (41.6)	81.9 (35.7)
Median (Q1–Q3)	102.2 (65.1–104.4)	87.3 (13.6–104.0)	104.1 (50.4–104.4)
Effectiveness outcomes during 24 -week follow-up period			
Overall platelet response, % (95% CI)¶	100.0 (81.5–100)	100.0 (86.3–100)	96.2 (87.0–99.5)
Durable platelet response, % (95% CI)¶	88.2 (63.6–98.5)	65.0 (40.8–84.6)	69.4 (54.6–81.7)
Time to first platelet response ≥50 x 10^9/L, days*	8.5 (7–14)	7 (7–13)	7 (7–14)
≥1 ITP therapy since initiation of romiplostim, n (%)	11 (61.1)	7 (28.0)	21 (39.6)
Bleeding events since initiation of romiplostim, n (%)	6 (33.3)	9 (36.0)	25 (47.2)
Type III or IV (transfusion required)	*3 (16.7)*	*0*	*1 (1.9)*
No transfusion since the initiation of romiplostim, n (%) ‖	13 (72.2)	23 (92.0)	43 (81.1)
ADRs during the 2-year follow-up period			
Total number of ADRs, n	38	14	46
Patients with any ADR, n (%)	6 (33.3)	6 (24.0)	19 (35.8)
Thrombotic ADR, n	0	0	0
Bone marrow fibrosis ADR, n (%)	0	0	2 (3.8)

ADR, adverse drug reaction; CI, confidence interval; ITP, immune thrombocytopenia; SD, standard deviation
*Median (Q1–Q3); †2 patients with persistent ITP and 1 patient with chronic ITP had missing data; ‡1 patient with newly diagnosed ITP had missing data; §Within 6 months prior to romiplostim initiation; ¶Patients for whom there was no data on the number of platelets or the timing of the platelet measurement were censored; ‖Including platelet transfusions, red blood cell transfusions, and other types of blood transfusions

Summary/Conclusion: In this observational study, clinically meaningful platelet responses were achieved by romiplostim-treated pts in all ITP phases. Romiplostim was well tolerated. This cohort, representative of routine clinical practice in Germany, supports the effectiveness and safety of romiplostim in pts with newly diagnosed and persistent ITP in routine clinical practice, in line with recent guidelines.

EP1158 ASSOCIATION OF IMMUNE THROMBOCYTOPENIA AND COELIAC DISEASE IN CHILDREN

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Background: Coeliac disease (CD) is often associated with other autoimmune disorders: the association with Immune Thrombocytopenia (ITP) has been investigated in some cohorts and case reports with contradictory results especially about gluten-free diet efficacy on ITP. No study aimed to describe the specific features of this association in pediatric age.
Aims: The aim of this study was to characterize the association of Cd and ITP in Italian children.

Methods: This is a multicenter retrospective study investigating the coexistence of CD and ITP in 28 children diagnosed from January 1th 2000 to December 31th 2019. A case report form was sent to all 55 A.I.E.O.P. Centers collecting information about patients up to 18 years of age with both CD and ITP. Informed consent was obtained from the parents or the legal guardians of all patients. CD was classified as *classic* (presence of symptoms of malabsorption, positive CD specific antibodies and biopsy, and symptoms resolution on a gluten-free diet), *silent* (positive CD specific antibodies, HLA DQ2 or DQ8 and biopsy without symptoms), *latent* (presence of HLA DQ2 or DQ8 and histological alterations typical of CD in duodenal biopsy at some point of their life, but neither symptoms nor positive antibodies) and *potential* (positive CD-specific antibodies and HLA without histological abnormalities in duodenal biopsies). ITP was defined as *newly diagnosed* (within 3 months from diagnosis), *persistent* (between 3 and 12 months from diagnosis) and *chronic* (cITP, lasting for more than 12 months). The ITP bleeding score was defined as *Type A: asymptomatic-paucisymptomatic ITP*, clinical symptoms ranging from no bleeding to few petechiae and some bruises without mucosal hemorrhages; *type B: intermediate ITP*, clinical picture with more petechiae, bruising and mucosal hemorrhages; *type C: severe ITP*, clinical picture with severe cutaneous and mucosal bleeding symptoms. As timing of diagnosis the patients were classified as *CD first*: CD was diagnosed before ITP; *ITP first*: ITP was diagnosed before CD; *Simultaneous diagnosis*: the second disease (CD or ITP) was diagnosed during hospitalization or initial ascertainment for the other disorder.
Results: The most relevant clinical features of this cohort are shown in table I. The first diagnosis was ITP in 16 (57.2%) and CD in 9 patients (32.1%) respectively. In 3 patients (10.7%) the two diagnosis were simultaneous. The bleeding score of ITP was A in 67.9% and B in 32.1% of patients. ITP turned to be persistent in 44.4% and chronic in 40%. At the last FUP 28.6% of patients were still presenting cITP. The CD was classified as classical in 60.7% of children, silent in 25%, latent in 7.1% and potential in 7.1%. At ITP onset 21.4% of the patients were not treated (wait&see), 64.3% received iv immunoglobulin (IVIG) and 14.3% oral prednisone. Subsequent rescue therapies for ITP were attempted in 12 patients (42.9%). All the potential and silent CDs in our cohort were diagnosed in the 2 groups of *ITP first* or *simultaneous diagnosis*. In all children ITP was mild and in 2 out of 8 patients not recovered from ITP at the time of CD diagnosis a normalization of platelet counts (> 100,000/mmc) occurred after 3 and 5 months from starting gluten free diet.

Table 1. Characteristics of the patients

Median age at CD diagnosis (years)	6.2 (range 0.6-27.6)
Median age at ITP diagnosis (years)	5.8 (range 0.5-15.1)
Median PLTs at ITP diagnosis	19,500/mmc (range 1,000-96,000/mmc)
Familiarity for autoimmune diseases	55.6%
Extaintestinal disorders	14.8%
CD type	Latent: 7.1% Potential: 7.1% Silent: 25% Classic: 60.7%
ITP score bleeding	score A: 67.9% score B: 32.1%
Time of diagnosis	ITP first: 57.2% CD first: 32.1% Simultaneous: 10.7%
Gluten-free diet efficacy on ITP	NR: 77.8% CR: 22.2%
cITP at 12 months	40%
First line therapy for ITP	IVIG: 64.3% Wait&see: 21.4% Oral prednisone: 14.3%
First rescue therapy for ITP	42.9%
Second rescue therapy for ITP	21.4%
Median FUP from ITP diagnosis (years)	4.4 (range 0.2-16.5)
Median FUP from CD diagnosis (years)	2.3 (range 0.02-15.2)

CD: coeliac disease; ITP: immune thrombocytopenia; FUP: Follow UP; PLTs: platelets; NR: no response; CR: complete response; cITP: chronic immune thrombocytopenia; IVIG: iv immunoglobulin.

Summary/Conclusion: We think that screening for celiac disease should be considered in children with ITP, regardless the presence of

gastrointestinal symptoms. About one fourth of patients recover from ITP after starting gluten-free diet.

EP1159 EPIDEMIOLOGY AND MANAGEMENT OF IMMUNE THROMBOCYTOPENIA IN ADULT PATIENTS IN ALGERIA

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Background: Immune thrombocytopenia (ITP) affects 2–4/100,000 adults globally. Recent ASH and ICR guidelines recommend short duration (<6 weeks) corticosteroids as first-line therapy for ITP, and thrombopoietin receptor agonists (TPO-RAs) and rituximab as second-line therapy before splenectomy. There are limited data on the epidemiology and management of ITP patients (pts) in Algeria.

Aims: Here we investigate the epidemiology and management of ITP pts treated in public hospitals in Algeria from September 2017–August 2018.

Methods: This was a non-interventional, longitudinal, nationwide estimation study of ITP pts ≥16 years (y) of age, either previously (before 1 September 2017) or newly (September 2017–August 2018) diagnosed with ITP. Assessments included pt characteristics, disease etiology, ITP incidence (by age, sex, diagnosis stage, and Algeria province), ITP prevalence, and ITP treatment regimens.

Results: Overall 1746 pts were listed of whom 587 did not provide consent; 1159 were included in the analysis. Among eligible pts, 895 (77.2%) were women, 173 (14.9%) were newly diagnosed, and 986 (85.1%) were previously diagnosed with ITP. A total of 966 pts (83.3%) had no comorbidities conferring bleeding risk. Etiological investigations for diagnosis showed that a majority of pts were evaluated for autoimmune disease (79.9%) and/or lymphoid hemopathy (75.9%) (Table). At diagnosis, median age was 36y (range 0–94y), and platelet counts (10^3/mm^3) were 0–30 in 124 pts (71.7%), 30–50 in 20 pts (11.6%), 50–100 in 28 pts (16.2%), and >100 in 1 (0.6%) pt. Khellaf score was ≤8 for 45 (26.0%) pts, >8 for 8 (4.6%) pts, and missing for 120 (69.4%) pts. Bleeding risk was grade 0 (low), 1, 2, 3, and 4 for 50 (28.9%), 24 (13.9%), 34 (19.7%), 52 (30.1%), and 13 (7.5%) pts, respectively; 55 (31.8%) pts were asymptomatic, 58 (33.5%) ecchymotic, and 60 (34.7%) severely hemorrhagic.

The incidence (95% CI) of ITP was 0.85 (0.75, 0.96) per 100,000 inhabitants, increasing with age from 0.5 (0.43, 0.68) for pts 15–35y old to 2.4 (1.60, 3.51) for pts ≥75y old. Women had a higher incidence of ITP than men (1.2 [1.02, 1.37] vs 0.5 [0.43, 0.67]). Incidence of ITP varied with diagnosis stage (asymptomatic: 0.4 [0.31, 0.45]; ecchymosis: 0.1 [0.10, 0.19]; severe hemorrhage: 0.1 [0.06, 0.13]), and Algeria province (lowest in a public site in Tebessa: 0.1 [0.02, 0.92], highest in a public site in Sidi Bel Abbès: 1.6 [0.93, 2.89]). The prevalence (95% CI) of ITP was 5.7 (5.39, 5.93) per 100,000 inhabitants, increasing with age from 3.2 (2.78, 3.67) for pts 15–25y old to 11.9 (9.68, 13.08) for pts 65–75y old, and then decreasing to 7.6 (4.79, 12.06) for pts ≥85y old. Women had a higher prevalence of ITP than men (8.8 [8.33, 9.29]) vs 2.6 [2.34, 2.85]). Corticosteroids were the primary treatment for new (136 [78.6%]) and previously (795 [80.7%]) diagnosed pts. Last/ongoing treatments at study inclusion were corticosteroids (712 [72.2%]), rituximab (56 [5.7%]), immunoglobulins (30 [3.0%]), TPO-RA (romiplostim: 19 [1.9%]), and antibacterials (4 [0.4%]). Among previously diagnosed pts, 172 (17.4%) had splenectomy with a median time of 19 months from ITP diagnosis.

Table. Summary of Etiological Investigations of ITP Patients in Algeria

Test done	Total N = 1159
Autoimmune disease, n (%)	
Done	925 (79.9)
Missing	1 (0.09)
Not Done	233 (20.1)
Lymphoid hemopathy, n (%)	
Done	879 (75.9)
Missing	1 (0.09)
Not Done	279 (24.1)
Viral hepatitis serologies, n (%)	
Done	850 (73.4)
Missing	1 (0.09)
Not done	308 (26.6)
HIV serology, n (%)	
Done	848 (73.2)
Missing	1 (0.09)
Not Done	310 (26.8)
Helicobacter pylori infection, n (%)	
Done	161 (13.9)
Missing	1 (0.09)
Not Done	997 (86.1)
Viral infections preceding thrombocytopenia (sore throat, flu, other), n (%)	
Done	30 (2.6)
Missing	6 (0.5)
Not done	1123 (97.4)

HIV, human immuno-deficiency virus; ITP, immune thrombocytopenia.

Summary/Conclusion: The incidence and prevalence of ITP in Algeria increased with age, and both were higher in women than men, conforming to global trends. The results highlight the need to reduce corticosteroid treatment duration and improve second-line therapy options such as TPO-RAs before splenectomy (in line with the recently updated ASH and ICR guidelines) for management of adult ITP pts in Algeria.

EP1160 THE CLINICAL UTILITY OF ALINITY HQ STANDARD AND RESEARCH CBC PARAMETERS IN THE DIFFERENTIAL DIAGNOSIS OF ITP

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Background: Immune thrombocytopenia (ITP) is diagnosed in patients with a platelet (PLT) count below 100 x 10^9/L in whom other causes of thrombocytopenia have been ruled out. Myelodysplastic syndrome (MDS), aplastic anemia, myeloproliferative and lymphoproliferative diseases are among the main causes that are considered in the differential diagnosis.

Aims: As complete blood count (CBC) is one of the first tests that is performed on any patient who presents with clinical symptoms, our goal was to evaluate if standard and research CBC and reticulocyte parameters reported by Alinity hq can help differentiating ITP from other forms of thrombocytopenia.

Methods: The patient population (n=117) was selected to include samples with a PLT count of < 100 x 10^9/L. The cohort included 38 unique samples from patients with ITP and 79 samples with other forms of thrombocytopenia, such as MDS, aplastic anemia, primary myelofibrosis and idiopathic cytopenia of undetermined significance, among others. CBC and reticulocyte results were generated with the Abbott Alinity hq hematology analyzer. Hematological parameters were compared between the two thrombocytopenic groups by the Mann-Whitney test. The effectiveness of standard and research CBC parameters and mathematical formulas to differentiate ITP for other forms of thrombocytopenia was assessed by ROC analysis. Patients who have received RBC

transfusion in the past eight weeks were excluded from the analysis of RBC and reticulocyte parameters.
Results: PLT counts were not significantly different between ITP and the other thrombocytopenia group (medians: 55.3 vs 46.9 x 10^9/L). Several CBC parameters demonstrated significant differences between the two populations.
The five parameters that showed the largest difference between the two groups (MPV, RBC, RDW-MATH SD, %HPO and HDW) produced area under the curve (AUC) values ranging from 0.676 (MPV) to 0.828 (HDW). Several mathematical formulas also demonstrated good performance. The formula of (RBC / HDW x MPV) resulted in an AUC of 0.848, and a sensitivity of 80.6% and specificity of 81.4% for differentiating ITP from other forms of thrombocytopenia.

Measurand	Other thrombocytopenia	ITP	p value
	Median and interquartile range		
MPV (Mean platelet volume)	7.9 (7.0-8.9)	9.0 (8.0-10.2)	0.0001
Absolute neutrophil count	1.58 (0.81-2.66)	2.66 (1.79-3.80)	0.0007
RBC (Red blood cell count)	3.41 (2.74-3.84)	4.12 (3.76-4.63)	<0.0001
RDW (Red cell distribution width)	12.7 (11.6-15.3)	11.5 (11.2-12.6)	0.001
RDW-MATH SD (RDW expressed as standard deviation)	13.3 (12.0-14.7)	11.3 (10.7-12.4)	<0.0001
%MAC (% macrocytic RBC)	10.8 (3.7-22.1)	2.6 (1.0-8.4)	0.0007
%HPO (%hypochromic RBC)	11.2 (4.7-16.1)	2.1 (0.9-4.4)	<0.0001
HDW (HGB distribution width)	10.1 (7.9-11.8)	6.3 (5.9-7.7)	<0.0001
IRF (Immature reticulocyte fraction)	0.39 (0.31-0.46)	0.32 (0.31-0.36)	0.0002

Summary/Conclusion: Several Alinity hq standard and research CBC and reticulocyte parameters have demonstrated significant differences between ITP and other forms of thrombocytopenia. These differences are likely related to the fact that erythropoiesis and myelopoiesis are commonly affected in many forms of thrombocytopenia such as MDS or aplastic anemia, while they are not impacted in ITP. In addition, accelerated thrombopoiesis is present in ITP, but usually not in other types of thrombocytopenia. These results demonstrate the clinical utility of Alinity hq standard and research hematology parameters in the differential diagnosis of ITP.

EP1161 CHANGES IN THE EXPRESSION OF PROTEINS INVOLVED IN THE CA2+ HOMEOSTASIS IN NEONATE PLATELETS.

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Background: Calcium homeostasis is crucial for platelet function and Store Operated Calcium Entry was found to be the main Ca^{2+} entry mechanism in non-excitable like in platelets[1]. SOCE relays in the association of the DTS, STIM1, and the plasma membrane calcium channels, Orais and TRCPs[2]. Changes in the Ca^{2+} homeostasis of neonate platelets were early described[3], but most of the main components of SOCE were unknown by that time[1,2], which has been revisited in the present research work
Aims: The aim of the present work is to investigate the possible alteration in the regulatory proteins involved in the intracellular calcium homeostasis in human platelets from neonates respect adults.
Methods: Upon platelet isolation they were subjected to either protein- and mRNA isolation protocols and alternatively were used in functional experiments as well as for analysis of intracellular calcium homeostasis using fura2.
Results: mRNA analysis and protein evaluation by Western blotting revealed interesting differences between neonate platelets and platelets from adults like the one shown in the Figure representing STIM1 and SARAF (Fig A), which are relevant for SOCE and therefore, those changes may explain the physiological and functional changes in neonate platelets previously described by others (Fig B and C)[4].
Summary/Conclusion: Here, we describe some of these key proteins involved in Ca^{2+} entry through SOCE that are modify in neonate platelets.

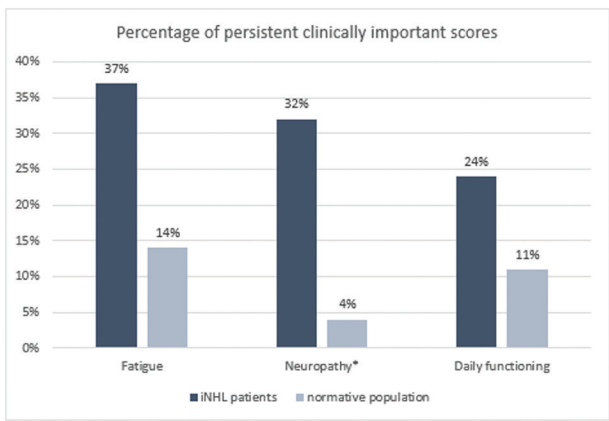
Quality of life, palliative care, ethics and health economics

EP1162 PERSISTENT CLINICALLY IMPORTANT OUTCOMES OF FATIGUE, NEUROPATHY AND PROBLEMS WITH DAILY FUNCTIONING AMONG INDOLENT NON-HODGKIN LYMPHOMA SURVIVORS.

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Background: Clinical outcomes and survival rates for indolent Non-Hodgkin Lymphoma (iNHL) have greatly improved in the past two decades. It, however, does not necessarily mean that these survivors live in good health. Patients often experience relapses of their disease and need to undergo several treatment lines. They are therefore at risk for adverse physical and psychosocial effects, such as fatigue, neuropathy and anxiety. To date, most information has been obtained from clinical trials and cross-sectional studies and little is known about persistent (long-term) symptoms and problems in a population-based setting.
Aims: (1) To evaluate the course of symptoms and daily functioning among iNHL patients, up to ten years after diagnosis in a prospective observational population-based cohort, (2) to determine the number of patients with persistent fatigue, neuropathy and problems in daily functioning and (3) to identify sociodemographic, clinical and psychological factors associated with this.
Methods: Patients diagnosed with iNHL between 1999 and 2014, 18 years and older, were invited for a longitudinal population-based survey. Patients received subsequent questionnaires every six months (≤ three years after diagnosis) and once a year (> three years after diagnosis), starting from the time of enrollment until spring 2019. Data collection was done within the PROFILES registry. Sociodemographic and clinical data were obtained from the Netherlands Cancer Registry. The EORTC QLQ-C30 was used to assess daily (role) functioning and fatigue and the CLL-16 was used for neuropathy. Psychological distress was measured with the Hospital Anxiety and Depression Scale. Persistent symptoms and problems in daily functioning were defined with the thresholds for clinical importance of the QLQ-C30. Data of patients were compared to an age- and sex-matched normative population. Individual Growth Curve models with maximum likelihood estimation and Generalized Estimating Equation analysis were performed using SPSS.



*No longitudinal neuropathy data was available for the normative population, this neuropathy score was therefore based on a cross-sectional measurement.

Results: 669 iNHL patients were included who completed on average 4 measurements. Patients had a mean age of 64.8 years at inclusion and 60% were male. Mean survival time at inclusion was 3.6 years [range 0.4-10.5 years]. Primary treatment was watchful waiting (52%), chemotherapy (29%) or radiotherapy (14%). The growth model shows that the course of symptoms and daily functioning remains stable up to 10 years after diagnosis. Respectively, 37% reported persistent fatigue, 32% persistent neuropathy and 24% persistent problems in daily functioning. This was 2-3 times higher than the normative population. Factors associated with worse persistent outcomes were: receiving chemotherapy as primary treatment, having comorbidities, lower education, not having a partner and experiencing psychological distress (all p's <0,05).
Summary/Conclusion: A quarter to one-third of iNHL patients experiences persistent fatigue, neuropathy and problems with daily functioning. To organize early detection and supportive care for those in need, further research is needed to better understand the underlying mechanisms of symptoms and daily functioning (e.g. the role of physiological and biological factors). Additionally, it will lead to better expectation management and informed decision-making for iNHL patients.

EP1163 QUALITY OF LIFE WITH REGN5458 IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): PATIENT-REPORTED OUTCOMES (PROS) FROM THE FIRST-IN-HUMAN PHASE 1/2 TRIAL

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Background: The phase 1 portion of the phase 1/2 trial of REGN5458, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, demonstrated an acceptable safety and tolerability profile with early, deep and durable efficacy in heavily pre-treated patients with RRMM (NCT03761108).[1]
Aims: To report the effects of REGN5458 on patient-reported outcomes (PROs).
Methods: Patients with progressive RRMM (≥3 prior lines of systemic therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody) were enrolled in the study. Patients received weekly doses of REGN5458, followed by continuous dosing, administered every 2 weeks. A modified 3+3 dose escalation design (4+3) was used. PROs were assessed using multiple instruments including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Analyses were performed on patients (N=49) who received REGN5458, pooled across dose levels 1 to 6, at baseline and Weeks 4, 8, 12 and 24. These included A) descriptive mean scores at each assessment, B) change from baseline scores over time and C) estimated overall change from baseline using mixed-effects model for repeated measures analysis [and 95% confidence intervals (CI)] in the global health status/quality of life (GHS/QoL), and all functional and symptom scales from the EORTC QLQ-C30. No multiplicity adjustments were made, and findings are exploratory. Clinically meaningful change was defined as a ≥10-point change from baseline, statistical significance was interpreted using 95% CIs of change from the baseline.
Results: At baseline, patients had a median of five prior lines of therapy. Statistically significant and clinically meaningful overall improvements from baseline in GHS/QoL (10.7 [95% CI: 6.2, 15.1]) and patient-reported pain symptoms (-10.2 [95% CI: -16.2, -4.2]) were observed with REGN5458. Statistically significant overall improvements from baseline in emotional functioning (7.6 [95% CI: 3.4, 11.7]) and social functioning (8.9 [95% CI: 1.6, 16.3]) were also seen. Across remaining EORTC QLQ-C30 functional (Figure 1A) and symptom (Figure 1B) scales, improved trends were observed, with the exception of physical functioning (-0.2 [95% CI: -5.0, 4.6]), fatigue (0.3 [95% CI: -4.0, 4.6]), and appetite loss (3.0 [95% CI: -2.6, 8.5]).

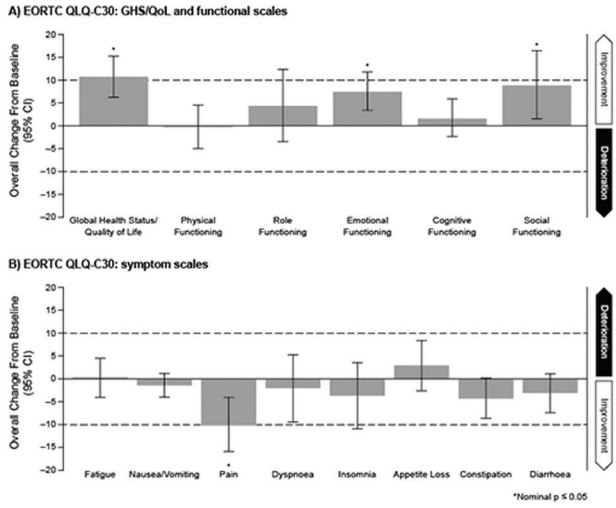


Figure 1 Overall change from baseline (repeated-measures mixed-effect model) (A) EORTC QLQ-C30: GHS/QoL and functional scales (B) EORTC QLQ-C30: symptom scales

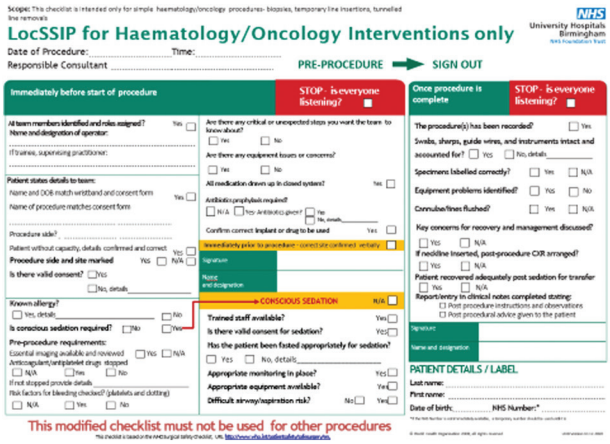
Summary/Conclusion: Patients who received REGN5458 showed statistically significant and clinically meaningful overall improvements in GHS/QoL and pain symptoms. Furthermore, there was no statistically significant overall deterioration in PROs even in a heavily pre-treated population. Additional and longer follow-up PRO data are warranted to confirm the benefit-risk profile of REGN5458 in heavily pre-treated patients with RRMM. 1. Madduri D et al. ASH 2020. O291

EP1164 LOCAL SAFETY STANDARDS FOR INVASIVE PROCEDURES (LOCSSIPS) IN HAEMATOLOGY

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Background: A study in 2009 demonstrated there were a number of preventable serious incidents occurring in hospitals around the UK. These were termed Never Events(NE). In 2015, as a way to mitigate these serious incidents, the National Patient Safety Agency(NPSA) released a report, recommending the creation and implementation of National Safety Standards for Invasive Procedures(NatSSIPs), which at a local level would be named Local Safety Standards for Invasive Procedures(LocSSIPs). In 2017, University Hospitals Birmingham(UHB) NHS Foundation Trust set up a LocSSIP steering committee, with the commitment to create and implement LocSSIPs across the trust.
Aims: Our aim was to create and develop LocSSIPs within the haematology department and audit its implementation.
Methods: The project plan was divided into 4 phases: scoping, development, implementation and maintenance and monitoring. We identified a LocSSIP 'champion' within haematology and identified key procedures which would require LocSSIPs. Our safety standards were framed on NPSA guidance and standards of the WHO checklist but tailored for procedures within haematology. Following implementation, compliance was audited.
Results: The LocSSIP checklist was successfully developed and approved for implementation. Pre-procedure and sign-out sections were created to allow safety checks before and after the procedures whilst allowing for efficiency and effective use. All questions were tailored to haematology such as bone marrow biopsies, lumbar punctures, and line insertions. Additionally, key safety questions for conscious sedation were created in line with local Trust and NICE guidance. Compliance of haematology LocSSIPs was 93.5% involving 31 procedures.
Informal feedback overall mentioned that staff members felt safer using LocSSIPs. Standardisation further facilitated patient safety following redeployment of staff due to the pandemic and recent merger of Trusts.


LocSSIP for Haematology/Oncology Interventions only

University Hospitals Birmingham NHS Foundation Trust

Date of Procedure: Time:

Responsible Consultant

PRE-PROCEDURE → SIGN OUT

Immediately before start of procedure — STOP - is everyone listening?

Once procedure is complete — STOP - is everyone listening?

All team members identified and roles assigned? Name and designation of operator:

If trainee, supervising practitioner:

Patient states details to team:

Name and DOB match wristband and consent form

Name of procedure matches consent form

Procedure site?

Patient without capacity, details confirmed and correct

Procedure side and site marked

Is there valid consent?

Known allergy?

Is conscious sedation required?

Pre-procedure requirements:

Essential imaging available and reviewed

Anticoagulant/antiplatelet drugs stopped

If not stopped provide details

Risk factors for bleeding checked? (platelets and clotting)

Are there any critical or unexpected steps you want the team to know about?

Are there any equipment issues or concerns?

All medication drawn up in closed system?

Antibiotic prophylaxis required?

Confirm correct implant or drug to be used

Immediately prior to procedure - correct site confirmed - verbally

Signature

Name and designation

CONSCIOUS SEDATION

Trained staff available?

Is there valid consent for sedation?

Has the patient been fasted appropriately for sedation?

Appropriate monitoring in place?

Appropriate equipment available?

Difficult airway/aspiration risk?

The procedure(s) has been recorded?

Swabs, sharps, guide wires, and instruments intact and accounted for?

Specimens labelled correctly?

Equipment problems identified?

Cannulae/lines flushed?

Key concerns for recovery and management discussed?

If nexidine inserted, post-procedure CXR arranged?

Patient recovered adequately post sedation for transfer

Report/entry in clinical notes completed stating:

- Post procedure instructions and observations
- Post procedural advice given to the patient

Signature

Name and designation

PATIENT DETAILS / LABEL

Last name:

First name:

Date of birth: NHS Number:*

This modified checklist must not be used for other procedures

Summary/Conclusion: We have successfully demonstrated implementation and compliance of a LocSSIP in haematology. As with every quality improvement project, the work is longitudinal and the troubleshooting process is still ongoing. Continuous auditing and monitoring of their use is required as well as the long term effects on serious incidents.

EP1165 SYSTEMATIC LITERATURE REVIEW (SLR) OF THE EFFICACY AND SAFETY OF SECOND-LINE (2L) TREATMENTS FOR RELAPSED OR REFRACTORY (R/R) LARGE B-CELL LYMPHOMA (LBCL)

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Background: More than one-third of patients with diffuse LBCL, the most common LBCL subtype, relapse after standard first-line therapy. Standard of care (SoC) in 2L R/R LBCL is salvage chemotherapy (CTx), followed by high-dose CTx (HDCT) and hematopoietic stem cell transplantation (HSCT) in eligible patients. However, only roughly 30% of R/R patients eventually proceed to HSCT. High-risk patients with early first-line relapse obtain only a limited survival advantage with HSCT.
Aims: We conducted an SLR to identify clinical evidence regarding the efficacy and safety of therapies used in the treatment of patients with 2L R/R LBCL, including transplant-eligible (TE) and transplant non-eligible (TNE) patients.
Methods: The Population, Intervention, Comparator, Outcome, and Study (PICOS) framework was used for the search strategy for identifying English-language publications from January 2003 to July 2020. Articles were searched in MEDLINE, Embase, and the Cochrane Library databases; abstracts were identified from key congresses (2017–2020). Selection criteria included (but were not limited to) 2L R/R LBCL, ≥25 participants per treatment arm or ≥50 per study, single- or multiagent chemotherapy or immunotherapy, chemoimmunotherapy, CAR T cell therapy, HSCT, and efficacy (overall response rate [ORR], overall survival [OS], and progression-free survival [PFS]).
Results: Of 3417 records screened, 68 were included (28 publications, 37 conference abstracts, and 3 trial records), representing 55 unique studies. Most were observational studies (n=36), followed by randomized controlled trials (n=8), single-arm trials (n=7), and nonrandomized controlled trials (n=4). Exclusions included studies that were preclinical, duplicates, or studies with incomplete data. The study populations included TE (n=15), TNE (n=9), and mixed/unspecified (n=31). Salvage CTx (with or without HSCT) was the most common treatment (n=42), followed by HSCT (n=3) and CAR T cell therapy (n=1); 6 observational studies had no specified treatment and 3 were prognostic. ORR with salvage CTx ranged from 37%–69% for TE patients (with an outlier reporting an ORR of 23% due to a high-risk population) and from 48%–74% for TNE patients. Interim efficacy data for a CAR T cell therapy in TNE patients were reported from one ongoing phase 2 trial: an ORR of 89% and a complete response rate of 56% were observed in 27 patients who received lisocabtagene maraleucel. Median OS was reported in 18 studies, ranging from 13.2–16.7 months in the intent-to-treat population of TE patients and 8.7–24.2 months in TNE patients. Median OS with HSCT in 3 studies ranged from 12.4–36.7 months.
Summary/Conclusion: Most studies in 2L LBCL explored salvage treatment regimens with intent of HDCT/HSCT follow-up treatment. Despite limited data, this SLR identified a lack of a clear SoC in TNE populations who have a dismal prognosis. Historically, ~30% of patients proceed to receive HSCT, indicating a critical need for effective therapeutic options that are more broadly accessible to all 2L patients, with a greater long-term benefit in high-risk subgroups.

EP1166 ERECTILE DYSFUNCTION (ED) IN PATIENTS WITH LIGHT-CHAIN AMYLOIDOSIS (AL): DIAGNOSIS AND CORRELATION WITH THE HEMATOLOGIC DISEASE.

C. Giordano [1,*], G. Cerciello [1], N. Pugliese [1], D. De Novellis [1], A. D'Ambrosio [1], A. Salemme [1], A. Vincenzi [1], F. Garifalos [2], R. Pivonello [2], M. Picardi [1], F. Pane [1]

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Background: AL is caused by the amyloid deposition of a misfolded protein responsible for organ damage. In men, ED can be an early disease related feature, but the real incidence and pathogenesis is not well established. ED can be psychogenic or organic.
Aims: Our aim is to investigate the incidence and evaluate the presence and possible causes of ED in male patients with AL.
Methods: All male adult patients with a confirmed diagnosis of AL attending the Haematology Department of Federico II University were enrolled in the study, from July to November 2020. Patients older than 70 years and/or with ECOG ≥ 2 were excluded. All patients underwent a diagnostic work up, comprehensive of hematologic and andrological assessments. Andrological assessment, performed by G.F and P.R, consisted in physical examination, power doppler ultra-sound (PDUS) evaluation and a structured questionnaire concerning sexual activity [International Index of Erectile Function (IIEF-15)]. Mayo clinic staging assessment was reported for all patients at diagnosis and enrolment (Table).
Results: A total of 13 patients were included (Table): five patients were enrolled at AL diagnosis ("treatment naïve") while eight patients were in follow-up after Bortezomib-based treatment ("Off-therapy"). In the latter group, hematologic complete response and Very Good Partial Response were observed in 5/8 and 3/8 patients, respectively (median 38 and 57 months, respectively); complete organ response was recorded in all patients. Assessments of hormonal dosages resulted within the reference limit for all patients and nobody resulted suffering from pathological depression according to our psychologist consultant (S.A). ED prevalence was 92.3% (12/13): 9 subjects with severe ED, 1 with moderate ED, and 2 with mild ED (the patient with localized AL was the only one not suffering from ED). The flowmetric indices showed a reduction of peak systolic value (PSV) in 76.9% of patients and a pathological acceleration (Acc) in 4/13. The population was analyzed based on both andrological and haematologic characteristics. Patients with pathological Acc showed a higher age (p=0.05) and worse scores at IIEF-TOT (p=0.006), at Desire Function (p=0.011), at Overall Satisfaction (p=0.034); patients with severe ED showed a higher age (p value = 0,003) and a pathological left Acc value (p value= 0,04); patients with mild ED and patient with normal erectile function (localized AL) showed normal right PSV (P value = 0,004) and normal left PSV (p value= 0,006) in comparison with patients with moderate and severe ED. Overall, no statistical difference was found for the two groups of patients: ED prevalence and ED stage was homogenous as the flowmetric characteristics. In the "off-therapy" group no differences were found according to hematologic response.

Table 1: Patients clinical and haematologic characteristics

	Treatment naive group (n=5)	Off-therapy group (n=8)	p value
Age, median (range)	53 (41-62)	61 (55-69)	0,49
Time from diagnosis, median (range)	5 days (2-8)	66 months (10-112)	
Characteristics at AL diagnosis			
Localized AL	1 (0,2)	0	
Lambda isotype	2 (0,4)	6 (0,75)	0,28
Monoclonal component g/l, median (range)	3 (4,1-12,3)	4 (3,5-7,2)	0,63
Dflc mg/l, median (range)	223,4 (2,7-560)	77,9 (0,32-248)	0,17
Cardiac involvement	4 (0,7)	5 (0,6)	0,21
Revised Mayo clinic stage III	1 (0,2)	2 (0,25)	
Revised Mayo clinic stage IV	3 (0,6)	3 (0,37)	0,47
Troponin (median, ng/l)	96 (10-100)	90 (20-420)	0,93
NT-ProBNP (median, ng/l)	6037 (80-9588)	4829 (80-29133)	0,92
Renal involvement	3 (0,6)	7 (0,87)	0,07
Proteinuria g/24h, median (range)	1474 (140-14250)	5169 (30-7193)	0,01
Neurological involvement	0	1 (0,12)	
Liver involvement	1 (0,2)	0	
Gastrointestinal involvement	0	1 (0,12)	
Number of organs involved			
1 organ	3 (0,6)	2 (0,25)	
2 organs	0	5 (0,6)	0,04
3 organs	2 (0,4)	1 (0,12)	

Values are n (%) unless otherwise specified

Summary/Conclusion: In our study a strong association between arterial inflow deficit, penile hemodynamic alteration, and ED was outlined. Having ruled out all possible causes for secondary ED, an arteriogenic cause, sustained by a possible cardiotoxic effect of extracellular light chain, was disclosed by the presence of early endothelial dysfunction in systemic AL patients independently of AL treatment received, time from AL diagnosis and organ involvement (the patient with localized AL was the only one not suffering from ED). A possible indication our study may provide is that any patient seeking medical advice for unexplained ED (common secondary ED causes ruled out) should undergo AL screening with QPE and FLC assay.

EP1167 COST-EFFECTIVENESS ANALYSIS OF AXICABTAGENE CILOLEUCEL VS TISAGENLECLEUCEL FOR THE MANAGEMENT OF DIFFUSE LARGE B-CELL LYMPHOMA IN SPAIN

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Background: Diffuse large B-cell lymphoma (DLBCL) represents approximately 30% of non-Hodgkin lymphomas, identified as one of its most common and aggressive forms. The recent inclusion of chimeric antigen receptor T-cell (CAR-T) treatments into the therapeutic scheme of DLBCL has been recognised as a change of paradigm in terms of survival and safety. Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are CAR-T therapies approved in Spain for the treatment of relapsed/refractory (R/R) DLBCL after ≥2 lines of systemic therapy in adult patients.
Aims: The aim of the study was to compare the cost-effectiveness of axi-cel vs tisa-cel for the treatment of adult patients with R/R DLBCL after ≥2 lines of systemic therapy, from the Spanish National Health System (NHS) perspective.
Methods: A lifetime partitioned survival mixture cure model, which comprises of pre-progression, post-progression, and death partitioned states, was used in the base case to estimate the accumulated costs and outcomes in terms of life years (LY) and quality-adjusted life years (QALY). Long-term survival with both therapies was estimated through a matching-adjusted indirect comparison (MAIC) that aligned the patient characteristics for the pivotal trials, fitting the patient-level data of ZUMA-1 trial for axi-cel to the aggregate-level data of JULIET trial for tisa-cel (Oluwole et al, Biol Blood Marrow Transplant, 2020). Utility values were extracted from EQ-5D data from ZUMA-1. The analysis was performed from the NHS perspective, thus only direct costs were included. Drug costs were estimated based on ex-factory prices with national mandatory deduction applied. Costs related to administration and monitoring of CAR-T therapy, apheresis, conditioning chemotherapy, disease management, stem cell transplant, hospitalisation and adverse events were derived from local cost databases and literature. A 3% annual discount rate was applied for costs and outcomes. Efficiency was expressed as incremental cost-effectiveness ratio (ICER; incremental cost vs effectiveness measured as LY), and incremental cost-utility ratio (ICUR; incremental cost vs effectiveness measured as QALY). One-way sensitivity analyses (OWSA) were carried out modifying discount rate, unitary costs, utilities, days of hospitalisation and simulating alternative scenarios such as naïve comparison without MAIC and partitioned survival model. A probabilistic sensitivity analysis (PSA) was also developed.
Results: In the base case, discounted results are as follows: axi-cel provides 9.45 LY and 7.47 QALY (7.24 in the pre-progression and 0.23 post-progression states), compared to 6.71 LY and 5.16 QALY (4.87 in pre-progression and 0.29 in post-progression) with tisa-cel. Thus, axi-cel generates 2.31 incremental QALY with an additional cost of €30,135 vs tisa-cel. The higher costs with axi-cel are mainly attributed to a longer progression-free survival, implying higher disease management costs in the pre-progression state. Hence, the ICER and ICUR are €10,999/LY and €13,049/QALY, respectively. OWSA and alternative scenario analyses show that the results are robust. The most influential parameters are the utility in the pre-progression state and the naïve comparison without MAIC. In the PSA, ICUR is ≤€22,000/QALY and ≤€60,000/QALY in 92.3% and 99.2% of the iterations, respectively.
Summary/Conclusion: Considering the frequently assumed willingness-to-pay thresholds in Spain, axi-cel is likely to be a cost-effective treatment vs tisa-cel for adult patients with R/R DLBCL in Spain.

EP1168 IMPLEMENTATION OF A HOSPITAL-AT-HOME (HAH) UNIT FOR HEMATOLOGICAL PATIENTS DURING THE COVID-19 PANDEMIC: SAFENESS AND FEASIBILITY.

I. Gómez-Centurión [1,2,*], G. Oarbeascoa [1,2], M. C. Garcia [2,3], M. C. López Fresneña [2,3], M. J. Martínez Carreño [2,3], V. Escudero Vilaplana [2,4], E. González-Haba [2,4], R. Bailén [1,2], N. Dorado [1,2], L. M. Juárez [1,2], G. Rodríguez Macías [1,2], P. Font López [1,2], C. Encinas [1,2], M. Bastos Oreiro [1,2], J. Anguita [1,2], A. Herranz [2,4], J. L. Díez-Martin [1,2], M. Kwon [1,2]

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Background: COVID-19 fatality can be as high as 30% in patients with hematological malignancies and hematopoietic stem cell transplant (HSCT) recipients.
Hospital-at-home (HAH) programs have significantly spread out in the last years and have demonstrated to improve patients satisfaction, avoid unnecessary hospital admissions and reduce healthcare costs.
Aims: To describe the implementation of an HAH unit for patients with hematological malignancies and HSCT recipients during the COVID-19 pandemic.
Methods: We retrospectively analysed the implementation of an HAH unit for caring hematological patients in our centre. In January 2020, we started our HAH unit, initially created for specific programs: at-home autologous HSCT for patients with multiple myeloma (MM), at-home consolidation treatment for patients with acute leukemia and intravenous treatment delivery. During March and April, simultaneously with the highest peak of the pandemic, the program expanded to other areas as part of our department strategy to ensure safe and high quality care for our patients. Besides, prevention measures were adopted to avoid cross-infection between patients and nurses.
At-home episode was defined as any time a patient was included in the HAH unit for a specific program previously described until patient was discharged.
Results: One hundred and five patients were included in the HAH unit between January 2020 and November 2020, with a total of 204 at-home episodes (Table 1). Nine at-home autologous HSCT were performed in 8 patients with MM (1 patient received a tandem transplant). All patients were discharged the day after infusion, except one with persistent vomiting, later discharged on day +5. Engraftment was achieved in a median time of 17 days (range 14-29) after transplant. Febrile neutropenia and engraftment syndrome rate was 0%.
Three patients were included in the at-home consolidation treatment program: 2 patients with AML and 1 with high-risk acute promyelocytic leukemia (APL). They were discharged from the hematology ward the day after cytarabine was fully administered.
Clinical and analytical monitoring or electrolyte replacement was performed at home in 32 patients (43 episodes). Five of these patients were autologous recipients who were discharged from HSCT unit before achieving engraftment, 15 were allogeneic HSCT recipients and 2 had received CAR-T cells therapy.
Azacitidine was administered at home to 22 patients (83 episodes), bortezomib to 22 patients (34 episodes) and carfilzomib to 8 patients (12 episodes).
Other episodes are described in Table 1.
Overall, more than 1000 visits were made to patients homes by nurses from the HAH unit, a median of 17 (IQR 13-19) days of admission per patient and a total of 239 visits to the hematology day-care hospital were avoided.
In summary, 28 patients (14% of all episodes) needed admission to the hospital while being treated by HAH unit, 4 of them because of SARS-CoV-2 related pneumonia. None of the nurses from the HAH unit

developed SARS-CoV-2 infection while being actively caring patients at home, thus cross-transmission was discarded.

Table 1. Main characteristics of patients and at-home episodes.

Patients, n	105
Episodes, n	204
Median age, years (range)	63 (20-92)
Female, n (%)	50 (47%)
Diagnosis, n (%)	
MM	35 (33%)
AML	27 (26%)
NHL	16 (15%)
MDS	15 (14%)
ALL	5 (5%)
Others	7 (7%)
Program, episodes (%)	
Admission avoidance programs	
At home autologous HSCT	9 (5%)
At home consolidation in acute leukemia	3 (1.5%)
Monitoring and electrolyte replacement (early discharge)	43 (21%)
Antimicrobial drugs delivery	16 (8%)
Venetoclax dose ramp-up	4 (2%)
Day-hospital avoidance programs	
Azacitidine	83 (40%)
Bortezomib	34 (16.5%)
Carfilzomib	12 (6%)
Re-admissions, n (%)	
SARS-CoV-2 related pneumonia	4 (2%)
Other causes	24 (12%)

Summary/Conclusion: Implementation of a hematology HAH unit was feasible, safe and provided a thorough advanced care to a high risk population. Admissions and visits to day hospital were significantly reduced and SARS-CoV-2 infection rate was low and probably not related to cross-transmission between patients and nurses from the unit. In our experience, the use of advanced care at-home resulted crucial during times of COVID-19 to minimize treatment interruptions and reduce the risk of cross-infections.

EP1169 USE OF CHIMERIC ANTIGEN RECEPTOR T CELL THERAPIES IN PATIENTS WITH LARGE B-CELL LYMPHOMA IN THE REAL-WORLD SETTING: SYSTEMATIC LITERATURE REVIEW

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Background: Use of chimeric antigen receptor (CAR) T cell therapies for relapsed/refractory (R/R) large B-cell lymphoma (LBCL) was first approved by the United States (US) Food and Drug Administration in 2017 (with lisocabtagene maraleucel approved in 2021) and by the European Medicines Agency in 2018. A growing body of evidence has been published recently on the effectiveness and safety of CAR T cell therapies in the real-world (RW) clinical setting. The landscape of this evidence is of particular interest to clinicians and researchers.
Aims: This systematic literature review was designed to identify and characterize the effectiveness, safety, and quality of life (QOL) of tisagenlecleucel and axicabtagene ciloleucel (axi-cel) in the treatment of R/R LBCL in the RW setting.
Methods: Study eligibility criteria were defined using the PICO (Population, Intervention, Comparators, and Outcomes) framework. Embase, MEDLINE, and relevant conference proceedings were searched from database inception to November 23, 2020. Interventional or observational studies with RW data on specific survival, response, safety, and QOL outcomes in patients with LBCL treated with tisagenlecleucel and axi-cel were included. Study quality was assessed using the Newcastle-Ottawa Scale for non-randomized studies.
Results: After study selection, 68 publications pertaining to 67 unique studies were included, comprising 21 full-text articles and 46 conference abstracts. The majority of the studies were conducted in the US (n=49), followed by the United Kingdom (n=6), Germany (n=6), France (n=4), Spain (n=1), and the US and Canada (n=1). Fifty-two (78%) studies had a sample size of <100 patients. Ten (15%) studies had >1-year follow-up, 37 (55%) had ≤6-month follow-up. Median age ranged from 50–72 years, with median or mean prior lines of therapy ranging from 3–5. Diffuse LBCL (de novo) was the most common disease histology. Use of bridging therapy varied widely from 2%–98% where reported (17 studies). Overall response rates and complete response rates ranged from 32%–84% and 12%–80%, respectively, at 3 months. Median progression-free survival (PFS) ranged from 0.8–13.8 months; median overall survival (OS) ranged from 7.9–35.0 months. PFS at 6 and 12 months ranged from 29%–60% and 20%–47%, respectively; OS ranged from 50%–100% and 56%–80%, respectively. Cytokine release syndrome (CRS) and neurological events (NEs) were reported in 49 (72%) and 47 (69%) studies, respectively. While synthesis of CRS and NE rates was limited by differences in data collection between studies, the reported rates of grade ≥3 CRS and NEs ranged from 0%–43% and 3%–41%, respectively. Only 1 study of 29 patients reported QOL outcomes (Short Form-36 QOL questionnaire), in which authors observed nonsignificant (P > .05) improvements from baseline to 90 days post-treatment with axi-cel in both the physical health and mental health components.
Summary/Conclusion: The RW evidence on the effectiveness and safety of commercially available CAR T cell therapies is growing, and a large number of observational studies on axi-cel and tisagenlecleucel in LBCL have been conducted, particularly those investigating axi-cel. The RW evidence suggests CAR T cell therapy is generally effective, based on survival and response outcomes, and safety is similar to that of clinical trials. Additionally, data on QOL are severely limited. Future prospective RW studies with large populations and incorporation of patient-reported outcomes are warranted.

EP1170 OUR EXPERIENCE OF NEGATIVE SYNERGISM BETWEEN STEROIDS AND LMWH IN PATIENTS WITH AGGRESSIVE LNH ON SKELETAL EVENTS (BONE FRACTURES)

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Background: Low molecular weight heparins (LMWH) are widely used in thrombosis prophylaxis in treated lymphoma patients with central peripheral venous device (PVD). The negative effect of heparin on osteogenesis is known, it is not clear how anticoagulants vit K inhibitors act while the role of LMWH is controversial. The negative effect of steroids on osteogenesis is also documented but there are no data on negative synergy related to the simultaneous intake of steroids and LMWH.
Aims: The aim of our study is to evaluate the bone events (bone fractures) observed retrospectively in a consecutive cohort of lymphoma patients treated with chemotherapy (with or without steroids) from January 2014 to January 2021 with at least 6 months of follow-up.
Methods: From January 2014 to January 2021 we observed 197 patients with a median follow-up of 38 months (range 6-85 months); 90 with aggressive NHL treated with CHOP or similar 34 f and 56 m with a median age of 59 years (range 23-77 years); 53 with indolent NHL treated with bendamustine based therapy; 23 f and 30 m with median age of 65 years (range 42-81 years) and 54 with HD treated with ABVD or similar; 26 f and 28 m with a median age of 34 years (range 16-75 years). All patients with PVD and all treated in prophylaxis with LMWH (enoxaparin or nadroparin) 4000 U / day.
Results: In the NHL group treated with steroids and LMWH the observed bone events (fractures) were 13/90 patients (14.5%), 6 M and 7 F with a mean age of 63 years (range 39-73 years) all patients had vertebral involvement, while in 2 patients, in addition to the vertebral, with the femur involvement were documented. In the NHL group treated with LMWH but non-steroids, the observed bone events were 3/53 patients (5.5%) all female with a mean age of 66 years, while in the HD group it was 2/54 patients (3.8%) all females with a mean age of 72 years, all with vertebral involvement only.
Summary/Conclusion: These data show a higher incidence of bone events in patients receiving steroid and LMWH therapy. This evidence suggests a negative synergism between the association of steroids and

LMWH on bone metabolism and also probably confirms that vitamin D metabolism in patients with aggressive NHL may be implicated in the prognosis of these lymphomas.
This evidence suggests the need to integrate vit D with or without calcifying into the therapy of patients with aggressive NHL and to evaluate the possibility of proposing prophylaxis for thrombosis not with LMWH but with the new oral anticoagulants.
A prospective study is needed which also includes the study of calcium metabolism and bone mineralization both at diagnosis and over time in the various subtypes of NHL and which supportive treatments they have received.

EP1171 LANDSCAPE REVIEW OF THE PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE) IN ONCOLOGY: ADOPTION AND RECENT LEARNINGS

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Background: The PRO-CTCAE is a patient-reported outcome measure of symptomatic toxicity in oncology trials designed to complement CTCAE criteria (clinician's measure of adverse events [AEs]). Items for evaluation are selected from 78 symptomatic toxicities in the CTCAE. PRO-CTCAE uptake and use has not been uniformly assessed; understanding how to best analyze and present PRO-CTCAE data is important.
Aims: We reviewed literature on clinical trials reporting the PRO-CTCAE to ascertain its use and current analytical methods to inform future analyses.
Methods: A review of the literature and ongoing oncology trials using PubMed, oncology and outcomes research conferences (ASCO, ASH, ISOQOL, ISPOR), and ClinicalTrials.gov was completed August 2019; updated November 2020. Selected literature included guidance on: item selection; analytical methods; PRO-CTCAE data/endpoint use in clinical trials. Analytical and visualization methods from the literature were used to inform the specification of PRO-CTCAE analyses conducted on data from the DREAMM-2 (NCT03525678) trial of single-agent belantamab mafodotin (belamaf), a B-cell maturation antigen–binding antibody–drug conjugate, in relapsed/refractory multiple myeloma.
Results: After screening (n=197), 45 articles were reviewed: 13 related to recommendations for use/analysis, 7 to item selection, and 25 to examples of PRO-CTCAE use. 118 completed/ongoing trials reported PRO-CTCAE use (17 [14%] Phase I or I/II; 73 [62%] Phase II, II/III, or III; 3 [3%] Phase IV; 25 had no phase reported). Most (92/118, 78%) trials included the PRO-CTCAE as a secondary endpoint. The number of trials using the PRO-CTCAE increased from 3 in 2015 to 30 in 2020. PRO-CTCAE data in the literature were reported descriptively using tables (maximum post-baseline ratings; mean change over time; ratings higher than a predefined cutoff) and graphs (line graphs; stacked bar charts; heatmaps). These and more sophisticated analyses were applied to DREAMM-2 data to best capture the dynamics of patient-reported AEs over time, or control for baseline PRO-CTCAE ratings (eg, Toxicity over Time approach; ordinal log-linear models).
Summary/Conclusion: The importance of tolerability and symptomatic AEs for patients is increasingly recognized, particularly for new therapies. This landscape review demonstrates recent growth in interest and adoption of PRO-CTCAE. There are few existing standards for analysis; this research increases understanding of existing methods and further evaluates ways of analyzing and presenting PRO-CTCAE data over time. Additional research exploring innovative methods to analyze PRO-CTCAE data and address its challenges is needed.
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Encore statement: ©2021 American Society of Clinical Oncology, Inc. Reused with permission. All rights reserved. This abstract was previously submitted to the American Society of Clinical Oncology (ASCO) Annual Meeting, June 4–8, 2021, and is submitted on behalf of the original authors with their permission.

EP1172 THE PSYCHOSOCIAL IMPACT OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION ON ADULT PATIENTS WITH LYMPHOMA, LEUKAEMIA OR MYELODYSPLASTIC SYNDROMES – A LITERATURE REVIEW

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Background: Haematopoietic stem cell transplantation (HSCT) using multipotent haematopoietic stem cells from either the patient (autologous) or a donor (allogeneic) is often the only potentially curative treatment for haematological malignancies such as lymphoma, leukaemia and myelodysplastic syndromes. In addition to the physical effects exerted by the transplantation procedure and the underlying disease, HSCT may have a psychosocial impact on patients, families and carers.
Aims: To identify the areas of psychosocial impact experienced and reported by adult patients with lymphoma, leukaemia or myelodysplastic syndromes who have undergone HSCT.
Methods: A targeted literature search was conducted to identify relevant research published between 1 January 2009 and 30 January 2021 by searching CINAHL, EMBASE, IPA, MEDLINE, and PsycINFO using combinations of search terms referring to HSCT, the disease areas of interest, and phrases related to psychosocial impact (e.g. patient experience). Abstracts and full text articles were screened for relevance by two independent researchers, and the PRISMA statement was followed for this literature review.
Results: Our search retrieved 868 unique records; 826 records were excluded through abstract and full-text screening. The 42 remaining articles were deemed relevant and included in our analysis. Using meta-ethnography, a method for synthesising qualitative research and interpreting findings across multiple studies, we identified three key themes ("feelings about transplantation", "changes in psychosocial functioning after transplantation", "coping") and eight associated categories that describe the impact of HSCT. Among these categories, psychological distress was most frequently discussed, suggesting it contributes considerably to the psychosocial burden. This category includes issues such as anxiety that can be experienced by both patients and caregivers, occurring with greater intensity at certain stages of the treatment journey and potentially lasting for years post-transplantation. Altered relationships was the second most discussed category, when patients are being drawn nearer to or pushed away from others. Expectations of survivorship and lack of preparedness was the next most discussed category, where patients are confronted with the reality of life after transplantation, as they often experience persistent health effects and do not return to their lives pre-diagnosis as hoped.
Summary/Conclusion: HSCT exerts a considerable psychosocial impact on patients, their families and carers. Psychological distress – the most frequently mentioned experience – is not restricted to the period of transplantation but can persist for many years after transplantation. Patients feel unprepared for the journey ahead of them and are required to make significant adjustments at the survivorship stage. Furthering our understanding of this burden might contribute to improved patient support systems, and knowledge of both the psychosocial and physical burden of HSCT could potentially enable patients to make more informed treatment decisions when comparing transplantation with other treatment options.

EP1173 COST EFFECTIVENESS COMPARISON OF BELANTAMAB MAFODOTIN AND SELINEXOR IN RELAPSED REFRACTORY MULTIPLE MYELOMA

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Background: Highly effective drugs have significantly affected the outcomes of multiple myeloma, with a five-year survival improving from

34.6 % in 1998 to 53.9% in 2016. Since 2009 alone, more than a dozen new treatments have been approved by FDA continuing to improve quantity and quality of life in pts with MM. However, these drugs come at a huge financial cost and cost effectiveness analysis is commonly used tool to study economic impact of novel treatments.
Aims: Multiple drugs are being developed and approved for R/R Multiple Myeloma that has been treated with Immunomodulatory drugs, Proteasome Inhibitor and anti-CD38 monoclonal antibody (TCE). We aim to study economic evidence for FDA approved therapies in TCE Multiple Myeloma
Methods: Using survival probabilities by three response groups (partial or complete response; stable disease; and progressive disease) from clinical trials for Selinexor (STORM) and Belantamab mafodotin (DREAMM-2), we estimated incremental cost effectiveness ratios from a healthcare sector perspective comparing the two treatments. We modeled 12-month treatment and severe adverse effects costs, life-years gained, and an incremental cost-effectiveness ratio among a hypothetical cohort of adults age 40 to 80 using a Markov model.
Results: The expected value of the 12-month treatment costs per life gained were $251,211 and $239,749 for Selinexor and Belantamab, respectively. Extrapolating response rates for the hypothetical cohort over a longer period suggested Selinexor treatment costs $96,170 per discounted quality-adjusted life-year (QALY) and Belantamab costs $89,521 per discounted QALY.
Summary/Conclusion: Outcomes for patients with TCE Myeloma is poor with limited therapeutic options and carry a significant cost burden. With scientific advances, we are at verge of paradigm shift with anticipated regulatory approval of therapeutic options agents like novel alkylating agents, newer immunomodulatory drugs, CAR T-cell and Bispecific Antibodies. Our study is the first to provide critically required economical perspective in choosing appropriate agents in TCE Multiple Myeloma.

EP1174 COST-EFFECTIVENESS OF ZANUBRUTINIB VERSUS IBRUTINIB IN ADULT PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

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Background: The efficacy of zanubrutinib and ibrutinib was examined in the randomized ASPEN trial (NCT03053440) in adult patients with Waldenström macroglobulinemia (WM).
Aims: This analysis aimed to assess the cost-effectiveness of zanubrutinib versus ibrutinib in this population from a US payer perspective.
Methods: A 3-state (pre-progression, post-progression, and death) partitioned survival model was used to estimate the life years (LYs), quality-adjusted life years (QALYs), and costs for each treatment over a 30-year lifetime horizon. Overall survival (OS), progression-free survival (PFS), and time-to-discontinuation (TTD) curves were fitted using parametric distributions to extrapolate long-term outcomes. Selection of the parametric models for each outcome and treatment was based on assessments of 1) the proportional hazard assumption, 2) goodness-of-fit, and 3) clinical plausibility of extrapolated mean OS and associated hazard patterns (based on literature and US clinical expert input) and the alignment between PFS and TTD. Background US mortality was accounted for in the model. Utilities were based on the ASPEN EQ-5D data and literature. Costs (2020 US$) included drug (wholesale acquisition cost from RED BOOK) and adverse event management (Healthcare Cost and Utilization Project) for zanubrutinib and ibrutinib, routine care, and terminal care. Sensitivity analyses were conducted to evaluate the impact of parameter uncertainty. All outcomes were discounted at 3% annually.
Results: In the base case analyses using the dependent exponential model for all outcomes over a 30-year time horizon, zanubrutinib led to 0.94 LY and 0.84 QALY gained with an additional total cost of $11,132. This additional cost was primarily driven by patients staying on zanubrutinib treatment longer as zanubrutinib has longer time to treatment failure. However, this is partially offset by zanubrutinib's lower monthly drug acquisition, reduced cost of routine care (–$2,935) and terminal care (–$2,964) than ibrutinib. The incremental cost-effectiveness ratio (ICER) of zanubrutinib was $13,205 per QALY gained. The deterministic sensitivity analyses showed that ICER was most sensitive to the monthly costs of routine care. The probabilistic sensitivity analyses showed that the mean probabilistic ICER was $16,804, and that the probability of zanubrutinib being cost-effective was 61% at a willingness-to-pay threshold of $100,000 per QALY gained. Varying the time horizon to 5, 10, or 15 years consistently led to zanubrutinib being dominant (i.e., greater QALYs but lower costs).

CE results

	Zanubrutinib	Ibrutinib	Incremental
LY	11.33	10.39	0.94
QALY	8.75	7.90	0.84
Costs	$1,547,630	$1,536,498	$11,132
Cost/LY gained	-	-	$13,205
Cost/QALY gained	-	-	$11,806

Summary/Conclusion: Zanubrutinib appears to be cost-effective compared with ibrutinib for the treatment of patients with WM in the US.

EP1175 QUANTIFYING PATIENT PREFERENCES FOR TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA: A DISCRETE-CHOICE EXPERIMENT

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Background: Currently available second and third generation tyrosine kinase inhibitors (TKIs), offer a variety of treatment options for chronic-phase chronic myeloid leukemia (CP-CML) patients and prescribing physicians. Indirect comparisons suggest the efficacy of these TKIs are similar, however each have distinct dosing requirements and safety profiles. Patient preferences for TKI dosing and safety have yet to be quantified, but are valuable for optimizing healthcare decisions and outcomes.
Aims: The aim of this study was to quantify CP-CML patient preferences and perspectives regarding treatment attributes for TKI therapies.
Methods: US-based patients (N=200) with self-reported CP-CML completed an online discrete choice experiment. Choice tasks were based on key treatment attributes: 1) dosing requirements (number of tablets and consumption with/without food), and incidence of 2) nausea, 3) fatigue, 4) pain in muscles and/or joints, 5) diarrhea, 6) blockage to a major blood vessel and 7) pleural effusion. Attributes were identified from the published literature, approved TKI labels, qualitative interviews with CML patients (N=12) and consultation with clinical experts. Hierarchical Bayesian estimation was used to calculate part-worth utilities to estimate relative importance (RI) and category-level preference of each attribute. Latent class analysis investigated preference patterns among patients.
Results: The sample included 149 females and 51 males (median age 54 years). Patients had been diagnosed for <1 year (n=31), 1-5 years (n=74), >5-10 years (n=47) and >10 years (n=48). Current treatments included dasatinib (n=62), imatinib (n=61), nilotinib (n=43), bosutinib (n=16) and ponatinib (n=1). Blockage to a major blood vessel emerged with the highest RI: 34%. RI of remaining attributes were comparable: pleural effusion (12%); fatigue (12%); pain in muscles and/or joints (11%); dosing requirements (11%); diarrhea (10%); nausea (9%). Similar findings were observed in demographic (gender, age) and clinical characteristic (time since diagnosis, current TKI) subgroups. Evaluation of mean part-worth utilities for individual attribute levels indicated preference for once daily dosing compared with twice daily dosing on an empty stomach. Lower incidences of diarrhea (20% vs 85%) were preferred, but duration of diarrhea (1-5 days vs 10+ days) had limited impact on preferences. Latent class analysis identified a number of distinct groups of participants which varied with respect to those attributes driving preferences in each group. Blockage to a major blood vessel was important in all groups, but was not always the most important attribute.

Summary/Conclusion: The likelihood of experiencing serious adverse events (blockage to a major blood vessel) was a key driver of CP-CML treatment preferences. However, heterogeneity in treatment preference patterns highlight the importance of discussions regarding dosing and treatment toxicities for optimizing individual treatment decisions.

EP1176 A NEW OPTION IN PAIN PREVENTION WITH BLISS©, A THERAPEUTIC VIRTUAL REALITY SOLUTION IN BONE MARROW CONTEXT: RESULTS OF A FRENCH OPEN-LABEL MULTICENTER RANDOMIZED PHASE II/III STUDY (REVEH TRIAL)

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Background: The prevention of care-induced pain is a central concern for all healthcare teams in hematology units. Use of MEOPA (Oxygen + Nitrous Oxide) is today a standard of care for relaxation procedure. Distraction through immersion in virtual reality (VR) has already documented its analgesic effects in several phase II trials but comparison with standard treatments in a large randomized study is needed.
Aims: We assessed the safety and efficacy of a new therapeutic virtual reality solution for pain distraction, Bliss©, in prevention of pain and anxiety before performing a bone marrow biopsy.
Methods: We conducted an open-label multicenter randomized phase II/III trial (ClinicalTrials.gov identifier: NCT03483194) in 5 sites in France. Bliss© is a VR software with four imaginary interactive environments in three dimensions. Binaural sound and specific music programs were created to promote immersion and relaxation. The program runs on a smartphone and a GearVR head-mounted display. Efficacy was evaluated by pain intensity with visual analog scale (score from 0 to 10) just after the biopsy and anxiety by 2 questionnaires (fear of pain before the biopsy and revised STAI questionnaire before and after the biopsy). The primary end point was patient-assessed pain intensity after the bone marrow procedure. Statistical analysis was performed with modified intention to treat (Fisher test).
Results: A total of 126 patients were enrolled with previously untreated malignant hemopathy or suspected between September 6, 2018 and May 18, 2020. They were randomly assigned in a 1:1 ratio to receive pain prevention with MEOPA (n=63) or Bliss© (n=63) before and during their bone marrow biopsy. All patients received a local anesthesia with lidocaïne before the biopsy. In addition, patients, nurses and physicians performed efficacy and safety measures during a 1-month follow-up assessment.
Median age of the study population was 65.5 years old (range 18 to 87) and 54.2% were men. The average pain intensity was 3.5 (standard deviation 2.6) for the MEOPA group and 3.0 (SD 2.4) for the VR group (p=0.26), without any significant difference according to age, gender or hemopathy. Concerning anxiety, 67.5% of patients were afraid before the biopsy and anxiety scores were moderate to very high in 26.3% of patients before the biopsy (STAI questionnaire) and 9.0% after the biopsy for all patients without any significant difference between the 2 groups (17.3% of reduction in anxiety for the MEOPA group and 17.2% for the VR group, p=0,83). Immersion in VR was well tolerated in 100% of patients included in the VR group. Physicans were very satisfied by the relaxation procedure in 64.9% of cases (52.5% in the MEOPA group and 77.6% in the VR group, p=0,01) and recommended re-use of the technique in 54.2% in the MEOPA group and 79.1% in the VR group (p=0,02).



Summary/Conclusion: The intensity of pain did not significantly differ in both arms. Bliss©-based relaxation method was well tolerated and the satisfaction of patients and physicians was very high in VR group. This study validates the use of immersion in VR with Bliss© as a new digital therapeutics and support the integration of the software in the panel of supportive care.

EP1177 A CROSS-SECTIONAL STUDY EXAMINING THE IMPACT OF AGEING ON THE PSYCHOSOCIAL EXPERIENCES OF PATIENTS WITH LYMPHOMA

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Background: Patients with lymphoma face various emotional consequences as a result of their diagnosis and treatment. Progress in providing high-quality care for the psychosocial impacts of lymphoma has not matched the advances in lymphoma detection and treatment. Patients in different life stages may experience different psychosocial issues or varying intensities of psychosocial issues because of their lymphoma.
Aims: Using data from the Lymphoma Coalition (LC) 2020 Global Patient Survey (GPS) on Lymphomas and CLL, this study examines the impact of ageing on the psychosocial experiences of patients with lymphoma.
Methods: Globally, 11,878 respondents including 9,179 patients and 2,699 caregivers took part in the LC 2020 GPS. There were 9,078 patients included in this analysis who self-identified their age. These patients were grouped into five age groups for analysis: 18-29 (n=638), 30-39 (n=1,196), 40-59 (n=3,261), 60-69 (n=2,216), and 70+ (n=1,767). Demographics of the five age groups were examined, and descriptive analyses for all questions relating to psychosocial issues were performed in IBM SPSS v27.
Results: The five age groups differed significantly ($p< 0.001$) in all the demographic categories examined. These categories included lymphoma subtype, sex, area of residence, education level, employment status, and household status.
Patients were asked which psychosocial issues they had experienced over the last 12 months because of their lymphoma diagnosis. The oldest age group (70+) reported the lowest prevalence of every psychosocial issue listed (table 1). The oldest age group (70+) also reported the highest prevalence of experiencing no psychosocial issues ('none')(39%). In all cases, each psychosocial issue was most prevalent in the youngest age groups (18-29 and 30-39), with prevalence decreasing with increasing age (table 1).
Patients who reported experiencing symptoms of lymphoma/CLL were asked how these symptoms impacted their life, including everyday activities, employment, social life, and relationships (table 1). The lowest prevalence for each of these impact categories was observed in the oldest age group (70+) (table 1). The highest prevalence for each category, except for social life, was observed in the youngest age group (18-29) (table 1).
Patients who reported experiencing treatment-related side effects were asked how these side effects impacted their life, including everyday activities, employment, social life, and relationships (table 1). The lowest prevalence for each of these impact categories was observed in the oldest age group (70+) (table 1). In all cases, the greatest prevalence of each

impact was observed in the youngest age groups (18-29 and 30-39), with the prevalence of each issue decreasing with increasing age (table 1).

Table 1. Quality of life issues that patients with lymphoma reported experiencing due to their disease and treatment by age group

	Prevalence of issues by age group					
Psychosocial issues experienced in the last 12 months	18-29 %	30-39 %	40-59 %	60-69 %	70+ %	X^2 (p-value)
Loss of self-esteem	43	38	25	14	7	578.10 (p< 0.001)
Concerns about body image	51	45	28	20	14	497.18 (p< 0.001)
Changes in relationships	34	30	19	11	8	379.57 (p< 0.001)
Isolation	29	24	20	15	10	156.86 (p< 0.001)
Depression	48	39	33	24	17	298.96 (p< 0.001)
Anxiety	51	51	37	24	14	559.45 (p< 0.001)
Fear of cancer relapse	68	69	56	41	29	474.69 (p< 0.001)
Fear of lymphoma progression	39	42	41	41	31	49.60 (p< 0.001)
None	9	9	15	24	39	512.98 (p< 0.001)
How lymphoma/CLL symptoms affected day-to-day life (those who strongly agree or agree)	18-29 %	30-39 %	40-59 %	60-69 %	70+ %	X^2 (p-value)*
Negative impact on everyday activities	60	53	56	53	47	146.49 (p< 0.001)
Unable to work/change job or working pattern	50	49	48	38	18	632.39 (p< 0.001)
Negative impact on social life	50	49	51	43	33	254.50 (p< 0.001)
Created problems with partner, friends, relatives	44	43	37	23	14	574.02 (p< 0.001)
How treatment-related side effects affected day-to-day life (those who strongly agree or agree)	18-29 %	30-39 %	40-59 %	60-69 %	70+ %	X^2 (p-value)*
Negative impact on everday activities	68	66	63	56	49	212.17 (p< 0.001)
Unable to work/change job or working pattern	59	57	53	38	16	781.49 (p< 0.001)
Negative impact on social life	59	61	54	45	34	353.27 (p< 0.001)
Created problems with partner, friends, relatives	43	45	34	21	13	537.56 (p< 0.001)

*Chi square values calculated based on the inclusion of all question response options, though only the percentages for those who strongly agree or agree are displayed in the table.

Summary/Conclusion: This analysis revealed that compared to the mid to oldest patient groups, younger patients with lymphoma are disproportionately affected by psychosocial issues resulting from their disease and treatment. These psychosocial issues can negatively impact quality of life. Psychosocial assessment and intervention should be high priority for all patients with lymphoma; however, younger patients may require additional attention and support. In the future, LC would like to explore how demographic differences may have confounded results.

EP1178 TARGETED LANDSCAPE REVIEW FOR UNDERSTANDING LYMPHOMA PATIENT-REPORTED OUTCOME ASSESSMENT IN THE ERA OF EMERGING THERAPIES

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Background: The lymphoma treatment landscape is changing with the introduction of chimeric antigen receptor (CAR) T cell therapies and there is a need to better understand the patient experience. During development of new therapies, patient-reported outcome measures (PROMs) provide useful information on clinical outcomes from the patient perspective. A targeted landscape review of data from published literature, clinical trial databases, and health technology assessment (HTA) reviews is a traditionally required step to identify appropriate PROMs to inform clinical development programs of new treatment options.

Aims: This landscape review aimed to identify and summarize evidence on the use of PROMs in lymphoma based on publicly available literature, product labels for medications approved by the United States Food and Drug Administration and/or the European Medicines Agency (EMA) for the treatment of lymphoma, and existing HTA information (eg, clinical effectiveness, safety, patient and social aspects) for lymphoma.

Methods: We conducted a targeted literature search using the Ovid platform and clinical trial registries from 2009–2020. English-language titles, abstracts, and clinical trial outcome measure descriptions that focused on lymphoma were reviewed, and those that mentioned the use of a PROM were deemed eligible for inclusion. Product labels were reviewed for 7 medications approved for the treatment of adult lymphoma (ie, brentuximab vedotin, lenalidomide, idelalisib, axicabtagene ciloleucel, tisagenlecleucel, pembrolizumab, pixantrone), and a review of HTA reports was carried out for non-Hodgkin lymphoma indications in 9 countries and regions over the last 5 years.

Results: A total of 1683 articles and conference abstracts were identified and screened from the Ovid platform, of which 78 were considered eligible for inclusion. In addition, 1541 clinical trials were identified and reviewed, of which 129 reported PROM use. Among literature included, a total of 67 different PROMs were identified. The most used PROMs were Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – 30 items (EORTC QLQ-C30), and EQ-5D (See Table). The most frequently cited PROMs evaluated fatigue, pain, sleep, dermatological symptoms, and neurotoxicity. Out of 7 medications approved for adult lymphoma, brentuximab vedotin was the only one that included PROMs in its EMA labeling (EORTC QLQ-C30, EQ-5D, FACT-General); however, no clinically meaningful difference between treatment arms was reported. According to the HTA review of the 7 medications, the FACT-Lym, 36-Item Short Form Health Survey (SF-36), and Skindex-29 were all consistently accepted as relevant, validated measures to capture PRO assessments for lymphoma indications. However, treatment benefit reported by PRO data was limited by an absence of comparative data, exploratory analyses, low number of patients, and a short length of follow-up.

Table. Frequency of use of PROMs in publications and clinical trials.

Measure	No. of times found in the literature	
	Publications	EU and US clinical trials
FACT-Lym	13 (1 CAR T cell therapy)	41 (2 CAR T cell therapy)
EORTC-QLQ-C30	19 (0 CAR T cell therapy)	77 (6 CAR T cell therapy)
EQ-5D	19 (0 CAR T cell therapy)	54 (5 CAR T cell therapy)

Summary/Conclusion: A multitude of PROMs have been employed in assessing patient burden in lymphoma. Health authorities and HTA centers recognize sensitive, validated, and reliable PROMs that report on lymphoma-specific symptom burden and patients' health-related quality of life and well-being as critical for assessing treatment benefit and interpreting patient burden. With appropriate study design and robust PRO data collection (eg, comparative data, validated instruments), PROMs should be considered in assessing patients' quality of life for emerging lymphoma therapies.

EP1179 CLINICALLY IMPORTANT CHANGE IN FACIT-FATIGUE SCORE FOR PATIENTS WITH COLD AGGLUTININ DISEASE: AN ANALYSIS USING THE PHASE 3 CARDINAL AND CADENZA STUDIES

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Background: Sutimlimab (formerly BIVV009) is a humanized monoclonal anti-C1s antibody with a clinical trial program to support its development as a treatment for cold agglutinin disease (CAD). CARDINAL (NCT03347396) and CADENZA (NCT03347422) are Phase 3 clinical trials for sutimlimab in patients with CAD. As fatigue is one of the most common symptoms of CAD (Su et al. ASH 2020; 2484), one of the secondary aims of CARDINAL and CADENZA was to examine treatment-related change in fatigue using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue outcome measure.

Aims: To estimate the clinically important change (CIC) for FACIT-Fatigue in patients with CAD using pooled data from CARDINAL and CADENZA. The CIC reflects the smallest score change that indicates a meaningful treatment benefit for individual patients.

Methods: CARDINAL is an open-label, single-arm, multicenter study in patients with CAD with a recent blood transfusion. CADENZA is a randomized, double-blinded, placebo-controlled study in patients with CAD without a recent blood transfusion. Data from the Part A, 26-week component of both studies were combined for these analyses. Anchor- and distribution-based analyses were performed to estimate the CIC. Anchor-based approaches (mean change and model-based) examined the relationship between change in FACIT-Fatigue scores and change in related anchor variables from baseline to Week 26. The independent variable was change in FACIT-Fatigue score and dependent variables were binary (improvement vs. no improvement). The anchor variables were change in self-assessed general health perceptions (as measured through change in response to the general health scale [GH01] of the Short Form 12-Item (version 2)® Health Survey [SF-12v2]), change in Patient Global Impression of (fatigue) Severity (PGI-S), Patient Global Impression of Change (PGIC), and change in hemoglobin levels.
Results: Fifty-five patients were included from CARDINAL (n=17) and CADENZA (n=38 [n=19 placebo, n=19 sutimlimab]). The median (range) age was 70 (46–88) years and 76% (n=42) were female. Mean FACIT-Fatigue score rose from 32.6 at baseline to 39.3 at Week 26, an improvement of 6.7 points. Correlations between FACIT-Fatigue scores and GH01, PGI-S, and PGIC exceeded 0.40, indicating moderately strong associations (**Table 1**). When using an anchor-based approach that evaluates mean change in FACIT-Fatigue score, CIC estimates ranged from 9.20 (PGIC) to 15.69 (PGI-S). Results from the two model-based anchor approaches that estimate CICs using receiver operating characteristic–based and logistic regression–based analyses ranged from 2 (hemoglobin) to 8.87 (GH01) (**Table 2**). CIC estimates generated from the anchor-based approaches ranged from 2 to 16 (interquartile range [IQR], 5–10). Distribution-based analyses determined the CIC to be 5.62 when based on one-half standard deviation of FACIT-Fatigue at baseline, and 2.78 when based on the standard error of the measure. The empirically determined CIC for patients with CAD for FACIT-Fatigue was 5, a median estimate produced by model-based analyses that falls within the IQR of all anchor-based analyses and converges with estimates produced by distribution-based analyses.

Table 1. Polychoric correlation coefficient between FACIT-Fatigue and anchors

Anchors		N	FACIT-Fatigue at baseline	FACIT-Fatigue at Week 26	Change in FACIT-Fatigue
GH01	Baseline	53	0.63	–	–
	Week 26	53	–	0.78	–
	Change	53	–	–	0.64
PGI-S	Baseline	35	0.83	–	–
	Week 26	35	–	0.87	–
	Change	35	–	–	0.80
PGIC	Week 26	53	–	–	0.56
Hemoglobin	Baseline	55	0.20	–	–
	Week 26	55	–	0.41	–
	Change	55	–	–	0.54

Table 2. Results of ROC-based and logistic regression–based analyses

				ROC-based analyses				Logistic regression–based analyses
Anchors	N, total	N, improved	Percentage with improvement	AUC	Sensitivity	Specificity	CIC	CIC
GH01	53	21	39.62	0.79	0.71	0.78	8	8.87
PGI-S	35	15	42.86	0.93	0.87	0.85	5	7.01
PGIC	53	34	64.15	0.74	0.68	0.74	4	4.15
Hemoglobin	55	30	54.55	0.73	0.73	0.68	2	5.66

AUC, area under the receiver operating characteristic curve; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; GH01, general item of the 12-item Short Form Health Survey; CIC, clinically important change; PGIC, Patient Global Impression of Change; PGI-S, Patient Global Impression of (Fatigue) Severity; ROC, receiver operating characteristic.

Summary/Conclusion: This study estimated a CIC of 5 for FACIT-Fatigue in patients with CAD, a CIC consistent with estimates for other disease areas (eg, rheumatoid arthritis, systemic lupus erythematosus, anemia related to cancer). This analysis demonstrated that the FACIT-Fatigue Scale may be an appropriate and interpretable assessment of fatigue among patients with CAD.

EP1180 INCREASED ANTIDEPRESSANT USE AMONG NEWLY DIAGNOSED PATIENTS WITH COLD AGGLUTININ DISEASE COMPARED WITH OTHER PATIENTS IN A LARGE US HEALTHCARE SYSTEM

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Background: Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia (AIHA) that accounts for approximately 20% of all AIHA and is characterized by classical complement pathway–mediated hemolysis. Clinical manifestations of CAD can include complement-mediated chronic hemolytic anemia, profound fatigue, as well as transient agglutination-mediated circulatory symptoms (Swiecicki et al. *Blood* 2013). CAD (formerly primary CAD) is clinically distinct from secondary cold agglutinin syndrome (CAS), which is caused because of an underlying condition (coexisting diagnosis of overt malignancy or infection). Recent research has shown that patients with anemia are more likely to develop depression and anxiety (Shafi et al. *J Coll Physicians Surg Pak* 2018; Vulser et al. *Acta Psychiatr Scand* 2016); however, this has not been studied in patients with CAD.
Aims: To determine the antidepressant (AD) use in patients with CAD (includes patients with both primary CAD and secondary CAS) versus those without CAD in a large United States (US) healthcare system.
Methods: We conducted a matched-cohort comparison study evaluating AD use in patients with and without CAD. All patients with CAD were identified in the Optum Claims-Clinical database by reviewing clinical notes for CAD terms. Patients with CAD were matched (1:10) to patients without CAD by age (±3 years), sex, race, region of residence, and active time and season and year of entry date in the Optum health plan. Patients ≥25 years of age with no history of anxiety or depression were included in the study. Patients were considered to be on ADs if they had at least three medication codes recorded in the database on different dates. Cox regression models were built to estimate time to first medication use, adjusted for age, sex, race, region, comorbidity score, and cluster (matched CAD and non-CAD cohorts). A subset analysis was also performed in patients with primary CAD. Medication use was further described using univariate analyses.
Results: A total of 317 patients with CAD (mean [standard deviation (SD)] age, 70.1 [12.7] years) and 1965 patients without CAD (comparison; mean [SD] age, 69.9 [12.4] years) were identified between 2006 and 2016 and included in the study. Patients with CAD were twice as likely to have medically attended anxiety and depression than their comparisons (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.03–2.75). On average, patients with CAD with medically attended anxiety and depression started ADs 15 months (SD, 17 months) after diagnosis. The top three ADs used in patients with CAD and medically attended anxiety and depression included benzodiazepines (76%), antipsychotics (24%), and selective serotonin reuptake inhibitors (SSRI; 10%). A similar pattern was seen for comparisons, but the proportion using benzodiazepines was less versus patients with CAD (76% vs 60%). Comparisons used more SSRIs versus patients with CAD (31% vs 10%). Patients with and without CAD used a similar proportion of antipsychotics (24% vs 21%, respectively). Sub-analysis of patients with primary CAD reported a higher risk for AD use versus those without CAD (HR, 2.37; 95% CI, 1.34–4.20). A similar pattern for the specific AD use was also reported.
Summary/Conclusion: Our study indicates that ADs are used more often in patients with CAD versus patients without CAD. These findings suggest that patients with CAD may experience extra-hematologic manifestations of the disease that potentially have a broader impact on their overall mental health, physical health, and quality of life. Further investigation on this topic is warranted.

EP1181 A MACHINE LEARNING APPROACH TO IDENTIFICATION OF CLINICALLY RELEVANT HEMATOLOGY-ONCOLOGY RESEARCH PUBLICATIONS

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Background: In the last 10 years, the amount of clinical research published in the field of oncology has grown dramatically due to accelerated pace of drug development and increased use of combination treatments. Concurrently, the problem of finding high-quality clinical research publications to develop evidence-based treatment plans for individual patients has become more challenging. Commonly used solutions primarily rely on bibliographic metadata and expert curation. Here, we describe a tool for fast automatic identification of clinically relevant publications that does not use the tags associated with the publication or curation.
Aims: Here, we describe a tool for fast automatic identification of clinically relevant publications that does not use the tags associated with the publication or curation.
Methods: We used a machine learning approach, trained on the titles of PubMed publications downloaded to the database through OncoTriage.com service. Papers predominantly describing clinical trials in hematological malignancies and clinical cases were used in the analysis. Balanced training data included texts cited in expert-curated sources to form a "*relevant*" dataset (i.e., high quality publications describing treatment of hematologic malignancy), and an "*irrelevant*" dataset that did not include data relevant to therapy. We used a Bayes approach with a binary classification. Briefly, 26,667 texts were processed to get a document-term matrix representation of both the training and the test set (80/20 split).
Results: Our model for "*irrelevant*" detection classified papers in the test dataset with AUC 0.859 accuracy (95%CI 0.853-0.865, p<0.0001), with sensitivity 0.93 and specificity 0.72. The balance of the model was biased towards the sensitivity. We speculate that our training dataset for the model was skewed towards publications describing clinical trials. Therefore, several clinically relevant categories of publications describing treatments were labeled as "irrelevant". An expert examination of the false positives has revealed that these publications included therapy reviews, single center practices and observational studies that nonetheless are informative for clinical practice. We plan to address these drawbacks in future iterations of the model by incorporating supervised or reinforcement learning approaches. The interactive web app is available at https://luchinin.shinyapps.io/PubMed_Triage/
Summary/Conclusion: Machine learning is an effective approach for a large-scale automaticidentification of clinically relevant publications from a variety of databases, such asPubMed and conference abstracts. The use of machine learning techniques as one of the filtersto build a database tailored for clinicians. In the future tools using this database may help tominimize the time clinicians spend finding high-quality publications that fit their patient's profile.In addition, it can be used as a clean-up step for getting a list of publications for further curationby the subject matter experts. Future work will extend this approach and may be integrated intodecision support systems and knowledge management databases.

EP1182 HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN PATIENTS (PTS) WITH MYELODYSPLASTIC SYNDROMES (MDS) IN THE CONNECT® MYELOID DISEASE REGISTRY

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Background: At diagnosis, disease risk and transfusion burden (TB) can impact HRQoL in pts with MDS. The impact of disease status and higher transfusion requirements on HRQoL has not been well studied.
Aims: We used data from the Connect® Myeloid Disease Registry, an ongoing, prospective, observational cohort study that includes adult pts with lower-risk (LR) and higher-risk (HR) MDS, to investigate factors influencing baseline (BL) and subsequent HRQoL.
Methods: BL and Month 6 (M6) data from pts enrolled from Dec 12, 2013 to Mar 6, 2020 (data cutoff) were analyzed. Pts were stratified by International Prognostic Scoring System (IPSS) risk (LR, HR), treatment (Tx) within 45 days post-enrollment (no Tx, best supportive care [BSC], active Tx), and TB 16 weeks post-BL (non-transfusion dependent [NTD], low TB [LTB]; 1–3 transfusions, high TB [HTB]: ≥4 transfusions). Pts completed EuroQol 5 dimensions (EQ-5D), Functional Assessment of Cancer Therapy-Anemia (FACT-An) trial outcome index (TOI), and FACT-Fatigue (FACT-F) questionnaires at BL and quarterly thereafter. Clinically meaningful change, based on minimally important differences, was defined as a change of ±0.07 for EQ-5D, ±6 for FACT-An TOI, and ±3 for FACT-F.
Results: At data cutoff, 830 (489 LR, 341 HR) pts were enrolled. Median age was 74 years. 278 pts received no initial Tx, 161 BSC, and 378 active Tx. At BL, 470 were NTD, 197 LTB, and 163 HTB. Of 670 pts still on-study at M6, 462 completed the questionnaires at both BL and M6.
At BL, clinically meaningful differences were observed in FACT-An TOI and FACT-F scores, but not EQ-5D, between LR- and HR-MDS and the Tx subgroups. From BL to M6, no clinically meaningful changes were observed in mean scores for each questionnaire. For the TB subgroups, meaningful differences were observed at BL in FACT-An TOI and FACT-F scores, but not EQ-5D (Table). From BL to M6, meaningful decreases in scores were reported by 26%, 30%, and 35% of NTD, LTB, and HTB pts in EQ-5D, 41%, 43%, and 48% for FACT-An TOI, and 40%, 42%, and 48% for FACT-F; increases were reported by 19%, 19%, and 20% pts for EQ-5D, 31%, 32%, and 39% for FACT-An TOI, and 30%, 39%, and 40% for FACT-F.

Table. Mean HRQoL scores in pts with MDS

		EQ-5D		FACT-An TOI		FACT-F	
		BL (n=807)	M6 (n=459)	BL (n=803)	M6 (n=463)	BL (n=810)	M6 (n=464)
IPSS risk	LR	0.80	0.79	92.3	92.4	23.4	24.1
	HR	0.75	0.79	83.9	87.5	20.5	22.2
Tx	None	0.81	0.80	96.0	95.9	25.6	25.9
	BSC	0.78	0.77	87.2	88.2	20.3	21.7
	Active	0.76	0.78	84.3	87.3	20.6	22.2
TB	NTD	0.80	0.81	92.9	95.9	24.2	25.7
	LTB	0.75	0.75	83.6	82.0	19.4	19.6
	HTB	0.76	0.75	83.6	84.3	19.8	20.8

BL, baseline; BSC, best supportive care; EQ-5D, EuroQol 5 dimensions; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; HRQoL, health-related quality of life; IPSS, International Prognostic Scoring System; HTB, high transfusion burden; LTB, low transfusion burden; M6, Month 6; MDS, myelodysplastic syndromes; NTD, non-transfusion dependent; pt, patient; TB, transfusion burden; TOI, trial outcome index; Tx, treatment.

Summary/Conclusion: This preliminary analysis suggests that pts with HR-MDS, and transfusion-dependent pts, generally had worse HRQoL at BL, providing further support to initiating active Tx in pts with TB. Possible limitations of the analysis are lower completion rates in pts with more severe disease, and EQ-5D may not capture changes in these subgroups at M6. A longer follow-up may help delineate the impact of Tx on HRQoL assessments in pts with MDS.
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EP1183 PROSPECTIVE COMPARISON OF POINT-OF-CARE INR VERSUS PLASMA INR IN SUPRA-THERAPEUTIC INR VALUES

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Background: Point-of-care testing (POCT or bedside testing) provide faster results than those obtained in hospital laboratory analyzers, but should not compromise quality and safety. Compared to arterial and venous blood, capillary blood can be easily collected from the fingertip and does not require a skilled worker. Therefore, it has excellent potential as an ideal blood source for disease diagnosis and health monitoring. In coagulation, these systems are very useful in obtaining the INR test for the monitoring of vitamin K antagonist (VKA) oral anticoagulants therapy. Xprecia Xtride™, Siemens®, is a POC system, with an ergonomic design, touch screen and intuitive software that, after performing an automatic calibration and two quality control checked on each test strip, provides INR after analyzing a sample of 6 µl of capillary blood, reporting data between 0.8 and 8. It uses Innovin® reagent with ISI 1. It is stablished that a POC device should be assessed for reproducibility against a central laboratory analyser, since INR is essential for proper management of oral anticoagulation. Regarding to NCCLS guidelines, statistically there is an equivalence of INRs obtained from POC systems that are within 0.4 at a target INR of 2.5 and 0.7 at a target INR of 3.5. Results exceeding an INR of 5.0 generally have reduced trueness, precision, and linearity, both in POC and laboratory-based testing.
Aims: This is a comparative study of INRs obtained by a POC system (POC-INR) compared to INRs obtained from plasma of venous samples collected in citrate tubes (P-INR), both from the same patient at the time. In previous studies of our own we found linearity between both methods and no statistically significant differences. In this study, our intention was to demonstrate if there was such correlation exclusively in supra-therapeutic INR results.
Methods: POC-INR was obtained from capillary sample analyzed with POC Xprecia Xtride™, Siemens®. If INR was superior to 3.0, a venous citrated sample was recolected and P-INR was obtained from ACL-TOP500 hospital analyser, Werfen®, using as reagent Hemosil Recombiplastin® ISI 1. The results were compared with the statistical package Medcalc to calculate Pearson correlation coefficient and non-parametric Passing-Bablok regression analysis, suitable for method comparison studies.
Results: We obtained 215 samples of POC-INR higher than 3.0 and P-INR from the same patients at the time. A correlation coefficient r=0.7698 with a 95% confidence interval (0.7091 to 0.8192) was obtained, with the regression equation y=0.160+0.967 X, where y=P-INR, x=POC-INR: a=0.160 CI 95% (-0.4238 to 0.6581), b=0.9667 CI 95% (0.8762 to 1.0692) with a value of p=0.73, being evident that there are no significant differences regarding the deviation of the linearity between both techniques.
Summary/Conclusion:
POCT Xprecia Xtride™ system, Siemens®, offers INR results statistically comparable to those obtained from plasma in a laboratory analyzer, even with supra-therapeutic INR values.
POCT allows the accessibility of the patient for the monitoring of VKA oral anticoagulant therapy; with the transmission of results via web, the decentralization of the control in the Health Centers is facilitated, allowing the validation and dosage from the hospital.
It offers a valid alternative to the historical pattern in which testing was mostly confined to the medical laboratory and provides continuous improvement in patient care quality.

EP1184 FERTILITY PRESERVATION IN LYMPHOMA PATIENTS TREATED WITH IMMUNOCHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY: RESULTS OF A RETROSPECTIVE MULTICENTER STUDY OF THE FONDAZIONE ITALIANA LINFOMI (FERTY CARE).

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Background: In the last decades, a significant improvement in overall survival (OS) of patients (Pts) affected by lymphoma has been observed. Fertility and gonadal function represent one of the most important aspects for long-term lymphoma survivors.
Aims: We designed this retrospective, multicentric, observational study, with the primary end point to describe the application in real-life of different methods of fertility preservation during treatment in lymphoma pts afferent to the Fondazione Italiana Linfomi (FIL) centers participating. Other end points were: to determine amenorrhea rate after first and subsequent lines of treatment and possible risk factors in young female lymphoma patients and to record rate of pregnancy and miscarriage after treatment in this population.
Methods: All female pts, aged from 18 to 40 years old, diagnosed with Hodgkin (HL) or non-Hodgkin's lymphoma (NHL) in the timeframe between Oct 1st/2010 and May 31st/2018, treated with chemoimmunotherapy (CHT) regimens and/or radiotherapy (RT) were included in the analysis. Histology included were: HL, primary mediastinal B-cell (PMBCL), diffuse large B-cell (DLBCL), follicular (FL), mantle cell (MCL) and T-cell Lymphoma.
Results: A total of 414 women were enrolled in the study. Median age was 28 years old (range 18-40), histology were: HL 308 (74%), PMBCL 56 (13%), DLBCL 43 (10%), FL plus MCL plus T-cell lymphoma 7 (3%). Advanced Ann Arbor stage III-IV was seen in 164 (40%) of pts. First line treatment were: ABVD in 295 (71%), R-CHOP like in 102 (25%), higher intensity regimens (BEACOPP/high dose chemotherapy plus autologous stem cell transplantation (ASCT) in 17 (4%) cases. 203 (49%) patients received RT. A relapsed/refractory disease was observed in 48 (11%) cases, and 52% of them received ASCT. Pretreatment data recorded: regular period in 80%, previous pregnancy in 26%, previous miscarriage in 9%. Overall, 76% of the ptsreceived GnRH analogues during chemotherapy; 10% took OCs and 14% nothing. Oocytes and ovarian tissue cryopreservation were performed in 55 and 42 pts, respectively (23%). In 7 pts were proposed with cryopreservation but not performed for therapy urgency. Post treatment data were transient amenorrhea in 216 (75%), premature ovarian failure (POF) in 33 (9%), a restored regular period was observed in 293 (90%) on cases. After treatment were recorded 43 (10%) pregnancies and 17 (4%) miscarriages. Most pregnancies (88%) were observed in women under 30 years of age and subjected to a single line of therapy. Median age of menopause onset was 34.5 ± 7.8 years old (19.0-47.0). In multivariate analysis median age at diagnosis and number of lines of treatment correlate with higher rate of amenorrhea, risk of POF and menopause. No protective effect of GnRHa administration of amenorrhea, POF and menopause was observed. Even if 23% of pts performed oocytes and ovarian tissue cryopreservation, this was not used in any case.
Summary/Conclusion: Pregnancy in long term lymphoma survivors should be considered possible and safe. Median age at diagnosis and number of treatment lines correlate with amenorrhea, POF rate and menopause. The use of GnRHa and OCs not seem protective for fertility. Our study confirm the need to a correct and multidisciplinary approach to fertility preservation in young lymphoma patients for a correct strategy in relation to the patient's age, type of disease and chemotherapy treatment

EP1185 IMPACT OF THE COVID-19 PANDEMIC ON HEALTH-RELATED QUALITY OF LIFE AND ANXIETY IN PEDIATRIC HEMATOLOGY/ONCOLOGY PATIENTS: A SINGLE EGYPTIAN CENTER EXPERIENCE

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Background: Since the World Health Organization declared coronavirus disease 2019 (COVID-19) pandemic, the strain on healthcare services affected patients suffering from various comorbidities and added to the psychological burden.
Aims: To assess anxiety level and it's impact on the health-related quality of life (HRQoL) of pediatric Hematology/Oncology patients during the COVID-19 pandemic.

Methods: A cross-sectional study on convenience sample of 292 children with chronic hematological/oncological disorders attending Alexandria University Children's Hospital with their parents/guardians available were included. Patients' recruitment was done from May to June 2020 during the peak of the pandemic in Egypt. A Three groups were included: Patients with bleeding/coagulation disorders, transfusion-dependent patients, and patients receiving chemotherapy. HRQoL was assessed using a validated Arabic version of Parent proxy-report of Pediatric Quality of Life Inventory ™ (PedsQL™ 4.0 Generic Core Scales). Anxiety was assessed using the Arabic version of the Spence Children's Anxiety Scale (SCAS). The preschool (PAS) and parent versions of the scale (SCAS-P) were completed by the caregivers. The preschool anxiety scale was used to measure anxiety in children aged 2.5-6.9 years.
Results: The mean age was 8.72 ± 3.66 years, 52.4% were males and 65.4% were transfusion-dependent patients. Almost 60% of children were aware of the pandemic and 60.3% had blood transfusion difficulties. Males had lower anxiety levels than females ($p < 0.001$), and transfusion-dependent patients had lower anxiety levels than patients receiving chemotherapy ($p < 0.001$). Children who were aware of the COVID-19 pandemic had lower anxiety levels than those who were not ($p = 0.006$), while those suffering from fewer clinic days had higher anxiety levels ($p = 0.02$). Anxiety significantly reduced the three HRQoL domains ($p < 0.001$).
Summary/Conclusion: The present study demonstrated the degree of anxiety and HRQoL affection during the COVID-19 pandemic in children with chronic hematological/oncological diseases and malignancies. The anxiety score was highest in patients receiving chemotherapy, while the HRQoL was lowest in patients with bleeding/coagulation disorders. These findings help a better understanding of the psychological impact of the pandemic on the studied group as a crucial step in guiding policies and interventions to maintain their psychological wellbeing.

EP1186 THE IMPACT OF COVID-19 ON A RURAL HEMATOLOGY OUTREACH SERVICE, AN AUSTRALIAN EXPERIENCE

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Background: The COVID-19 pandemic has had widespread and drastic impacts on healthcare delivery across the world, aside from the direct effects of the virus itself. Patients in rural areas represent a particularly vulnerable population who may be heavily impacted by changes to healthcare provision.
Griffith is a regional city in New South Wales, Australia with a fortnightly outpatient outreach hematology service provided by visiting hematologists travelling by plane from St Vincent's Hospital in Sydney. Hematologists were abruptly unable to continue regular in-person visits to Griffith after the COVID-19 pandemic caused flight disruptions and travel bans in April 2020. Rapid shifts to telemedicine consultations for remote specialist patient management were imposed due to the travel changes, supported by a pre-existing hematology-specific integrated and unified electronic health record between the two sites as previously reported[1]. This system offered the ability to continue the safe prescribing, monitoring and multidisciplinary management of haematology patients including those with malignant diseases.
Aims: To review the impacts of the COVID-19 pandemic on a rural hematology outreach service, including on clinical service activity and patient transfer rates to the metropolitan tertiary referral centre.
Methods: We reviewed the Griffith hematology outreach service activity for the 12 month period before and following the COVID-19 pandemic began significantly impacting rural Australian health services by causing flight cancellations and reliance on telemedicine reviews alone. Data was collected for the time periods April 2019-March 2020 and April 2020-March 2021 inclusive [remaining data to be presented]. Clinical service activity and patient admission rates to the metropolitan tertiary referral centre were assessed.
Results: Prior to the pandemic, an average of 39 patients were seen in the Griffith clinic each month, compared to an average of 47 per month after the change to telemedicine, Figure 1. The number of new patient consultations performed increased over time, from 64 new patient reviews to 79 from April 2020. The St Vincent's Hospital hematology clinic service was similarly able to sustain it's activity with increases seen in both total and new patient reviews, increasing by 12% and 15% respectively.
There was no increase seen in the number of hematology patients from the Griffith region needing treatment at the tertiary referral centre due to disruptions in care. In the 12 months prior to the service disruption (April 2019- March 2020), 18 patients were treated or required hematological investigation at the tertiary referral centre at St Vincent's Hospital in Sydney, compared to nine patient over the 10 month period following.

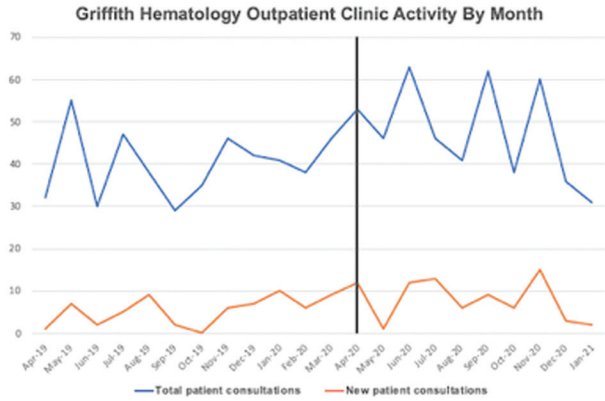


Figure 1: Griffith hematology outpatient clinic activity by month, April 2019-January 2021.
The black line denotes the change to telemedicine consultations due to flight disruptions.

Summary/Conclusion: We demonstrate how a rural outreach hematology service was able to continue with minimal disruption after the COVID-19 pandemic caused an abrupt transition to exclusively remote patient reviews and chemotherapy management. The use of an integrated digital platform shared between the two sites allowed the remote telehealth service to be maintained. Significant increases in rural patients requiring transfer or admission to the tertiary referral centre in Sydney were not seen. With continued uncertainty and unpredictable flight changes, we demonstrate long term and sustainable adjustments are feasible and necessary to serve rural populations from potentially detrimental changes to already fragile health services.

EP1187 APPRAISAL OF THE CONSISTENT USE AND REPORTING OF PATIENT-REPORTED OUTCOMES IN MULTIPLE MYELOMA CLINICAL TRIALS: DOES IT MATTER?

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Background: The treatment landscape for the management of multiple myeloma (MM) has substantially evolved over the past decade. Inclusion of humanistic outcomes reported by patients (PROs) to supplement the clinical outcomes is becoming increasingly important in MM clinical trials to ensure the intended benefits based on patients' perspective. For patients with MM, PRO measurement is essential to understand the impact of treatment on their physical and psychosocial functional behaviour and evaluate the benefit-risk balance of specific treatments. However, it is unclear which PRO instruments are utilized in multiple myeloma trials, how often they are used and whether results are consistently reported.
Aims: The aim of this project was to explore the use and frequency of PRO instruments in randomized controlled trials (RCTs) for MM and to assess the consistency of their reporting.
Methods: Under the auspices of the European Hematology Association (EHA), development of guidelines for the use of PROs in adult patients with hematological malignancies was conceptualised. MEDLINE and CENTRAL were systematically searched for RCTs investigating multiple myeloma between 2015 and 2020. Study design, disease and treatment characteristics, primary outcome, PRO instrument(s) as well as the methods of their reporting were extracted using a pre-defined template. To assess the consistency of PRO reporting, study registries were compared

with publications, study protocol and Health Technology Assessment (HTA) reports, where available.
Results: Overall, 10,707 records were found. Following screening for RCTs, 283 ongoing, completed or published studies were included for review. 118 studies planned the use of PROs. The most frequently used PRO instrument (92 studies) was the EORTC QLQ-30 measuring health-related quality-of-life (HRQoL) in cancer patients. The disease-specific questionnaire EORTC-MY20 was also frequently used (50 studies). Likewise, the HRQoL instrument EQ-5D was used in 50 studies. Overall, 38 different PRO instruments were reported. In 39 studies for which a study protocol was found, only 19 reported PRO instruments consistently with the trial registry for the study. In addition, in 30 studies for which a publication reported PRO results (58 overall), the information on PRO instruments differed between publication and the trial registry. Further, information on PRO in HTA reports was available for 26 studies of which 18 reports were consistent with the trial registries.
Summary/Conclusion: The findings indicate that despite the general agreement on the importance of measurement of PROs in multiple myeloma RCTs, they remain under-utilized and under-reported. While most studies identified in this review comply with the recommendations for incorporating PROs into adult oncology trials, they are often inconsistently reported. Thus, guidelines for the appropriate use of PROs are needed to ensure standardisation in selection and reporting of PROs.

EP1188 FERTILITY ANALYSIS IN MALE PATIENTS LONG SURVIVING BY HODGKIN'S LYMPHOMA

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Background: The outcome of patients with Hodgkin's lymphoma (HL) has greatly improved in recent years, which is why the attention of doctors and researchers has increasingly been diverted towards the well-being of these young patients. Consistent with this, the study aimed to analyze the influence of HL and its treatment on the fertility status of young males and detect new predictors affecting the likelihood of parenthood.
Aims: Consistent with this, the study aimed to analyze the influence of HL and its treatment on the fertility status of young males and detect new predictors affecting the likelihood of parenthood.
Methods: In this retrospective study, the fertility status of 42 male patients (mean age 25 years) with HL treated at the University Hospital of Bari (Italy) between 2008 and 2016 was studied. All were assessed for fertility at diagnosis, while 24 had post-treatment fertility status checks. All patients underwent ABVD as first-line chemotherapy, of them 6 patients with relapsed/ refractory disease underwent autologous hematopoietic stem cell transplantation (ASCT).
Results: At the time of diagnosis, we found that 15 (35%) patients had normozoospermia, 19 (45%) oligozoospermia (of these 14 had other despermias), and 8 (19%) only other despermic conditions. After treatment, 17% of patients had azoospermia (all had undergone ASCT). Of the 9 normozoospermic patients at the time of diagnosis, 5 (55.5%) maintained that condition after treatment, while 4 (45.5%) developed azoospermia associated with other types of despermia (all undergoing ASCT). Of 11 patients with oligozoospermia and other types of despermia at the time of diagnosis treated with first line alone (no ASCT group), 6 (54%) normalized the fertility status after treatment; in the same group, 5 of 6 patients (83%) with normozoospermia at diagnosis maintained the status after treatment. Furthermore, in patients who received first-line treatment only, the mean sperm concentration was increased post-treatment (5.53 x10e7 at diagnosis vs 4.02 x10e7 after treatment).
We also found that 4/6 patients undergoing ASCT had azoospermia and despermia in the post-treatment control. On the other hand, 2 of the 3 patients, who had oligozoospermia before treatment, became normozoospermic after therapy. Furthermore, in univariate analysis, we found that patients undergoing ASCT were associated with severe impairment of fertility in terms of sperm motility (74% at diagnosis versus 22% after ASCT; p = 0.025, Fig. 1). In patients not undergoing ASCT we found a statistically significant improvement in fertility in terms of motility (35% at diagnosis versus 50% after treatment; p = 0.009, fig. 1)

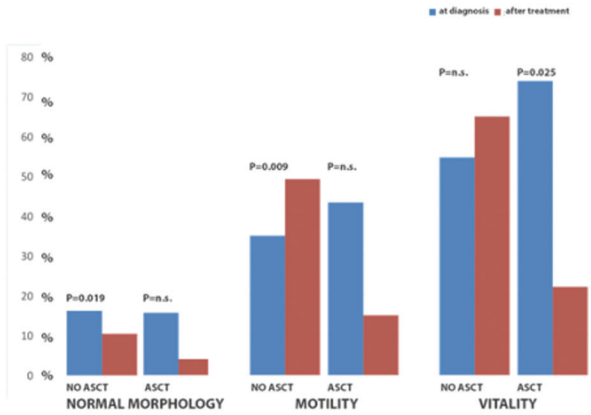


Figure 1: percentage of spermatoza normal morphology, motility and vitality at time of diagnosis and of post treatment control.

Summary/Conclusion: In this study we found that ASCT induces infertility in the majority of male patients with HL and that first-line treatment could improve the fertility status caused by the disease. Further studies are needed in a larger case series to investigate risk factors for impaired fertility at diagnosis and after treatment.

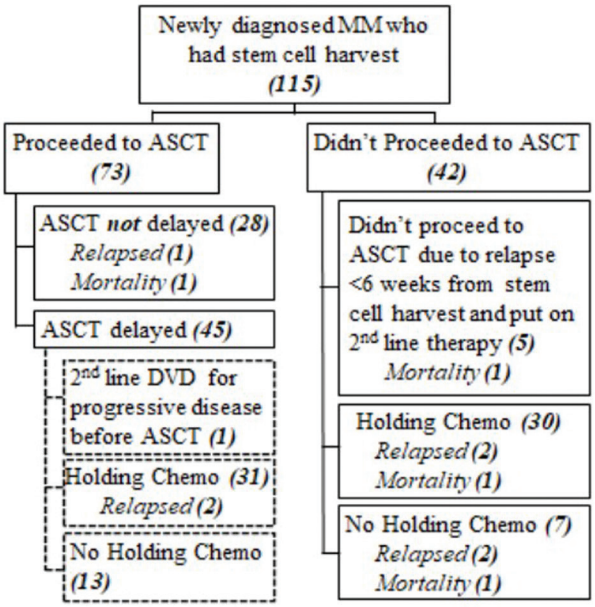
EP1189 IMPACT OF COVID-19 ON AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN MULTIPLE MYELOMA (MM) PATIENTS: A SINGLE-CENTRE, QUALITATIVE EVALUATION STUDY

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Background: ASCT is standard of care in biologically fit, newly diagnosed MM (NDMM) patients (pts), offering deeper responses with prolonged progression free/overall survival and improved quality of life (QOL). However, with the UK's 1st national lockdown on 23/03/2020, several guidelines recommended deferring ASCT for MM due to risks of infection, with resource limitations forcing some units to suspend ASCT entirely. Such changes to pts' treatment plans inevitably altered their lived experience during these uncertain times with expected impact on QOL.
Aims: To provide a snapshot of how COVID-19 affected the MM ASCT service in a single UK institution, including changes to chemotherapy treatment plans, timing, and prioritisation of ASCT. To gain insight into MM pts' understanding of their disease, initial therapy and ASCT, and their response to therapy changes.
Methods: We collected data on 115 NDMM pts who had a stem cell harvest (PBSCH) for upfront ASCT from December 2019–January 2021. During this time, 3 national lockdowns led to the ASCT service being suspended twice (March–June 2020 and January–February 2021). 25 pts within this cohort underwent a semi-structured interview via telephone. Inductive and deductive framework analysis was utilised to determine key themes and subthemes.
Results: Pts were discussed in multidisciplinary meetings and decisions taken to delay or defer ASCT based on pt fitness, disease risk and depth of response. 73 (63%) proceeded to ASCT and 42 (37%) were deferred indefinitely ($ASCT^{def}$). The 2 groups were similar in terms of gender, age and ISS, but there were more pts with adverse risk cytogenetics in the ASCT group (26% *vs* 12%). Both groups were predominantly treated with bortezomib-based induction; in 11/73 (15%) ASCT and 7/42 (16.7%) $ASCT^{def}$ pts treatment was changed to an oral, lenalidomide-based regimen to reduce hospital attendances for parenteral therapy. Overall response to induction in the 2 groups was similar; 97.3% and 95.2% and ^{3}VGPR 59% and 52.4% in ASCT and $ASCT^{def}$ pts respectively. 28/73 ASCT pts had no delay to ASCT and none received

bridging chemotherapy; 45/73 had delayed ASCT (median 11 months [5–17] from start of induction) of whom 31 were put on bridging chemotherapy. In the 42 ASCT^{def} pts, 5 relapsed within ≤6 weeks of PBSCH and received 2nd line therapy, 30 were put on holding chemotherapy (previously not offered in the UK) as per NHS England COVID-19 interim guidance and 7 remained treatment-free post-induction.
Thematic analysis identified 6 overarching themes: a) psychological response to diagnosis and initial therapy, b) beliefs and opinions about the benefits of ASCT, c) perceptions of information provided about MM and ASCT, d) high levels of fear and anxiety around COVID-19 and e) feelings about ASCT disruption or delay due to COVID-19 f) perceptions of care. Example subthemes were beliefs that ASCT would provide a long-remission/best chance of normality including freedom from chemotherapy and associated side-effects, disappointment and devastation at COVID-related treatment delays (in spite of high anxiety about infection) and exceptionally high levels of trust in the transplant team.



Summary/Conclusion: New COVID-19-adapted guidelines, and new ways of perceiving and balancing risks of ASCT, led to a substantial proportion of MM pts having a delayed or indefinitely deferred ASCT. Such enforced changes gave us an opportunity to explore pts' attitudes, perceptions, and expectations around MM and ASCT. Insights gained will help us adjust our service and counselling approaches to be more in tune with pts' priorities and expectations.

EP1190 OUTCOMES OF BRENTUXIMAB VEDOTIN AS ≥3 LINE TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: PHYSICIAN'S AND PATIENT'S PERSPECTIVE

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Background: For patients with relapsed/refractory classical Hodgkin Lymphoma (R/R cHL) who are ineligible for auto-SCT, or who are relapsed after auto-SCT, one of promising treatment options is brentuximab vedotin (BV). Real-world data about risks/benefits of this treatment are limited. Comprehensive evaluation of effects of BV, including patient-reported outcomes, in this patients population is worthwhile.
Aims: Here we demonstrate the results of multicenter observational study aimed to evaluate clinical and patient-reported outcomes in R/R cHL pts receiving BV as ≥3rd treatment line in the real world setting.
Methods: Pts with R/R cHL receiving BV 1.8 mg/kg q3w as ≥3rd treatment line were included in the real-world study. Treatment response was assessed using RECIST criteria v. 1.1. Duration of response (DOR) and progression free survival (PFS) were evaluated by Kaplan-Meier analysis. Adverse events (AEs) were evaluated in accordance with NCI CTCAE v. 4.0. For QoL and symptom assessment pts filled out RAND SF-36 and ESAS-R, accordingly. Generalized Estimating Equations (GEE), Friedman ANOVA and McNemar's test were used for statistical analysis.
Results: In total, 62 pts with R/R cHL (median age – 31 yrs, range 18–67, 53% males) were recruited in the study: 69% pts had advanced stage (III–IV) at diagnosis; 66% pts – B-symptoms; 18% pts – ECOG 2-3; 29% – comorbidities. All pts received 2-10 previous treatment lines (median – 3); 98% pts were primary refractory/relapsed, among them 19% relapsed after auto-SCT. Before BV treatment start 60% pts had severe/critical QoL impairment. All the pts experienced symptoms; 88.7% pts had moderate-to-severe symptoms, more than half pts had moderate-to-severe worse wellbeing (76%), tiredness (67%), drowsiness (60%), depression and lack of appetite (each 53%). At median follow-up of 8 mo (5.3–15 mo) one patient died at 2 mo after treatment start not because of HL, one patient was lost. For the entire follow-up period 68.3% pts achieved/maintained the objective response (OR). Among them 40% pts achieved the best response in terms of complete remission, 28.3% pts – partial remission. Median of DOR in 41 pts with OR was 11 mo (95% CI: 0.8– -).The median PFS was 10.6 mo (95% CI: 7.4-12.9). Most common AEs were peripheral neuropathy (55%) and fatigue (38%), AEs of grades III-IV were reported in 1.6% pts. SAE was reported in one case (sepsis, respiratory insufficiency due to agranulocytosis, BV was temporary stopped). During 15 mo of BV treatment significant QoL improvement was revealed for all SF-36 scales (GEE, p<.01). The most pronounced meaningful improvement was found for role physical functioning (Δ=60 scores), role emotional functioning (Δ=44) and vitality (Δ=28). Proportion of pts with severe/critical QoL impairment dramatically decreased during BV treatment (at 9, 12 and 15 mo, p<.05). The severity of all symptoms by ESAS-R decreased (p≤.001). Total Symptom Score by ESAS-R became significantly less after treatment start: 36.5 at baseline vs 5.6 at 15 mo (p<.001).
Summary/Conclusion: The results of this multicenter real world study confirm notable effectiveness and good tolerability of BV as a treatment modality for R/R cHL pts. Median PFS was 10.6 mo; 68.3% pts achieved OR (CR – 40%). Treatment toxicity is comparable with clinical data; AEs of grades III-IV – in 1.6% pts. BV treatment is accompanied with dramatical QoL improvement and significant decrease of symptom burden.

EP1191 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA'S HUMANISTIC AND ECONOMIC BURDEN IN PATIENTS RECEIVING C5 INHIBITORS IN EUROPE

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired and potentially life-threatening hematologic disease, characterized by hemolytic anemia, thrombosis and impaired bone marrow function. Treatment with the C5 inhibitors has resulted in a reduction in intravascular hemolysis and improvements in morbidity and mortality. Despite the clinical benefit for PNH patients (pts), real world evidence studies indicate that pts treated with C5 inhibitors eculizumab (ECU) and ravulizumab (RAV) experience continued impairment in productivity and overall quality-of-life (QoL), and that a significant proportion of pts, besides being anemic continues to experience fatigue and other symptoms.[1]
Aims: Assess the burden of illness in European PNH pts currently treated with C5 inhibitors, from a clinical, humanistic and economic perspective. Here, we present interim results to specifically, assess the impact of PNH on QoL and work productivity in a subgroup of pts receiving ECU in Germany, France, and the United Kingdom (UK), or RAV (Germany only).
Methods: A cross-sectional online survey administered to pts with self-reported PNH diagnosis. The survey, initiated in February 2021, aims to recruit 90 pts. Following a Central Institutional Review Board exemption, convenience sampling was used to recruit pts through patient advocacy groups in each country. Inclusion criteria required a self-reported PNH diagnosis, age ≥18 years, current treatment with ECU or RAV and agreement to informed consent and adverse event reporting. To assess the burden of illness in these pts, Work Productivity and Activity Impairment–General Health questionnaire, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (total score range: 0-52), and European Organization for Research and Treatment of Cancer QoL Questionnaire (EORTC-QLQ-C30; total score range: 0-100) were analyzed. For the interim analyses reported here, descriptive statistics are presented.
Results: In February 2021, 37 pts were included in the study, among which 21 were residing in Germany, 4 in France, and 12 in the UK. Pts with self-reported PNH diagnosis had a median age of 43 years (range 19-74) and most were female (70%). There were 32% pts on ECU, and 68% pts on RAV; all pts had been on treatment for at least 3 months and most for at least 1 year (96% ECU and 83% RAV). The FACIT-Fatigue total score (mean[±SD]: 35[±13]) was lower than the general population mean (~44, determined in a German population); and the EORTC-QLQ-C30 global health status score (67[±18]) was also below the mean of the European general population (~76). Furthermore, the EORTC-QLC-C30 physical functioning score mean (84[±15]) averaged lower than the general population mean (~93). Pts also reported 35%[±29] impairment in normal daily activities in the prior 7 days (37%[±31] ECU, 32%[±26] RAV). The 22 pts (60%) employed at the time of the study reported 6%[±22] absenteeism (proportion of work time lost due to being absent; ECU: 10% [±28], RAV: 1%[±4]) and 20%[±24] presenteeism (productivity impairment while working; ECU: 21%±[26], RAV: 19%[±23]). Total work productivity impairment was 29%[±32] (ECU: 48%[±34], RAV: 19%[±23]).
Summary/Conclusion: This burden of illness interim analysis among European PNH pts indicates a substantial unmet need in regards to economic burden and QoL as the results show relevant work-related productivity loss, diminished ability to work, limitations in daily life activities, and reduced QoL, despite treatment with ECU or RAV.
[1]*Levy AR et al. Blood. 2019;134(Supplement_1):4803*

EP1192 DEVELOPING TREATMENT ATTRIBUTES FOR A PATIENT PREFERENCE SURVEY: A QUALITATIVE MULTINATIONAL STUDY IN MULTIPLE MYELOMA

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Background: Patient preferences have become an important focus for inclusion in the drug development, regulatory, and reimbursement process for multiple myeloma (MM) treatments (Postmus et al, 2018; Fifer et al, 2020). Over the last decade there has been a rapid development of new medicines for MM, all with varying safety and efficacy profiles. Therefore, the need for a clear and standardized methodology for collection of patient preference data is important.
Aims: This study aimed to understand which characteristics of treatment MM patients find most important and should be included as attributes in a subsequent (quantitative) preference survey.
Methods: This research incorporates a literature review and qualitative discussions with patients to formulate attributes for inclusion in a subsequent quantitative patient preference survey. This qualitative study involved: i) a scoping literature review, ii) discussions with MM patients (n=24) in Belgium, Finland, Romania, and Spain using *Nominal Group Technique (NGT)*, and iii) a qualitative thematic analysis with multi-stakeholder discussions.
Results: After completion of the literature review, a patient consensus on MM treatment attributes was reached using *NGT*. Thematic analysis generated the following treatment attributes for inclusion in the subsequent quantitative patient preference survey: i) life expectancy, ii) life-threatening side-effects (such as the development of another cancer), iii) treatment response (i.e., a reduction of cancer signs), iv) nerve or bone problems affecting movement (such as fractures), v) thinking problems (such as concentration problems), vi) increased susceptibility to infections, vii) reduced energy, viii) pain (such as bone pain), ix) emotional problems (such as mood changes), x) eating and digestive problems (such as incontinence), and xi) vision problems (such as blurred vision).
Summary/Conclusion: Obtaining patient insights for inclusion in subsequent quantitative preference studies requires several steps. This study highlights the importance of the incorporation of the qualitative portion of a patient preference study, to ensure sensitive and appropriate attribute selection. This study illustrates that patients focus not only on treatment efficacy, but also value a reduction of MM-related symptoms and side effects.

EP1193 HEALTHCARE RESOURCE UTILIZATION AMONG PATIENTS WITH COLD AGGLUTININ DISEASE IN DENMARK

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Background: Cold agglutinin disease (CAD) is a rare, chronic type of autoimmune hemolytic anemia characterized by classical complement pathway–mediated hemolysis. Clinical manifestations may include chronic hemolytic anemia, profound fatigue, and transient agglutination-mediated circulatory symptoms. CAD (formerly primary CAD) is clinically distinct from secondary cold agglutinin syndrome, which is caused by an underlying condition (coexisting diagnosis of overt malignancy or infection). Healthcare resource utilization (HRU) for patients with CAD in Europe is unknown.
Aims: Compare overall and CAD-related HRU in patients with CAD versus matched comparators in Denmark.
Methods: Nationwide patient registries were used to identify newly diagnosed cases of CAD (International Classification of Diseases, Tenth Revision, code: D591A) in Denmark between January 1, 1999 and June 30, 2016. Each patient with CAD was matched 10:1 to a comparison patient from the general population by birth year, gender, and comorbidities. Inpatient, outpatient, and emergency room (ER) visits and transfusion use were assessed 6 months before and 12 months after the date of the first CAD diagnosis/index date. Descriptive statistics, conditional logistic regression, mixed-effect negative binomial regression, and zero-inflated binomial mixed model were used to compare HRU among patients with CAD versus matched comparators. CAD-related inpatient and outpatient visits were also assessed.
Results: A total of 104 patients with CAD and 1003 comparison cohort members were included. Women comprised over half of the cohorts (53% CAD; 52% comparator), and 60% were ≥70 years of age (59%

comparator). Nearly half of the cohort had ≥2 comorbidities (45% CAD; 43% comparator). At 6 months before CAD diagnosis/index date, 31% of patients with CAD experienced an inpatient hospitalization versus 13% of matched comparators (P<0.001). Outpatient and ER visits were experienced by 80% (vs 47% comparators; P<0.001) and 19% (vs 5% comparators; P<0.001) of patients with CAD, respectively. At 12 months after CAD diagnosis/index date, 53% of patients with CAD had an inpatient hospitalization (vs 23% comparators; P<0.001), 95% had an outpatient hospitalization (vs 59% comparators; P<0.001), and 19% had an ER visit (vs 14% comparators; P=0.231). Overall, 67% of inpatient hospitalizations for patients with CAD were due to anemia and pneumonia. Patients with CAD had significantly higher mean inpatient length of stay (10.6 vs 2.7 days; P=0.001). Analyses limited to inpatient hospitalizations or outpatient clinic visits associated specifically with CAD showed similar but stronger results for patients with CAD versus matched comparators during the 12-month post-diagnosis period (**Table**). Transfusion use was significantly greater for patients with CAD versus comparators (43% vs 1%; P<0.0001). Up to 5 years after diagnosis, relative risk remained high for patients with CAD compared with their matched comparators for an ER visit (1.36–2.18 from Years 1 to 5), an inpatient visit (2.30–2.36 from Years 1 to 5) and an outpatient visit (1.61–1.60 from Years 1 to 5). Sensitivity analysis for patients with primary CAD (representing 82% of identified patients with CAD) showed similar findings of significantly increased overall and CAD-related HRU versus matched comparators.

Table. Annualized overall and CAD-related HRU of the CAD and matched comparison cohorts within 12 months after the index date

	Overall HRU		CAD-related HRU	
	CAD (N=504)	Matched comparison (N=5000)	CAD (N=504)	Matched comparison (N=5000)
Inpatient hospitalizations				
Number of patients				
Cohort, n (%)	55 (53)	227 (34)	34 (33)	36 (4)
OR (95% CI)	3.9 (2.5–6.0)		15.3 (8.3–28.2)	
P value	<0.0001		<0.0001	
Number of admissions per patient				
Mean	1.8	0.5	1.0	0.1
Median (IQR)	1 (0–3)	0 (0–0)	0 (0–1)	0 (0–0)
RR[2] (95% CI)	5.1 (3.6–7.3)		40.1 (18.2–88.6)	
P value	<0.0001		<0.0001	
Number of hospital days per patient				
Mean	10.6	2.7	6.8	0.7
Median (IQR)	1.5 (0–14)	0 (0–0)	0 (0–6.5)	0 (0–0)
P value[1]	0.001		0.331	
Outpatient clinic visits				
Number of patients				
Cohort, n (%)	99 (95)	590 (59)	57 (95)	93 (9)
OR[1] (95% CI)	17.2 (6.8–43.1)		36.4 (18.2–72.7)	
P value	<0.0001		<0.0001	
Number of admissions per patient				
Mean	14.2	3.7	6.3	0.7
Median (IQR)	10 (4.5–19.5)	1 (0–4)	2 (0–9)	0 (0–0)
RR[2] (95% CI)	5.3 (4.1–6.8)		180.9 (88.9–368.1)	
P value[1]	<0.0001		<0.0001	

CAD, cold agglutinin disease; CI, confidence interval; HRU, healthcare resource utilization; IQR, interquartile range; OR, odds ratio; RR, rate ratio.
[1]OR estimated with conditional logistic regression.
[2]RR estimated with mixed-effect negative binomial regression.
[1]Zero-inflated negative binomial model, with significance test for the negative binomial part of the model.

Summary/Conclusion: Patients with CAD used significantly more healthcare services than matched comparators, both before and after their diagnosis. Current management of CAD has a substantial impact on HRU, placing a burden on patients and healthcare systems.

EP1194 THE LIFETIME ECONOMIC BURDEN OF PYRUVATE KINASE DEFICIENCY IN THE UNITED STATES

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Background: Pyruvate kinase (PK) deficiency is a rare, inherited disorder caused by autosomal recessive mutations in the *PKLR* gene, whereby a glycolytic defect causes reduced adenosine triphosphate levels and leads to hemolytic anemia. Patients with PK deficiency can experience serious complications associated with the disease and its treatment, including perinatal complications, iron overload, bone fractures, pulmonary hypertension, and liver cirrhosis. The current standard of care for PK deficiency is supportive, including blood transfusions, splenectomy, cholecystectomy, iron chelation therapy, and/or interventions for other disease-related morbidity. Recent studies have demonstrated that iron overload and need for chelation is common even in patients that do not require regular transfusions. There is no approved drug therapy for this condition. Although the clinical burden in patients with PK deficiency is well documented, the economic burden of long-term disease management, procedures, and clinical complications has not been investigated and is unknown.
Aims: This study aimed to estimate the lifetime burden of patients with PK deficiency, from the perspective of the healthcare payer, in the United States (US).
Methods: A micro-costing method was employed to determine the direct costs associated with the diagnosis, treatment and monitoring of PK deficiency, and complications over a patient's lifetime. The occurrences and frequency of complications and monitoring were derived from scientific literature and verified with clinical experts. Patient mortality was based on a previously published report of the PK deficiency population. Cost inputs were derived from public databases (eg, Medicare physician fee schedule, Healthcare Cost and Utilization Project [HCUP]) and economic literature from a US payer perspective. Total costs were calculated as the sum of early pediatric (0–5 y), late pediatric (6–17 y), and adult phases. Adult patients were grouped based on transfusion status (RT, regularly transfused [≥6 transfusions per year]; NRT, not regularly transfused; NT, never transfused). A univariate sensitivity analysis, at 10% variance, was conducted to identify major cost drivers.
Results: The mean lifetime direct cost of a patient with PK deficiency is $3.3 million with the majority of the costs occurring during the adult phase ($3.0 million). The mean lifetime cost varied by transfusion status with lifetime costs of $4.4 million, $2.8 million, and $2.4 million for RT, NRT, and NT patients, respectively (Table). Although transfusion and chelation costs were higher in those with a greater transfusion burden, the costs of complications, particularly from iron overload, were higher in the NRT and NT populations. The main cost-drivers overall were the adoption rate and cost of chelation therapies, the cost and frequency of transfusions, and the cost associated with complications.

Total Lifetime Direct Costs by Subgroup (2020 USD)

	RT	NRT	NT
Diagnosis	$10,689	$10,689	$10,689
Monitoring	$432,242	$129,470	$97,437
Transfusion	$1,076,923	$203,786	$94,644*
Chelation Therapy	$1,849,451	$1,030,223	$750,685
Procedures	$44,640	$42,263	$37,833
Disease Complications	$752,676	$1,187,667	$1,186,958
End of Life Care	$227,243	$227,243	$227,243
Total	**$4,393,864**	**$2,831,341**	**$2,405,489**

*Transfusion cost before adulthood
RT=regularly transfused (≥6 transfusions per year), NRT= not regularly transfused, NT=never transfused, USD=United States dollar

Summary/Conclusion: The results of this study suggest that the lifetime economic burden of PK deficiency, from the perspective of the healthcare payer, is substantial. A large proportion of the direct cost of PK deficiency comes from transfusion and chelation therapies. Although the model provides a foundation for further economic evaluations, additional research regarding real-world healthcare resource utilization and indirect costs would further improve our understanding of the economic burden.

EP1195 "SHEFAA" AN ITP PATIENT ADVOCACY GROUP: AN EGYPTIAN SINGLE CENTER EXPERIENCE

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Background: The patient is the main constant in the delivery of health care throughout the world, patient advocacy organizations play a critical role in increasing public awareness of a specific disease and in demanding

improvement in approaches to treatment. Patients advocacy group also enables patients to make informed decisions about their disease and to be responsible members of the health care team. To do this, patients must be informed about their condition and their treatment options, and given the opportunity to express their understanding, values and beliefs. They must be given the time and encouragement to ask questions, raise concerns, and express their feelings about what is happening to them.
Aims: We aimed to raise the awareness of Immune thrombocytopenia being not uncommon disease anymore
Methods: we targeted ITP patients as well as their families, friends and normal populations through regular direct group meetings, webinars, telemedicine and Facebook page in order to increase the awareness of ITP, correct the wrong believes about the disease which may leads to wrong behaviors.
Results: Our patient advocacy group was initiated in 2017 by doing many patients regular meetings explaining disease in simple Arabic language in collaboration with different medical specialties like gynecology, nutrition and psychiatry teams, raising the awareness of the disease by celebrating the ITP awareness month in September each year with patients and their families, also we became part of ITP global group actively participating in their activities. We initiated Facebook campaign supported by Novartis pharama. Our campaign achieved in 4 months duration (from august 2020 to December 2020) 155.537 followers, with 673.157 post engagements, 78% of the followers were female (68% of them were between 25-45 years old), 126.031 were Egyptian followers but other followers were from middle east countries as Saudi Arabia, Libya, UAE, Kuwait, Algeria, Jordon and morocco. All information about ITP were discussed in native simple language especially the nature of ITP, clinical pictures, diagnosis, goals for treatment, models of treatment, potential difficulties in adherence to treatment and Plan how to overcome these difficulties Most interaction were noticed in posts about COVID19 and ITP especially vaccination issue. Regarding questions which were asked frequently; "how to know that I have thrombocytopenia" "what to do in pregnancy" and "what are the symptoms of ITP".



Summary/Conclusion: Patient–health professional relationships which are grounded in effective communication, trust, reciprocal information, mutual understanding and respect are a foundation, and even a prerequisite for effective and efficient care

EP1196 CHRONIC MYELOID LEUKEMIA ACCESS TO TYROSINE KINASE INHIBITORS AND POLYMERASE CHAIN REACTION TESTING IN CENTRAL AND EASTERN EUROPE AND WEST ASIA REGION: A PATIENT ADVOCACY PERSPECTIVE.

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Background: Chronic myeloid leukemia (CML) patient organisation representing countries of the CML Advocates Network Easter Europe and West Asia region have come to conclusion that they share similar issues in access to treatment and monitoring tools. The reason is the lack of a common database with the relevant information about CML.
Aims: The goal was to create the CML Atlas of Central and Eastern Europe and West Asia region to showcase the most relevant data on CML about access to tyrosine kinase inhibitors (TKIs) and monitoring tools to support CML patient organisations' advocacy in those countries.
Methods: An European online survey was conducted, recruiting CML patient advocates and doctors from 19 countries, representing over 26.000 CML patients from Armenia, Croatia, Czech Republic, Georgia, Hungary, Kazakhstan, Kosovo, Kyrgyzstan, Lithuania, Moldova, North Macedonia, Poland, Russia, Serbia, Slovenia, Tajikistan, Turkey, Ukraine and Uzbekistan. The survey started on 1st December 2019 and lasted until 31st March 2020 covering the following topics: CML general information, availability of TKIs and PCR testing, clinical trials and treatment free remission data. Presented data as of 1st July 2020.
Results: 19 countries reported Imatinib available, 13 of them on insurance. Collected data show that in Armenia, Georgia, Kyrgyzstan, Moldova, Tajikistan and Uzbekistan availability was managed by donations; in Kazakhstan, Imatinib was available both on insurance and donations and no countries reported its availability in clinical trials.
18 countries reported Nilotinib available, with the exception of Kosovo, although 12 countries declared it was just on insurance. Data from Armenia, Georgia, Kyrgyzstan, Moldova, Tajikistan and Uzbekistan show that Nilotinib was available on donations and no countries reported its use in clinical trials.
16 countries informed on Dasatinib availability: the drug was obtainable on insurance in 10 of them, and through donations in Armenia, Kyrgyzstan, Moldova, North Macedonia, Serbia and Tajikistan. No countries reported access to Dasatinib through clinical trials.
9 countries reported that Bosutinib was available on insurance. Therefore, in 10 countries of the region, this drug was not available for CML patients.
Ponatinib reported as an available drug on insurance in 6 countries as well as on donations, while in 2 countries was reported as available in clinical trials. This medicine was not available in 6 countries of the region.
Collected data about testing demonstrate that PCR was available in all countries participating in the survey, except Kosovo. In the majority of countries, price of PCR is covered by public insurance. However, in countries as Armenia, Kyrgyzstan and Tajikistan access to PCR testing is provided through donations.



Note: Kosovo* is not presented as PCR is not available in the country.

Figure 1. PCR test data in the CML Advocates Network Easter Europe and West Asia region. July 2020.

Summary/Conclusion: There are important differences in access to TKIs to treat CML patients between countries of the Central and Eastern Europe and West Asia region. While five TKIs are available on these countries, the majority of them are just available on insurance and/or donations. Access to free PCR testing for CML patients is not ensured in all countries. There are opportunities to improve access to high-quality and safe therapies and effective monitoring tools for CML patients in the region.

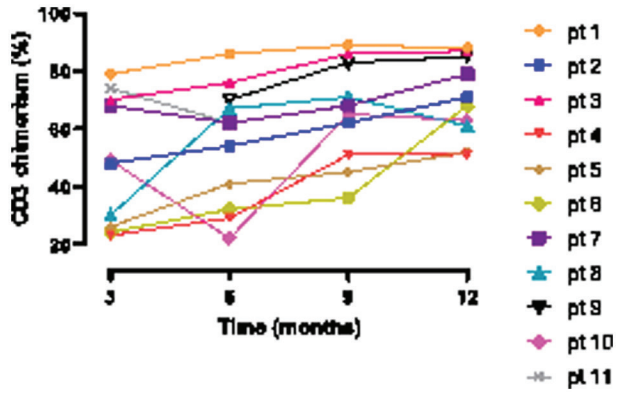
Sickle cell disease

EP1197 ADDING AZATHIOPRINE/HYDROXYUREA PRECONDITIONING TO ALEMTUZUMAB/TBI MAY REDUCE RISK OF GRAFT FAILURE IN MATCHED SIBLING DONOR ALLOGENEIC HSCT IN ADULT SICKLE CELL PATIENTS

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Background: Sickle cell disease (SCD) is a severe, inherited hemoglobinopathy, resulting in poor quality of life and reduced life expectancy. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only established curative treatment option for SCD. In adults, myeloablative conditioning is associated with significant toxicity. Matched sibling donor (MSD) transplantation with non-myeloablative conditioning (alemtuzumab/3Gy total body irradiation (TBI)) has shown promising results in adult SCD patients. Patients treated with this regimen had their sickle cell phenotype corrected with only mild complications and no reports of graft-versus-host disease (GvHD). However, a large part of these patients reached very low donor T-cell chimerism, resulting in 13% graft failure and necessitating chronic use of immunosuppression to avoid graft failure. We hypothesized that adding azathioprine (suppressing patient T-cells) and hydroxyurea (reducing bone marrow expansion) as preconditioning to the alemtuzumab/TBI regimen might improve donor chimerism and reduce risk of graft failure.
Aims: In this study we prospectively investigate the effects of azathioprine/hydroxyurea preconditioning on donor chimerism and graft failure in patients receiving non-myeloablative MSD HSCT for SCD.
Methods: Adult SCD patients with an MSD were eligible for this treatment. After 3 months of azathioprine 150mg qd and hydroxyurea 25mg/kg qd, erythrocyte exchange transfusion was performed on day −10. Alemtuzumab/TBI conditioning was started on day −7, as described by Hsieh et al (NEJM, 2009). Graft-vs-host-disease (GvHD) prophylaxis consisted of sirolimus.
Results: As of august 2020, eleven SCD patients (median age 26 (range 19-49) years) were transplanted. All patients engrafted successfully. After a median follow-up of 22 months, median donor myeloid and T-cell chimerism were 100% (range 84%>100%) and 68% (range 51%>88%), respectively. These donor chimerism percentages are higher than previously reported with alemtuzumab/TBI only. All patients had a corrected SCD phenotype with normalized hemoglobin levels. Patients reaching one year post-transplantation were able to stop sirolimus without decreases in chimerism. Only one patient developed acute grade II intestinal GvHD, that responded well to steroids. There were no viral reactivations or signs of macrophage activation syndrome.



Summary/Conclusion: Azathioprine/hydroxyurea preconditioning prior to alemtuzumab/TBI results in improved donor chimerism, potentially reducing risk of graft failure after non-myeloablatieve MSD transplantation in SCD patients. Importantly, in contrast to earlier studies, all patients in this study were able to stop sirolimus as scheduled. Adding azathioprine/hydroxyurea preconditioning renders the alemtuzumab/TBI non-myeloablative HSCT, with low risk of transplantation-related toxicity, a viable alternative for adult SCD patients.

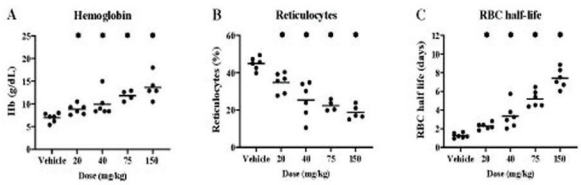
EP1198 GBT021601 IMPROVES THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE IN A MURINE MODEL

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Background: Sickle cell disease (SCD) is a genetic disorder caused by the inheritance of two alleles bearing a single nucleotide change in the β globin gene coding sequence. The pathophysiologic mechanism of SCD involves polymerization of intracellular sickle hemoglobin (HbS) following deoxygenation in the microvasculature, leading to decreased red blood cell (RBC) deformability, morphologic sickling of RBCs, decreased RBC survival, microvascular obstruction, and clinical complications. Voxelotor, a HbS polymerization inhibitor recently approved for the treatment of SCD in the United States, is an allosteric modifier of hemoglobin (Hb) that increases the proportion of oxygenated Hb in all RBCs. In clinical studies in patients with SCD, voxelotor demonstrated that doses of up to 1500 mg daily achieved Hb modifications of ~27%, was well tolerated and resulted in reduced hemolytic anemia. GBT021601 is a potent second generation HbS polymerization inhibitor with the potential to achieve even higher Hb modification in patients with SCD at lower doses and therefore with less pill burden.
Aims: To evaluate the effect of GBT021601, a second generation HbS polymerization inhibitor, in mouse model of SCD.
Methods: To evaluate its effect on the pathophysiology of SCD, GBT021601 was orally administered at 20, 40, 75, and 150 mg/kg once-daily doses for 21 days in Townes SCD mice (SS mice).
Results: At steady state, GBT021601-treated SS mice achieved Hb occupancies (at minimum concentration in plasma) of 6%, 12%, 21%, and 29% corresponding to 20, 40, 75, and 150 mg/kg doses, respectively. This resulted in a dose-dependent reduction in p50, partial pressure of oxygen at 50% Hb saturation, of SS mouse blood from ~28 mmHg (vehicle-treated) to 11 mmHg at the highest dose tested. Consequently, GBT021601 significantly reduced in vivo circulating sickled cells and ex vivo sickling of SS mouse blood under hypoxic conditions (pO_2, 20 mmHg). Consistent with its anti-polymerization activity, GBT021601 reduced hemolysis as demonstrated by: 1.) an increase in Hb of up to 6.7 g/dL (Figure 1A), thereby achieving the normal range for wildtype mice, and 2.) a reduction in the percentage of reticulocytes of up to 58% relative to vehicle-treated SS mice (Figure 1B). Additionally, GBT021601 treatment increased the percentage of mature RBCs, reduced the percentage of mitochondria-containing RBCs, and improved RBC deformability, collectively indicating an overall improvement in RBC health. Consistent with improved Hb levels, reduced hemolysis, and improved RBC health, GBT021601 dose-dependently increased RBC half-life from 1.3 days in vehicle-treated SS mice to 7.4 days in SS mice treated with 150 mg/kg GBT021601 (Figure 1C). Furthermore, treatment of SS mice with GBT021601 for 21 days led to a significant reduction in spleen weight, indicating an improvement in splenic blood flow and organ function. Lastly, GBT021601 treatment for longer than 21 days (up to 42 days) indicated a dose-duration dependent improvement in hemolysis markers including Hb level and reticulocyte count.

Figure 1. GBT021601 Treatment Was Associated With Dose-Dependent Changes in Hb, Reticulocytes, and RBC Half-Life.



Individual animal data and means are shown.
Data were analyzed by Student's t test and Hochberg's method for multiple testing. *$P<0.05$.
Hb, hemoglobin; RBC, red blood cell.

Summary/Conclusion: Together, these data demonstrate that GBT021601, a next generation HbS polymerization inhibitor, normalized Hb, reduced hemolysis, and significantly improved RBC health, RBC half-life, and organ function in a mouse model of SCD. These data support clinical development of GBT021601 as a potential best-in-class HbS polymerization inhibitor for patients with SCD.

EP1199 ELIGIBILITY FOR EMERGING THERAPIES IN SICKLE CELL DISEASE

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Background: Management of patients with sickle cell disease (SCD) in the UK relies largely on transfusion therapy and hydroxycarbamide alongside supportive care. New therapies to improve morbidity and mortality are needed. Two new therapies undergoing NICE technology appraisal are Crizanlizumab and Voxelotor. Crizanlizumab, a p-selectin inhibitor, has been shown to reduce the frequency of vaso-occlusive crisis in patients aged 16 or over in a randomised, placebo-controlled phase 2 trial (SUSTAIN)[1]. Voxelotor is an HbS polymerisation inhibitor and showed increased haemoglobin levels with reduced markers of haemolysis in a phase 3 trial (HOPE)[2]. Both were approved by the FDA in November 2019.

Aims: The eligibility criteria used in the SUSTAIN and HOPE trials have been compared against the Bristol Haematology and Oncology Centre and Oxford University Hospitals SCD cohorts to identify those patients who would be eligible for these emerging therapies.

Methods: The patient databases were cross-referenced with electronic notes to identify eligibility data. Vaso-occlusive crises (VOC) were determined by calls to the haemoglobinopathy team or helpline, attendance at the Acute Haematology Unit or admission. Electronic blood results were checked to ensure haemoglobin fell within the specified ranges.

Results: Results of analysis of SCD patient database according to eligibility criteria for Crizanlizumab and Voxelotor as described in the SUSTAIN and HOPE trials [1,2] are shown in Table 1. Results show that, out of 158 patients with eligible sickle cell disorders, only 7 (4.4%) were eligible for both therapies. 8 (5.1%) were eligible for Voxelotor only, and 2 (1.3%) were only eligible for Crizanlizumab. Patients with no VOC in 12 months were ineligible for either therapy (n=75, 47.5%) and just under half of these patients had a baseline haemoglobin over the range of eligibility for Voxelotor (n=37, 23.4%). 5 patients with a single VOC in 12 months had an Hb out of range for Voxelotor (3.2%). Regular transfusion therapy was the second most common exclusion (n=29, 18.3%). Age over 65 excluded 8 (5.1%) of our patients, and 6 (3.8%) had significant comorbidity that rendered them ineligible. 15 (9.5%) of our patients had moved out of area so estimates of VOC per year are likely to be inaccurate. Other reasons for exclusion included titration of hydroxycarbamide and family planning.

	Bristol	Oxford	Total
Ineligible for analysis	9	6	15 (9.5%)
Excluded - age	5	3	8 (5.1%)
Excluded – RCE	14	15	29 (18.4%)
Excluded – comorbidity	2	4	6 (3.8%)
Excluded – other	1	2	3 (1.9%)
Hb>105g/dL + insufficient no. VOC p.a.	22	15	37 (23.4%)
Insufficient no. VOC p.a.	26	12	38 (24.1%)
Eligible for both therapies	3	4	7 (4.4%)
Eligible for Crizanlizumab only	2	0	2 (1.3%)
Eligible for Voxelotor only	6	2	8 (5.1%)
Insufficient no. VOC p.a. for Crizanlizumab, Hb out of range for Voxelotor	5	0	5 (3.2%)
Total	95	63	158

Table 1: Results of analysis of SCD patient database according to eligibility criteria for Crizanlizumab and Voxelotor as described in the SUSTAIN and HOPE trials [1,2] (no. = number, p.a.= per annum)

Summary/Conclusion: Though new therapies are being developed for prevention of VOC in SCD, few patients in our cohort are eligible for these. Incidence of severe VOC may be underestimated as patients self-manage at home, particularly in the current Covid-19 pandemic. This should be kept under review and closer liaison with patients about their VOC may help identify eligible patients. Strict adherence to eligibility based on that of clinical trials is likely to result in very few patients benefitting from these new therapies.

EP1200 HEMOPEXIN PROTECTS HUMAN ENDOTHELIAL CELLS FROM HEME-DRIVEN ACTIVATION AND DAMAGE IN VITRO

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Background: One of the most abundant proteins in the human body is Hemoglobin (Hb). Upon rupture of red blood cells, cell-free Hb may initiate adverse pathophysiological reactions. A well characterized example of Hb-triggered pathophysiological disorders is sickle cell disease (SCD). SCD is characterized by a single nucleotide mutation of the β-globin gene resulting in Hemoglobin-S (HbS) instead of the normal HbA. Polymerization of HbS shortens the lifespan of sickle red blood cells and promotes intra- and extravascular hemolysis. In cell-free Hb ferrous Hb (Fe^{2+}) is oxidized into ferric Hb (Fe^{3+}) promoting the dissociation and transfer of heme into lipid compartments where the generation of cytotoxic and pro-inflammatory reaction products are triggered. These processes eventually lead to endothelial cell activation and damage. The natural plasma protein hemopexin (Hpx) is a heme scavenger and binds heme in a 1:1 binding ratio with highest affinity. Hpx-bound heme is rendered relatively non-reactive and is delivered safely to hepatocytes for endocytosis and degradation.

Aims: Investigating the protective function of Hpx on endothelial cells exposed to elevated levels of cell-free heme.

Methods: Human umbilical vein endothelial cells (HUVEC) were exposed in vitro to heme in the presence or absence of different Hpx doses. As a read-out, different markers for endothelial cell activation were analyzed by Western Blot, multiplexed particle-based flow cytometry (Luminex), flow cytometry or on mRNA levels by qRT-PCR. Briefly, confluent HUVEC were preincubated with Hpx at different concentrations for 5 min before stimulation with heme for various lengths of time. Following stimulation cells were analyzed by Western Blot for the expression of HO-1, a sensitive marker for heme exposure. Expression of pro-inflammatory cytokines IL-6 and IL-8, cell adhesion molecule VCAM-1 and blood glycoprotein von Willebrand factor (vWF) were analyzed on mRNA levels by qRT-PCR or in cell culture supernatants by Luminex. All these investigated proteins are well known markers for endothelial cell activation.
Alternatively, heme stimulation of Hpx-preincubated HUVEC was conducted for 25 min and cells were analyzed by flow cytometry for membrane bound P-Selectin expression, another robust endothelial cell activation marker.

Results: In the absence of Hpx, Heme consistently showed strong stimulatory capacity on HUVEC reflected in a robust upregulation of pro-inflammatory cytokines, VCAM-1, vWF, HO-1 and P-Selectin. Increasing Hpx concentrations during heme-mediated stimulation led to a dose-dependent reduction in HUVEC activation markers and once an equimolar ratio between heme and Hpx had been reached, the expression of HO-1, P-Selectin, VCAM-1, vWF and pro-inflammatory cytokines was lowered to background levels.

Summary/Conclusion: The presented data underlines on the one hand the stimulatory capacity of heme on endothelial cells and demonstrates on the other hand the efficient heme scavenging potential of Hpx. Hpx-bound heme molecules are rendered non-reactive and consequently, Hpx potently prevents the pro-inflammatory effect of heme on endothelial cells. This effect results in a strongly reduced expression of endothelial activation markers in heme-stimulated cells under an equimolar ratio of heme and Hpx. Hence, our study suggests a protective role of Hpx for endothelial cells exposed to elevated levels of cell-free heme due to intravascular hemolysis, a phenomenon seen in Hb-triggered pathophysiological disorders such as SCD.

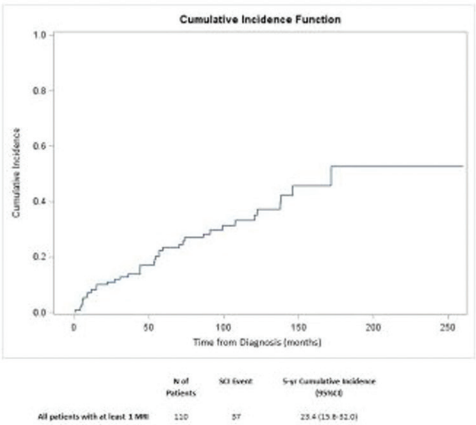
EP1201 SILENT CEREBRAL INFARCTS IN A PEDIATRIC SICKLE CELL DISEASE NATURAL HISTORY COHORT: TOO MANY, TOO SOON?

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Background: Cerebrovascular complications cause significant morbidity from childhood in patients with sickle cell disease (SCD). Stroke and large vessel vasculopathy are the most severe manifestations, but silent cerebral infarcts (SCI) are more common and impact neurocognitive development and quality of life. Routine use of Magnetic Resonance Imaging/Angiography (MRI/MRA) as a screening tool since childhood is suggested in some European guidelines. Risk factors for SCIs are known, but real-world studies documenting contemporary rates of SCI and evaluating the association between hemoglobin (Hb) levels and the incidence of SCIs are limited.
Aims: To determine the incidence and evolution of SCIs in a pediatric natural history cohort in Italy and investigate the correlation between hematological variables, treatment and SCI.
Methods: A retrospective analysis was performed in a cohort of children with SCD prospectively enrolled in a natural history study from Oct 2007 to Dec 2020. The standard care includes annual TCD from age 2, MRI/MRA from 6 years old, every 2 years; Hydroxyurea (HU), Chronic Red Blood Cell Transfusion and Bone Marrow Transplantation (BMT) are prescribed according to national guidelines. Two-sample t-test and Welch t- test for unequal variances were used to compare means of Hb values and hemolysis markers in patients with and without SCIs. Cumulative incidence function (CIF) estimated incidence of SCI occurrence. Patients were censored at the moment of BMT, death or loss to follow-up.
Results: Of the 182 SCD patients identified, 110 (60%) underwent 1 evaluable MRI/MRA. 51% were male; 81% HbSS, 6% HbSβthal^0, 12% HbSC, 1% HbSβthal$^+$, 80% were from Sub-Saharian Africa, 11% from Europe, 5% from North Africa. Median age at diagnosis was 25.4 months (IQR 8.4-59.3); 48% were diagnosed before 24 months. Median follow-up time was 113.9 months (range 6.2-301.0)(IQR 79.2-153.3). Overall, 55.5% received HU, 11% chronic transfusion, 19% HU and transfusion (only 4 in combination for recurrent VOCs or switch protocol, the remaining in sequence), 14.5% received no disease modifying therapy; 17% underwent BMT. Mean age of HU start was 92 months (range 10.1-236.9). Median age at first MRI was 6.5 years (IQR 4.64-10.01). SCIs occurred in 33.6% of patients with a MRI test performed with no difference between genotypes. A SCI was detected at first MRI in 78.3% of patients, with mean lesion burden of 1550.1 mm3 (range 60.6-5916). 22/37 had follow up MRIs evaluable in this analysis; in 6 patients the lesion burden increased (mean +290 mm3): 4/6 were teenagers with poor adherence to HU treatment or behavioural risk factors (cigarette smoke), 1/6 had large vessel vasculopathy, 1/6 had epilepsy.Patients with SCIs had lower Hb (8.3 vs 9 g/dl), higher indirect bilirubin (42.8 vs 34.9 umol/L) and reticulocytes (291932 vs 249719/mm3) compared to patients without SCIs (p ≤0.0001).The overall cumulative incidence of SCIs at 5 years from SCD diagnosis was 23.4 (95%CI 15.6-23.0) [Figure 1] generally increasing over time, and the 5-year cumulative incidence was 63.4 (95%CI 43.7-77.9) among patients with no therapy administered.

FIGURE 1. Cumulative Incidence of Silent Cerebral Infarcts in the Pediatric Sickle Cell Disease Population [Time from SCD diagnosis]



Summary/Conclusion: Our real-world analysis demonstrates that even in pediatric SCD patients who undergo regular screening and have access to treatments, SCI burden is still high, but could be stabilized with early therapy and additional interventions. Given the observed differences in markers among patients with and without SCIs, hematological or behavioral risk factors should be considered in screening programs.

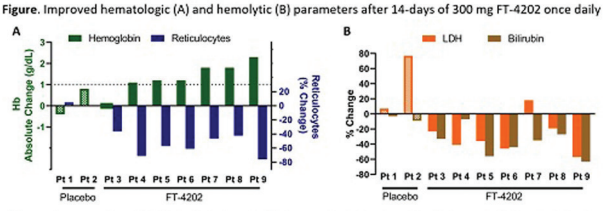
EP1202 FT-4202 IMPROVES HEMATOLOGIC AND HEMOLYTIC PARAMETERS IN A PHASE 1 STUDY OF PATIENTS WITH SICKLE CELL DISEASE

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Background: Polymerization of deoxygenated hemoglobin S (HbS) is the precipitating event leading to red blood cell (RBC) sickling, hemolysis, and vaso-occlusion. The pathogenesis of sickle cell disease (SCD) is exacerbated by increased levels of 2,3-DPG, which decrease O_2 affinity, and decreased levels of ATP, which impact RBC function. FT-4202 is a small molecule activator of erythrocyte pyruvate kinase (PKR) that decreases 2,3-DPG and increases ATP in RBCs. In healthy volunteers (HVs), FT-4202 was well tolerated in both single ascending dose (SD) and 14-day (2wk) once daily (QD) multiple ascending dose (MD) cohorts (Kalfa, 2019). In patients (pts) with SCD, a SD of FT-4202 was well tolerated and demonstrated similar pharmacokinetic (PK) and pharmacodynamic (PD) responses as in HVs (Estepp, 2020). Based on these initial results, two 2wk SCD MD cohorts (SCD MD1 [300mg FT-4202/placebo (P)] and SCD MD2 [600mg FT-4202/P]) were initiated in pts with SCD. The unblinded results of the SCD MD1 cohort are described here; data from the ongoing SCD MD2 and 12wk open label SCD MD (400mg FT-4202 QD) cohorts will be presented [NCT03815695].
Aims: To evaluate the safety and PK/PD of FT-4202 in HVs and pts with SCD.
Methods: In each 2wk SCD MD cohort, a minimum of 9 pts, randomized 7:2 to FT-4202:P, were required for safety/dose escalation decisions. Safety included treatment (Tx)-emergent adverse events (AEs), vital signs, ECGs and laboratory parameters. Blood sampling for PK and PD (RBC 2,3-DPG and ATP) was performed for up to 7 days after end of treatment (EOT). Exploratory studies included P_{50} and RBC deformability with controlled deoxygenation/reoxygenation and varying osmolality (Lorrca® oxygenscan and osmoscan).
Results: In the SCD MD1 cohort, of 9 pts (8 Hb SS; 1 SB+ thal) randomized 7:2 to FT-4202:P, 6 pts were on hydroxyurea. Eighteen AEs were reported in 7 pts (6 FT-4202, 1 P) with 16/18 AEs unrelated to study Tx; related AEs were headache and nausea (n=1 each). All AEs occurring in FT-4202 pts were ≤ grade 2. Three uncomplicated sickle pain events reported in 2 FT-4202 pts were consistent with SCD history and managed with standard home pain medications (no SAE/no hospitalization). Consistent with expected PD effects of PKR activation, rapid and sustained pharmacological activity was observed. In FT-4202 pts, 2,3-DPG levels decreased within 24h (p=0.031), while ATP levels increased through Tx day 7 (p=0.031). Both effects were sustained through the 2wk Tx period. In FT-4202 pts, Hb O_2 affinity was increased as demonstrated by decreased P_{50} (p=0.031), reaching comparable values to untreated HVs. The increased O_2 affinity and ATP were associated with improved sickle RBC deformability across an O_2 or osmotic gradient; this improvement persisted for up to 7 days post-Tx in some pts. After 2wks, Hb increased (median +1.2 g/dL, p=0.031), with 6/7 pts having a maximum increase of >1 g/dL, occurring at EOT in 5/6 pts. Significant decreases in reticulocyte count (median -57%, p=0.016), LDH (median -36%, p=0.031), and bilirubin (median -35%, p=0.016) were also observed (Figure).

Figure. Improved hematologic (A) and hemolytic (B) parameters after 14-days of 300 mg FT-4202 once daily



(A) In patients receiving FT-4202, 6 of 7 had a > 1 g/dL increase in Hb (median: 1.2 g/dL [range 0, 2.3]) and all 7 had a decrease in reticulocytes (median: -57% [range -36%, -76%]) over baseline. **(B)** In patients receiving FT-4202, 6 of 7 had a decrease in LDH (median: -36% [range +18%, -57%]) and all 7 had a decrease in total bilirubin (median: -35% [range -7%, -63%]) over baseline. Hb = hemoglobin; LDH = lactate dehydrogenase.

Summary/Conclusion: FT-4202 demonstrated a favorable safety profile in SCD pts when dosed at 300mg QD for 2wks. Consistent with PKR activation, FT-4202 decreased 2,3-DPG and increased ATP in RBCs, which correlated with increased RBC O_2 affinity and improved RBC deformability. FT-4202 improved hematologic and hemolytic parameters, with best responses often observed at the end of the 2wk Tx period. Data from the ongoing 2wk SCD MD2 (600mg FT-4202/P) and 12wk open label SCD MD (400mg FT-4202) cohorts will be presented.

EP1203 CYTOKINE MAPPING IN PAEDIATRIC SICKLE CELL DISEASE: ARE DIFFERENT SIGNATURES ASSOCIATED WITH DIFFERENT PHENOTYPES?

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Background: The mutation of the beta-globin gene that causes sickle cell disease (SCD), results in pleiotropic effects, such as haemolysis and vaso-occlusive crisis (VOC) that can induce inflammatory mechanisms with deleterious consequences on the organism. In fact, the activation of inflammatory cells (endothelial activation followed by a monocytic-neutrophilic response) and their intracellular pathways yield the production and secretion of numerous molecules that promote inflammation, including cytokines, chemokines, and growth factors. Few studies are currently available that evaluate the circulating levels of these molecules in a pediatric population.
Aims: The aim of this study is to identify a cytokine signature in a pediatric SCD population associated with specific clinical correlations.
Methods: This study includes 35 patients with SCD (23 males and 12 females, medium age 9.3 years, range 0-20 years) at steady state (no current haemolytic crises or VOC or other acute complications) and 10 healthy controls matched for age and ethnicity. A panel of 42 serum cytokines was measured using Luminex Performance Human XL-Cytokine-Discovery-Magnetic-Panel following the manufacturers' instructions (see table 1 for the list of analytes). These results were statistically related to clinical (age, gender, number of VOC per year, number of transfusions per year, pharmacological therapy) and laboratory data, such as hemoglobin (Hb)S, HbF and erythropoietin (EPO). Statistical analysis was performed to compare and correlate data. Data considered with statistical significance were those with p-value <0.05 and are therefore the ones presented in the results section.
Results: Significantly lower levels of IL-3, IL-4, IL-5, IL-7, IL-10, G-CSF and GM-CSF with higher levels of CXCL-2, CXCL-10, CCL-3, CCL-19 were observed in patients with SCD, compared to healthy donors. Furthermore, the group of patients who experienced VOC with higher frequency (1 or more crisis per year versus less than 1 crisis per year), showed lower levels of IL-3, IL-4 and IL-7. On the other hand, patients who underwent more frequently transfusion procedures (2 or more transfusions per year versus less than 2 transfusions per year) showed higher levels of IL-8, CCL-2, programmed death-ligand 1 (PD-L1), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TGF-alpha. We also related cytokines levels to laboratory data, finding a direct correlation between HbS concentration, EGF and CXCL-2; an inverse relation was observed between HbF and CCL-2. Also, a positive correlation was found between EPO, IL-3 and PD-L1.

IL-1 alpha	IL-6	IL-17A	CCL-3	CXCL-2	EGF
IL-1 beta	IL-7	IL-17E	CCL-4	CXCL-10	TGF-alpha
IL-1 RA	IL-8	IL-33	CCL-5	CX3CL-1	TNF-alpha
IL-2	IL-10	IFN-alpha	CCL-11	FLT3LG	TRAIL
IL-3	IL-12 p70	INF-beta	CCL-19	G-CSF	PD-L1
IL-4	IL-13	IFN-gamma	CCL-20	GM-CSF	CD40L
IL-5	IL-15	CCL-2	CXCL-1	VEGF	Granzyme B

Summary/Conclusion: These results showed that our population of patients with SCD displayed higher levels of specific chemokines compared to HDs and lower levels of cytokines related to a Th2 response, cytokines involved in bone marrow omeostasis (IL-3 and IL-7) and growth factors, possibly related to bone marrow exhaustion. Moreover, we interestingly found that different phenotypes of patients displayed different signatures of cytokines: in particular patients who experienced more VOC showed lower levels of Th2 related cytokines with lower concentration of IL-3 and IL-7 as well; on the other hand, patients with greater transfusion needs, expressed higher levels of cytokines related to apoptosis control and specific chemokines, as CCL-2; coherently, we observed that increased concentrations of EPO are related to higher levels of PD-L1.

EP1204 DISTINCTIVE EFFECTS OF SYSTEMIC IRON RESTRICTION BY FERROPORTIN INHIBITION THROUGH VIT-2763 AND DIETARY IRON LIMITATION IN A SCD MODEL

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Background: In sickle cell disease (SCD) a point mutation in the β-globin gene leads to synthesis of sickle hemoglobin (HbS) in erythrocytes. Upon deoxygenation in capillary blood vessels, HbS polymerizes in rigid fibers causing red blood cell (RBC) membrane distortion, intravascular hemolysis, increased endothelial adhesion and inflammation that might lead to vaso-occlusion (VO) and painful crisis. The kinetics of HbS polymerization is strongly dependent on the intracellular HbS concentration and a relatively small reduction of the cellular HbS concentration might prevent HbS polymerization and its sequelae. Clinical cases showed that iron deficiency in SCD patients decreases the mean corpuscular HbS concentration, intravascular hemolysis and pain crisis. A recent publication using the Townes mouse model of SCD showed that dietary iron restriction in juvenile mice (3 weeks old), fed low iron diet (LID) immediately after weaning, improved hemolysis, hematological and endothelial cell activation markers. Despite the promising effect in the mouse model, dietary iron restriction is not readily implemented in a compliant way for SCD patients. We have previously shown that iron restriction by inhibition of ferroportin, the unique iron transporter in mammals, reduced hemolysis, improved hemodynamics and prevented VO events in the Townes model of SCD.
Aims: To compare the effects of pharmacological iron restriction by the oral ferroportin inhibitor VIT-2763 to dietary iron restriction induced by low iron diet (LID) in adult Townes mice.
Methods: Townes mice (7 weeks old) engineered to synthesise exclusively human HbS were orally administered either the ferroportin inhibitor VIT-2763 (60 mg/kg bidaily) or vehicle for 6 weeks and received dietary iron corresponding to standard rodent diet (250 ppm iron). Dietary iron restriction was achieved by feeding Townes mice LID (10 ppm iron) for 6 weeks. Hematological parameters, hemolysis and vascular and systemic inflammation markers were evaluated at the study end.
Results: RBCs of Townes mice treated with VIT-2763, but not mice fed LID, showed hematological parameters indicating iron-restricted erythropoiesis: reductions in mean corpuscular volume (MCV), mean corpuscular Hb (MCH) and reticulocyte Hb content, whereas percentages of hypochromic and microcytic RBCs were increased with preserved RBC counts. Importantly, the intracellular HbS concentration, as measured by the corpuscular Hb concentration mean (CHCM) was significantly reduced in Townes mice receiving VIT-2763, but not in mice fed LID. In agreement with the determining effect of HbS concentration on intravascular hemolysis, mice treated with VIT-2763, but not mice fed LID, showed lower markers of intravascular hemolysis and endothelial dysfunction. Iron restriction by VIT-2763 but not via LID decreased blood leukocyte counts and circulating chemokines such as CCL5, suggesting the potential of VIT-2763 to reduce systemic inflammation in Townes mice. Iron restriction via LID, but not by VIT-2763, increased significantly erythropoietin (EPO) plasma levels, suggesting a feedback response to iron deficiency, which might further stimulate erythropoiesis.
Summary/Conclusion: This data demonstrated that VIT-2763 induced iron-restricted erythropoiesis and reduced vascular and systemic inflammation in adult Townes mice. The differential effects of VIT-2763 and LID in adult Townes mice highlight the role of systemic ferroportin inhibition for efficient iron restriction and therapeutic benefit.

EP1205 SYSTEMATIC, POINT-OF-CARE NEWBORN SCREENING FOR SICKLE CELL DISEASE IN RURAL MALI, WEST AFRICA

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Background: Sickle cell disease (SCD) is highly prevalent across sub-Saharan Africa and is a significant source of under-5 mortality. However, accurate characterization of the prevalence is difficult to determine due to the absence of systematic newborn screening in most African countries. Mali is a land-locked West African country with a high burden of sickle cell disease. Despite the critical need for early diagnosis of SCD to improve survival, wide scale diagnostic efforts utilizing isoelectric focusing (IEF) or high-performance liquid chromatography (HPLC) in sub-Saharan Africa have been limited by a paucity of laboratory equipment and trained personnel, unreliable supply chain for consumables, and overall expense. Point-of-Care (POC) testing for SCD is advancing rapidly and has the potential to reduce these barriers.
Aims: The objective of this study was to assess the feasibility and efficacy of systematic, POC newborn screening for SCD at a rural hospital in Mali, West Africa.
Methods: Between March 2019 and Jan 2021, all newborns at Koutiala Women's and Children's Hospital were offered screening for SCD with the Hemotype SC™ POC test kit (Silver Lake Research, Azusa, California, USA). Each kit included a plastic test tube, blood sampling device, and Elisa-based test strip. Verbal consent was obtained and heel-stick samples were procured within the first day of life. The samples were processed according to the package insert. The testing required 6 drops of unfiltered tap water. No other reagents or equipment were necessary. The results were available within 10 minutes and were provided to the caregiver prior to discharge. Newborns who were found to have sickle cell disease were referred to the SCD outpatient treatment program for ongoing management. Families of those with HbS trait or HbC trait received appropriate genetic counseling.
Results: 4822 infants were born over the study period and 4774 (99%) received POC screening. Screening results revealed Hemoglobin S trait; n=461(9.7%), Hemoglobin C trait; n=539 (11.3%), Hemoglobin SS; n=40 (0.84%), Hemoglobin SC; n=55 (1.2%), and homozygous C; n=16 (0.33%). In all, 95 infants (2.04%) were found to have sickle cell disease and were referred to the SCD outpatient treatment program. In addition, 22% of infants were found to be carriers of either HbC trait or HbS trait. The POC testing results were directly compared to historical pilot data of IEF-based SCD newborn screening at Koutiala Hospital between 2011-2014 (Table 1).

Table 1:

Newborn Screening Results Koutiala, Mali	Number of Infants 3/2019-1/2021	Incidence of Hemoglobin sub-type (POC)	Number of Infants 3/2011-6/2014	Incidence of Hemoglobin sub-type (IEF) **
Sickle Cell Trait	461	9.7%	414	9.5%
thal	40	0.84%	43	0.98%
Hemoglobin SC	55	1.2%	46	1.1%
Hemoglobin C trait	539	11.3%	386	8.81%
Homozygous C	16	0.33%	12	0.27%
SCD (any type)	95	2.04%	89	2.08%
Normal	3568	77.7%	3479	79.4%
Total Infants Screened	4774 (99%)		4380 (46%)	

** Pilot study data from IEF-based screening at Koutiala Hospital between 2011-2014 included to show the reliability of the POC testing platform.
This data was presented in abstract form at the Global SCD Network Symposium 2014, Rio de Janeiro, Brazil.

Summary/Conclusion: This pilot study is the first to examine the impact of systematic POC infant screening for SCD in Mali, West Africa. The rapidity of the POC testing resulted in a high newborn screening rate and increased the percentage of SCD-affected infants who successfully transitioned into the outpatient treatment program at the hospital. The POC testing results were very comparable and highly feasible when reviewed alongside historical IEF-based screening at Koutiala Hospital. While the incidence of hemoglobin abnormalities discovered by newborn screening was very similar between these different testing strategies, the percentage of evaluable births that were screened was much higher in this POC cohort than in the IEF pilot study (99% vs 46%). Overall, the low cost (<$2/test), ease of use, and reliability of the Hemotype SC™ POC test has the potential to make it a more desirable option for wider scale screening efforts in the future.

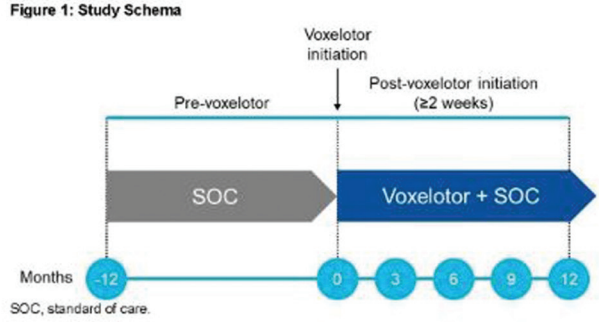
EP1206 REAL-WORLD EXPERIENCE OF PATIENTS WITH SICKLE CELL DISEASE TREATED WITH VOXELOTOR: A MULTICENTER, RETROSPECTIVE STUDY

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Background: Sickle cell disease (SCD) is an inherited disorder in which sickle hemoglobin (HbS) polymerization triggers red blood cell sickling, chronic hemolysis, anemia, and episodic vaso-occlusion. In addition to acute life-threatening events, SCD-related complications also include cumulative organ damage and early mortality. Voxelotor is an oral HbS polymerization inhibitor that increases hemoglobin (Hb) levels and reduces markers of hemolysis, and is approved in the United States for treatment of SCD in patients ≥12 years of age.
Aims: To characterize the real-world hematologic and clinical responses to voxelotor treatment in a multicenter, retrospective series of patients with SCD.
Methods: We collected and aggregated real-world, retrospective laboratory and clinical data on adolescents and adults (aged ≥12 years) with SCD treated with voxelotor as part of their usual care at multiple clinical centers in the United States. Laboratory and clinical data were collected 12 months before initiation of voxelotor and compared to similarly collected post-treatment data outcomes (Figure 1). Included patients received voxelotor for ≥2 consecutive weeks. Only data that were available from the patients' medical records and other secondary data sources were collected. Study data from 1 year before and up to 1 year after the first dose of voxelotor were entered in de-identified case report forms via an electronic data capture system.
Results: Approximately 300 patients have been treated across the 9 clinical centers participating in this study. Changes from the pre-voxelotor treatment period in Hb, hemolysis markers, and iron overload will be summarized descriptively. Changes in the annualized incidence rates of significant SCD-related clinical events from the pre-voxelotor treatment period will be reported, including vaso-occlusive crises, acute chest syndrome, priapism, cerebral infarcts (overt and silent), transient ischemic attack, leg ulcers, and measures of cardiac function, renal function, and tricuspid regurgitation velocity/pulmonary hypertension. The associations between changes in Hb, markers of hemolysis, and incidences of SCD-related clinical events will be evaluated. Health resource utilization changes from the pre-voxelotor treatment period will be reported, including acute clinic visits, emergency department visits, hospitalizations, acute and chronic transfusions, and home oxygen supplementation. Changes in health-related quality-of-life measures collected as part of usual care will be summarized descriptively. Adverse events by severity and relationship to voxelotor will be collected and tabulated.

Figure 1: Study Schema



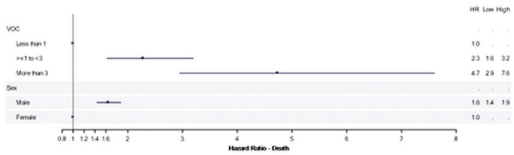
Summary/Conclusion: This study is the first to examine the real-world effectiveness of voxelotor in a multicenter, retrospective study and describe the observed changes in laboratory and clinical outcomes after at least 2 weeks of therapy in up to 300 patients.

EP1207 ASSOCIATION BETWEEN HOSPITALISED VASO-OCCLUSIVE CRISES AND MORTALITY IN SICKLE CELL DISEASE PATIENTS AGED 16 YEARS AND OLDER USING THE FRENCH NATIONAL HEALTH INSURANCE DATABASE (SNDS)

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Background: Patients with sickle cell disease (SCD) experience a wide range of complications thought to be due to the systemic impact of chronically inflamed vasculature, ongoing haemolysis, multi-cellular adhesion and ischemic damage. One of the most impactful complications is the vaso-occlusive crisis (VOC). An early study suggested a relationship between VOC occurrence and increased mortality. Reviewing this possible relationship, now that SCD management has improved, is important.
Aims: To assess the association between hospitalised VOCs and mortality, in SCD patients.
Methods: This study was a retrospective observational cohort study using the French national health insurance's claims database. This database gathers information on hospital records, primary and secondary care, and cause of death. Between 01-01-2012 and 12-31-2018, all 16 years and older patients identified as suffering from SCD (with either a hospital record or Long-Term Disease status with diagnostic ICD-10 codes D57.0-2) were included in the study. The index date was defined as the first interaction with the healthcare system (whether it was related to their SCD or not). Participants were followed-up for at least one year and until the end of the study (12-31-2018).
A hospitalised VOC was defined as a hospital stay of at least one night with a primary or related diagnosis of sickle-cell anaemia with crisis (D57.0), preceded by a transit through the emergency room (to avoid capturing SCD-related hospital stays for reasons other than VOCs).
The hospitalized VOC annual rate was defined as the total number of hospitalized VOCs during the follow-up divided by the number of follow-up years. Patients were categorised by the annual rate of VOCs they experienced into three groups: <1; 1 to <3; ≥3 VOCs per year.
Cox proportional hazards models using age as the time scale were used to study the effect of the cumulative rate of hospitalised VOCs on the risk of death, adjusted for gender.
Results: A total of 17,726 SCD patients were included in the study, of which 65.3% were females —a high proportion partly due to several hospitalizations found in women while pregnant. Ages ranged from 16 to 99 years and the average age was 35.0 years (±17.8, median 32.0).
Each calendar year, 86–89%, 9–10%, and 2–4% of patients experienced <1, 1 to <3, and ≥3 hospitalised VOCs, respectively. The mean age in increasing VOC groups was 36.3 (±15.8), 23.8 (±9.0), and 21.3 years old (±7.1), respectively. The proportion of women was 66.7%, 51.8% and 52.9%, respectively. The median time between two hospitalised VOCs was 37 days (Q1–Q3 22–96).
Over a median follow up of 7 years, 914 (5.2%) patients died; 75% died at the hospital. The mean age at death was 60.1 years (±19.7).
Patients with an average of ≥3 hospitalised VOCs per year over the follow-up were 4.73 times [2.95;7.61] more at risk of death during the follow-up period than patients with <1 hospitalised VOC per year.



Summary/Conclusion: Our study confirms, in a nationwide cohort in France in a real-life setting, that patients frequently experiencing hospitalised VOCs are at higher risk of death compared to patients seldom experiencing VOCs. The highest risk of hospitalized VOC recurrence was within 100 days of a prior hospitalized VOC. Therefore, patients with recurring VOCs are at greatest need for innovative therapies that could reduce or prevent these events. Patients who are able to reduce their annual number of VOCs may live longer.

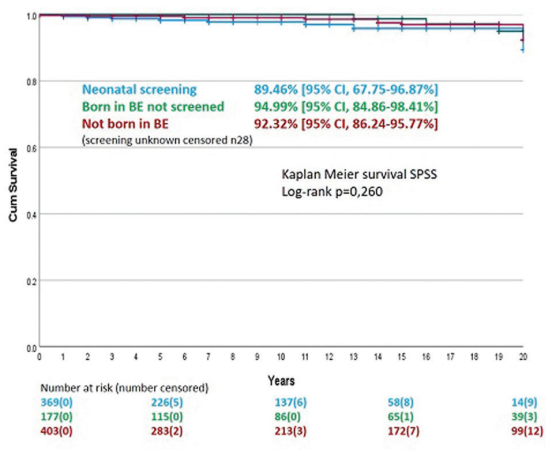
EP1208 BELGIAN SICKLE CELL DISEASE REGISTRY: DIVERSITY IN PRACTICE BUT LOW MORTALITY

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Background: The Belgian sickle cell disease registry (BSR) was initiated in 2008 and updated in 2018 to be a more user-friendly and easy-operable application.
Aims: To evaluate if disease modifying treatment (DMT) practice across centres participating in BSR is similar and what the mortality rate is among patients with sickle cell disease (SCD) included in the BSR.
Methods: All data from the initial 2008 database cohort were retrospectively encoded in the updated database format. All new data are recorded prospectively from neonatal screening or first contact until last annual follow-up (FU) or death. The data collected included diagnosis, demography, treatment and outcome data. Data were extracted from the database in January 2021 and were registered by 13 different centres.
Results: There were 977 patients registered with a median FU of 9 years (1-53 y). Median age at last FU was 13 (0-60 y). 654 (87,5%) have a severe phenotype (SS or Sβ°) and 51% are female. Among them, 546 (56%) were born in Belgium of which 369 (68%) were diagnosed by neonatal screening. In the absence of a neonatal screening, median age at diagnosis was 1 year (range 0-18). At last follow-up, 707 patients (72.3%) receive DMT: 523 patients receive hydroxyurea (HU), 126 underwent hematopoietic stem cell transplantation (HSCT), 53 are chronically transfused, 5 participate to a study with crizanlizumab.
Among not transplanted patients, the proportion of those receiving HU is significantly different among centres (46% to 75%; p<0,0001). The median age at which HU was initiated was also significantly different among the centres (4y to 21y; p<0,0001).
Most of HSCT were performed in two main centres i.e., 66 and 58, respectively. Median age at HSCT was significantly different between both centres (8y (2-15) versus 5y (0-19); p=0,004).
Twenty-four (2.5%) patients died which account for a mortality rate of 0.22/100 patients-years (PY) and a trend to increase with age (0,18/100PY < 18 years, 0.39/100PY 18 -40 years and 0.63/100PY > 40 years; p=0.056).
Kaplan-Meier estimate of survival at 20 years is similar regardless of the mode of diagnosis (89%, 95%, 92% respectively for neonatal screening, not screened and not born in Belgium; p=0.260)(Figure 1).

Overal survival cohort per screening group



Summary/Conclusion: Among the patient cohort recorded in the BSR, the proportion of patients receiving DMT, the age at start of HU and the

age at HSCT is significantly different between centres. A detailed analysis of practices based at least on demographic criteria, severity of the disease, etc. is needed to understand their causes. Mortality remains low but with a trend to increase with age. The absence of a national neonatal screening program, deaths occurring before diagnosis and no inclusion in the registry, represent a bias in the interpretation of the mortality. Survival status might be impacted by the proportion of patients that consented to participate to the BSR and could be different between the neonatal screening, born in Belgium not screened, and born abroad groups.

EP1209 REAL-WORLD EXPERIENCE OF VOXELOTOR FOR THE TREATMENT OF PATIENTS WITH SICKLE CELL DISEASE – A SINGLE-CENTER STUDY

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Background: Sickle cell disease (SCD) is an inherited disorder of the red blood cells (RBC) in which sickle hemoglobin (HbS) polymerizes and leads to a detrimental shape change in the RBC. This change, known as sickling, can trigger serious consequences including chronic hemolysis, anemia, and episodic vaso-occlusion and often leads to complications such as cumulative organ damage, disability, and accelerated mortality. Voxelotor is a first-in-class therapy that interferes with sickle cell polymerization, increases hemoglobin (Hb) levels, and reduces hemolysis. It is FDA approved for the treatment of SCD in patients 12 years of age and older.
Aims: The objective of this study was to quantify the clinical response to voxelotor treatment in a single-center series of 73 adult and adolescent patients with SCD.
Methods: We collected real-world clinical data from 73 adult and adolescent patients with SCD at the Prisma Health – Upstate Comprehensive SCD Program, Greenville, South Carolina, USA, under a data collection protocol for standard-of-care clinical data. Laboratory data were collected before initiation of voxelotor and were compared to the most recent laboratory value collected during treatment. All patients included in the analysis had received voxelotor for at least 2 consecutive weeks. Data from 13 patients were not included in the analysis, 7 patients who received less than 2 weeks of treatment, 3 after reporting adverse events (hypersensitivity reaction [n=2], diarrhea [n=1]), and 6 additional patients who did not receive medications due to insurance issues.
Results: Sixty patients were included in the current analysis. The age range was 12 to 70 years, average (SD) age was 31.1 years (15.36), and 61.7% were female. SCD genotypes represented included HbSS (85%), HbSC (6.7%), and HbSβ0 (6.7%). Mean baseline Hb was 8.2 g/dL. A stable dose of hydroxyurea (HU) was reported in 80.0% of patients at the time of voxelotor initiation and 26.7% of patients received exogenous erythropoietin (EPO) treatment plus HU. At the time of this analysis, patients received voxelotor for an average (range) of 3.9 months (0.5-13.6 months). Levels of Hb increased (post- vs pre-voxelotor, mean [SD]) by 2.0 g/dL (1.02 g/dL); whereas reticulocyte percentage decreased by 4.6% (3.7%), and total bilirubin decreased by 1.4 mg/dL (2.2 mg/dL). All patients who received exogenous EPO were able to either discontinue (n=11) or reduce the frequency (n=5) of EPO therapy after voxelotor initiation. The clinical improvements reported by patients included increased energy, improved activity tolerance, decreased pain symptoms, and reduced scleral icterus. The most common reported side effects were diarrhea, nausea, and rash. These side effects were mild and self-limited in most patients. Dose modification from 1500 mg to 1000 mg was only necessary in 3 patients with diarrhea.
Summary/Conclusion: The effects of voxelotor on Hb, reticulocyte percentage, and total bilirubin were of similar magnitude to values reported in the HOPE trial. In addition, consistent evidence of improved clinical status was associated with a robust hematologic response, including a reduction in EPO therapy. In summary, our study suggests that patients with SCD achieve meaningful clinical benefit with voxelotor therapy.

EP1210 PHARMACOKINETIC PROPERTIES OF A HUMAN PLASMA DERIVED HEMOPEXIN DRUG PRODUCT (CSL889) IN TOWNES HBSS-, WILD-TYPE MICE, RATS AND CYNOMOLGUS MONKEYS FOR THE TREATMENT OF ACUTE VOC IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited, autosomal recessive disorder that leads to hemolytic anemia and vascular disease, with a range of acute and chronic complications driven by self-perpetuating cycle of vaso-occlusion and vaso-occlusive crises (VOCs).
Aims: CSL889, a human plasma derived hemopexin, is being developed as a novel pharmacologic therapy to scavenge cell free toxic heme in patients with VOC, with the goal of reducing the duration and severity of acute VOC in adults and children with SCD.
Methods: In order to evaluate the pharmacokinetics (PK) of CSL889, single-dose PK studies were performed following intravenous (IV) administration in Townes HbSS mice, a model for sickle cell disease, (*Hbb*$^{tm2(HBG1,HBB*)Tow}$), wild type C57BL6 (WT) mice and rats at a dose of 35 mg/kg, and in cynomolgus monkeys at doses of 50, 150 and 500 mg/kg BW. Additionally, a PK following repeated dosing (up to 3 repeat doses each 4 hours apart at a dose of 500 mg/kg IV) in Townes HbSS mice was conducted. In addition to CSL889, the concentration-time profiles of hemopexin:heme complex and total heme were described. Townes HbSS mice were used because they express the human HbSS and mimic the major features of the human SCD (eg. sickled red blood cells (RBCs) with a half-life of 2.4 days vs normal RBCs with a half-life of 15.7 days in healthy mice). Quantification of total human hemopexin (CSL889) in mouse, rat and cynomolgus monkey was performed using LC-MS/MS.
Results: In comparison to WT mice, Townes HbSS mice showed a markedly decreased C_{max} (0.41 mg/mL vs 0.70 mg/mL) associated with a markedly increased clearance (23.0 vs 1.6 mL/kg/h) and consequently decreased half-life (7 vs 58 h) and mean residence time (MRT; 5 vs 81 h) following IV administration of CSL889. Similarly, the area under the curve (AUC_{0-inf}) was 14-fold higher in WT- compared to Townes HbSS mice (21.8 vs. 1.52 h*mg/mL). PK parameters of CSL889 in rats were comparable to that in WT mice - C_{max} (0.74 mg/mL), clearance (1.78 mL/kg/h), half-life (58 h) and AUC_{0-inf} (19.6 h*mg/mL).
For hemopexin, following repeated IV administration, plasma levels accumulated up to the 3rd dose, reached a plateau and declined subsequently over the following 24 hours. AUC_{0-inf} was 345 h*mg/mL, MRT 21.4 h, half-life 13.7 h and IVR 93%. For hemopexin:heme complex, the highest plasma levels were measurable at 5 min after the first dose of CSL889. Levels declined slightly until they reached a steady state after the last dose up to the last time-point measured. Total heme plasma concentrations first declined slightly and showed an increase to the end of the concentration-time profile (Figure 1).
In monkeys, C_{max} and AUC of CSL889 increased slightly less than dose-proportionally over the dose range of 50-500 mg/kg (C_{max} from 1.6 to 10.4 mg/mL and AUC_{0-inf} from 84.4 to 587 h*mg/mL). A slightly higher total clearance (Cl) [0.85 vs 0.66 vs. 0.61 mL/h/kg] was observed at the high dose compared to the intermediate and low dose. The terminal half-life following IV administration increased with dose from 80 to 103 h.

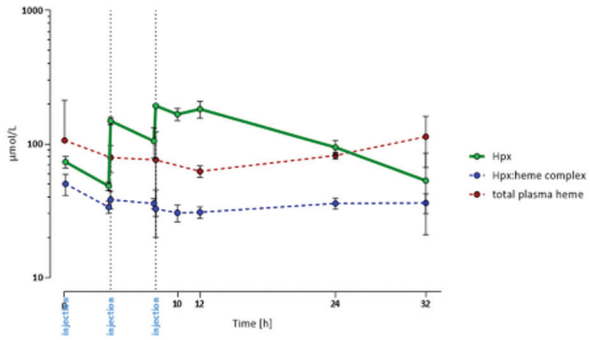


Figure 1: Hemopexin plasma concentration-time profile. For hemopexin (green solid line) plasma levels accumulated up to the 3rd dose, reached a plateau and declined subsequently over the following 24 hours. For hemopexin:heme complex (blue dotted line), the highest plasma levels were measurable at 5 min after the first dose of CSL889. Levels declined slightly until they reached a steady state after the last dose up to the last timepoint measured. Total heme plasma concentrations (red dotted line) first declined slightly and showed an increase to the end of the concentration-time profile. Baseline levels for hemopexin in plasma were below the LLOQ and for hemopexin:heme complex were slightly above the LLOQ.

Summary/Conclusion: Townes HbSS mice tested at 35 mg/kg showed a shorter half-life compared to the healthy rodent species (7 h vs. 58 h) suggesting an increased binding of CSL889 to accessible heme in SCD. Following repeated dosing in Townes HbSS mice increasing hemopexin concentration levels correlate with decreasing total heme plasma levels. The increase of total heme towards the end is most probably due to the saturation of the clearance mechanism and ongoing hemolysis.

EP1211 REAL-WORLD DATA FROM THE CRIZANLIZUMAB MANAGED ACCESS PROGRAM (MAP): BASELINE DISEASE BURDEN AND PRIOR TREATMENTS FOR PATIENTS WITH SICKLE CELL DISEASE (SCD) AND RECURRENT VASO-OCCLUSIVE CRISES (VOCS)

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Background: VOCs are the most common cause of SCD-related hospitalization and can lead to serious complications. Hydroxyurea (HU) has historically been a mainstay for VOC prevention, but new therapies are now available. Crizanlizumab is an anti-P-selectin monoclonal antibody approved in several regions to prevent/reduce VOC burden for SCD patients aged ≥16 years. Early access to crizanlizumab is possible before health authority approval in some countries via a MAP (NCT03720626). Baseline patient data are collected to assess their eligibility for MAP participation. We conducted a descriptive analysis of aggregated baseline data for patients eligible to enter the MAP in countries where publication of these data was allowed.
Aims: We analyzed baseline SCD characteristics and treatment history for patients participating in the MAP to assess real-world disease burden prior to receipt of crizanlizumab. The data set primarily included patients in Brazil, but also included those in Canada, Israel, Italy and Spain.
Methods: The MAP was designed to provide access to crizanlizumab for patients with serious or life-threatening disease for which no comparable or satisfactory alternative to crizanlizumab was available as treatment in their country. Crizanlizumab access was sought via independent request by each patient's physician. Other patient eligibility criteria were: age 16–70 years (18–70 years in Italy); confirmed SCD (any genotype); history of VOCs as assessed by the treating physician (including recurrent VOCs while receiving preventative therapies like HU); not eligible for a crizanlizumab clinical trial; and not participating in a chronic transfusion program (simple or exchange).
Results: As of 31 January 2021, baseline data were available for 124 patients eligible for this analysis. Median age was 33 years, 60% were female and 83% were from Brazil (Table). In the year before entering the MAP, 122 patients (98%) had experienced ≥1 home-managed VOC (median 6, interquartile range [IQR] 4–10), 118 (95%) had experienced ≥1 healthcare-managed VOC (median 4, IQR 2–5) and 106 (85%) had been hospitalized for SCD-related reasons (median 3, IQR 2–4).
Opioids had been taken by 118 patients (95%) in the year before entering the MAP; all of them took opioids for VOC-related pain. Of the 118 patients who took opioids, 47% took them <4 times a month, but 31% took them more than once a day (Table). Some physicians chose to provide specific HU-use information, for 93 patients, to help better characterize those patients' medical history. Of these patients, 24 (26%) had never taken HU and 69 (74%) had, either ongoing at baseline or at any prior point. Of those 69 patients, 66 (96%) reported opioid use in the year prior to MAP entry. Of those 66 patients, 55% took opioids <4 times a month, but 26% took opioids more than once a day (Table).

Table. Baseline characteristics and treatment history for patients eligible for the crizanlizumab MAP

Characteristic	Patients N=124
Median age, years (IQR)	33 (25–40)
Country, n (%)	
Brazil	103 (83)
Israel	8 (6)
Italy	6 (5)
Spain	6 (5)
Canada	1 (1)
Gender, n (%)	
Female	74 (60)
Male	50 (40)
Race/ethnicity, n (%)	
African American	64 (52)
Hispanic/Latino	20 (16)
Caucasian	15 (12)
Other	25 (20)
SCD genotype, n (%)	
HbSS	100 (81)
HbSβ°	10 (8)
HbSC	7 (6)
HbSβ+	6 (5)
Other	1 (1)
Taken opioids in the year before entering the MAP	**Patients N=118**
Frequency of opioid use	
Fewer than four times a month	56 (47)
More than once a day	36 (31)
More than once a week	13 (11)
Once a week	7 (6)
Once a day	6 (5)
Taken HU at some point (either currently or previously) and taken opioids in the year before entering the MAP	**Patients N=66**
Frequency of opioid use	
Fewer than four times a month	36 (55)
More than once a day	17 (26)
Once a day	6 (9)
More than once a week	5 (8)
Once a week	2 (3)

Summary/Conclusion: By analyzing baseline characteristics in this patient population prior to crizanlizumab treatment in the MAP, we observed a high burden of home- and healthcare-managed VOCs and SCD-related hospitalization. This high disease burden was seen despite many patients reporting use of HU and/or opioids, which illustrates their unmet medical need, hence their request to participate in the MAP. These real-world data demonstrate the need for alternative treatments targeting VOC burden for SCD patients, beyond HU. Reduction in VOC frequency would also be expected to reduce the need for opioids to manage acute pain. Additional data are required to assess if these observations are replicated in other SCD patient populations.

EP1212 COMPLICATIONS OF SICKLE CELL DISEASE IN EAST LONDON NEWBORN COHORT PATIENTS OVER THE YEARS 2015-2018

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Background: Hydroxyurea (HU) and chronic transfusion therapy (CTT) are the only treatments currently available in the UK to modify the course of sickle cell disease (SCD), while haematopoietic stem cell transplant (HSCT) is only available to a small minority with HLA-matched sibling donor. Numerous studies have shown reduction in acute vaso-occlusive and neurological complications (particularly ischaemic stroke) with these therapies. New therapies under development are expected to further improve outcomes, but there remains uncertainty towards the degree to which morbidity and mortality could be improved and how to evaluate their health economic potential. There is, therefore, a need for accurate, long-term follow-up studies demonstrating the range of complications, residual morbidity and early mortality. The East London Newborn Cohort Study aims to study long-term outcomes of patients with SCD in the UK. Outcomes have previously been reported up to the end of 2005 (Telfer et al, Haematologica, 2007). Here, we report on follow-up during the years 2015-2018 when HU and CTT were widely available to children and adults according to national and international guidelines.
Aims: To compare impact of current standard therapies on rates of acute complications.
Methods: Eligible patients were born in a designated local region, diagnosed by newborn screening between 1983-2018 and followed in our Specialist Centre. The age distribution in this cohort is currently paediatric and young adult. Recruitment was at birth, before any SCD complications could occur and represent the full spectrum of disease severity, avoiding any selection bias from clinical phenotype. For this study, we restricted the analysis to children and adults with HbSS and HbS beta thalassaemia who were followed in our centre during the period 2015-2018. Patients were categorised according to treatment received during follow-up (HU, CTT or no treatment), where duration was at least 6 months. Patients who switched were allocated according to the longest duration of therapy in follow-up. Data on all acute complications requiring hospital treatment (in patient, emergency department, or day unit) were collected. Sickle cell complications included acute (pain, chest syndrome, ischaemic stroke, hepatic/splenic sequestration), aplastic crisis, dactylitis, girdle syndrome, and priapism. Chi-squared tests were used to test for associations between categorical variables, and the Kruskal Wallis test for comparisons of continuous variables between the three treatment groups.
Results: 175 patients were included; 91 (52.0%) were female. Median age at study entry was 11.6 years (range 0.2 to 31.4 years). 47 (26.9%) patients were treated with HU, 53 (30.8%) with CTT, 72 (41.9%) were not treated, 2 (1.1%) died, and 1 (0.6%) received HSCT. There was a total of 695 patient-years of follow-up. Data on acute complications are presented in the table. More than one-third of the patients had a relatively mild phenotype and had not been treated with HU or CTT. This group had the lowest rate of acute SCD-related complications, while patients on HU had the highest rates of pain, acute chest syndrome, and sickle complications.

	HU N=47 Years of follow-up: 188	CTT N=53 Years of follow-up: 212	No Therapy N=72 Years of follow-up: 288	P value
Acute painful crisis[1]				
Patients with ≥1 episode	39 (83.0%)	31 (58.5%)	41 (56.9%)	X2=9.6 2 df, P=0.008[2]
Number of episodes	413	233	174	
Episodes per patient-year Median (range)	0.50 (0 - 54.25)	0.25 (0 - 13.50)	0.25 (0 - 7.50)	X2=10.3, 2 df P=0.006 [3]
Acute Chest Syndrome[1]				
Patients with ≥1 episode	10 (21.3%)	11 (20.8%)	8 (11.1%)	X2=2.9, 2 df, P=0.2[2]
Number of episodes	18	14	15	
Episodes per patient-year Median (range)	0 (0 - 1)	0 (0 - 0.75)	0 (0 - 1.25)	X2=2.8, 2 df, P=0.2[3]
All sickle related acute episodes[1]				
Patients with ≥1 episode	39 (83.0%)	34 (64.2%)	45 (62.5%)	X2=6.2, 2 df, P=0.04[2]
Number of episodes	451	275	199	
Episodes per patient-year Median (range)	0.75 (0 - 54.5)	0.50 (0 - 13.50)	0.25 (0 - 8.75)	X2=11.4, 2 df, P=0.003[3]
All non-sickle related acute episodes[1]				
Patients with ≥1 episode	22 (46.8%)	21 (39.6%)	28 (38.9%)	X2=0.82 2 df, P=0.7[2]
Number of episodes	52	42	66	
Episodes per patient-year Median (range)	0 (0 - 3.25)	0 (0 - 1.50)	0 (0 - 1.75)	X2=0.67 2 df, P=0.7[3]

[1]Applies to the 4 year period of follow-up 2015-2018, [2]Chi-Square test, [3]Kruskal Wallis Test

Summary/Conclusion: The results confirm that current standard therapies are only partially effective in controlling acute complications of SCD. There remains a significant unmet need for effective disease modifying or curative therapies for patients with more severe phenotype.

EP1213 LOW SARS-COV-2 SEROPREVALENCE IN A COHORT OF SICKLE CELL DISEASE (SCD) PATIENTS: POSSIBLE EFFECTS OF EMPHASIS ON SOCIAL ISOLATION FOR A POPULATION INITIALLY CONSIDERED TO BE AT VERY HIGH RISK

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Background: Although initially considered at higher risk for severe presentations of COVID-19, observational studies with SCD patients have mostly pointed to clinical severity similar to the general population. However, the level of vulnerability of these individuals to become infected and the determinants for their contagion are still uncertain.
Aims: To assess the prevalence of SARS-Cov-2 antibodies in SCD patients followed at a Brazilian center and its correlation with phenotypic and socioeconomic determinants.
Methods: A questionnaire was applied regarding demographics, socioeconomic status, use of Hydroxyurea, working status and income, COVID-19 symptoms, and the perceptions about social isolation measures. Blood samples were taken for chemoluminescence IgG (anti-N) and IgM (anti-S) anti-SARS-CoV-2 tests (Abbott Architect™, Ireland); specific neutralizing antibody titers were accessed observing the cytopathic effect in cells incubated with patient serum-virus mixture.
Results: From Jul/20 to Jan/21, 214 serological tests were performed on 135 patients (86% of SCD patients registered at the center): 82 HbSS (61%), 41HbSC (30%), 8Sβ+ (6%), 4Sβ0 (3%); 57% male and median age 42 (19-74). 66% were using Hydroxyurea and 4% were on chronic transfusion. In the analyzed period, 61 (45%) patients had vasoocclusive crises; 37 (27%) had symptoms suggestive of COVID-19, but only 2 patients had a positive PCR for SARS-Cov-2. When questioned, only 12% of patients did not consider themselves vulnerable to infection, and only 17% believed that individual and collective protection measures were expendable. In fact, 91% stated that they were able to adopt basic social distance measures, with 76% reporting cancellation of social events and 64% managed to reduce the use of public transport, but only 44% could work or study remotely. Regarding serological evaluation, 57 patients (42%) were tested more than 1 time during this period: 46 with 2 tests, 11 with ≥ 3 tests. Among all patients, 15 had positive results: 9 IgG/IgM+ and 6 IgG+ only, therefore with an overall seroprevalence of 11%. Seroconversion was documented for only 1 patient during the study period and, interestingly, with no signs and symptoms of infection. Moreover, 2 patients lost positivity for IgG 3 months after the initial positive test. The search for functionally neutralizing antibodies resulted in 9 patients with low titers (□1:40) and only 3 patients with remarkably high titers (≥1:640). There were no correlations between test positivity and education, income, number of household contacts and maintenance of work outside the home; however, serological positivity was associated with older age (40.3 x 22.9, p<.001) and regular use of public transport (Fisher exact test, p=0.02). Only 1 patient in this cohort needed hospitalization for COVID-19, including mechanical ventilation and exchange transfusions, but was discharged after 14 days
Summary/Conclusion: These data attest to the effectiveness of social distancing instructions given to patients in our SCD clinic throughout the pandemic, considering the low overall positivity and only 1 seroconversion during the study period. The fact that only 1 patient in our center had severe disease agrees with other reports showing less severity for SCD than initially expected. In fact, the transient positivity of serological tests and the low levels of functional neutralizing antibodies in SCD patients may indicate the acquisition of protective immune responses that are not dependent on antibodies and that still need to be better evaluated.

EP1214 EVALUATION OF DIFFERENT ESTIMATED GLOMERULAR FILTRATION RATE AS RELIABLE MEASURES OF RENAL FUNCTION IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Renal complications can occur throughout the life of a patient with sickle cell disease (SCD), starting with hyperfiltration and impaired urinary concentration in early childhood, leading to chronic kidney disease (CKD) with advancing age. As patients with SCD survive longer, the risk of these changes progressing to end-organ damage rises. Currently, there is no reliable marker for detecting early renal disease in childhood. Routine estimation of glomerular filtration rate (GFR) in children is derived from the height/plasma creatinine formula and is dependent on the accuracy of the creatinine analytical method used.
Aims: The aim of this study was to evaluate different equation methods for estimating GFR in comparison to the gold standard measure of GFR using clinical and demographic variables and markers of renal function, including creatinine.
Methods: Children aged 5-16 years followed for SCD (homozygous HbSS and $HbSb_0/b^+$) were prospectively recruited. Specific renal biomarkers were measured: formal GFR was measured using plasma disappearance of Inutest/Ihexol, plasma creatinine was measured either by standard laboratory method or by tandem mass spectrometry (MS). Estimated GFR was then calculated by using the "Bedside Schwartz method" with the formula: [(constant × height) ÷ plasma creatinine].
Results: A total of 79 patients (39 males, mean age 9.8±4.0 years) were enrolled. Anthropometric measures were collected: the mean height, weight and body surface area were 135.4±20.9 cm, 34±15 kg, and 1.1±0.3 m^2, respectively. Height/plasma creatinine was significantly correlated with Inutest GFR, r=0.86 (p<0.001). A revised eGFR constant was calculated for Schwartz equation from the slope of the plot of height/plasma creatinine versus GFR forced through zero. The new constant was determined as 30.86, or 31 for convenience. Standard renal measurements were available for all children. Mean values for GFR and laboratory plasma creatinine were 132.7±32.1 ml/min/1.73m^2 and 38.5±17.8 µmol/l, respectively. Mean values for eGFR derived from standard plasma creatinine was 122.4 ± 31.7 ml/min, with significant difference in comparison to GFR values (p=0.002). MS eGFR was calculated for 44 children, resulting with a mean of 120.5±34.4 ml/min, and there was no significant difference in comparison to GFR values (p=0.239).
Summary/Conclusion: In conclusion, in children with SCD the formula to calculate eGFR based on height and plasma creatinine determined with MS traceable creatinine methods provides a more reliable estimation of renal function in comparison to standard laboratory plasma creatinine derived values, as a possible effect of the hyperfiltration state of these patients.

EP1215 PRECLINICAL SAFETY AND TOXICITY ASSESSMENT OF A HUMAN PLASMA DERIVED HEMOPEXIN DRUG PRODUCT (CSL889) FOR THE TREATMENT OF ACUTE VOC IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited, autosomal recessive disorder that leads to hemolytic anemia and vascular disease, with a range of acute and chronic complications driven by self-perpetuating cycle of vaso-occlusion and vaso-occlusive crises (VOCs).
Aims: CSL889, a human plasma-derived hemopexin, is being developed as a novel pharmacologic therapy to reduce toxic cell-free heme in patients with VOC, with the goal of reducing the duration and severity of acute VOC in adults and children with SCD.
Methods: The *in-vivo* toxicological program included 2-week repeat-dose tolerability studies in wild-type (C57BL/6) and Townes HbSS sickle cell mice (*Hbb*$^{tm2(HBG1,HBB*)Tow}$), a 2-week repeat-dose toxicity study in rats and a 2-week repeat-dose toxicity study in cynomolgus monkeys including cardiovascular safety pharmacology. The latter studies included a treatment free period of 7 days. A single dose safety pharmacology study in rats assessed effects on respiratory parameters. CSL889 was administered intravenously (IV) at dose levels of 50 to 500 mg/kg. All studies were conducted under applicable animal welfare standards and regulatory approvals.
Results: Repeat-dose administration of CSL889 every other day over two weeks was well-tolerated in cynomolgus monkeys and rats. There were no mortalities or adverse findings regarding clinical observations, body weights, ophthalmoscopy, electrocardiography, blood pressure, respiratory rate, clinical pathology, urine analysis, organ weights, gross pathology or histopathology attributable to treatment with CSL889. Non-adverse and transient effects which returned to baseline levels after the 7-day recovery period included an increase of the beta-globulin serum levels in cynomolgus monkeys, an increase of the alkaline phosphatase (ALP) serum levels which did not clearly follow the dose-response principle in rats, and a small but statistically significant decrease from baseline activated partial thromboplastin time (aPTT). The observed formation of anti-drug antibodies (ADAs) against CSL889 in both species is an expected immune reaction after repeated application of the heterologous human protein to animals and is not considered predictive for the clinical situation. ADA formation did not have an impact on safety or exposure of the study animals. Safety pharmacology evaluation did not show any deleterious effects of CSL889 on cardiovascular and respiratory functions in cynomolgus monkeys and rats. The NOAEL for rats and cynomolgus monkeys was at least 500 mg/kg under the conditions of the study.
Daily IV administrations of hemopexin for two weeks to wildtype mice was well tolerated and produced no adverse clinical signs at 160 mg/kg. While there were no findings after the first dosing occasions, high dose animals (500 mg/kg) showed a short-lived, transient clinical reaction, ie reduced mobility and body temperature to the treatment on Day 8. There was no clear evidence of treatment-related changes to hematology or clinical chemistry parameters in any dose group at the end of the dosing period.
Daily IV administration of hemopexin for two weeks or six days (500 mg/kg only) to Townes HbSS mice was generally tolerated. Similar to the reaction observed in wildtype mice immunological reactions were observed in some dosing groups after repeat administration, which are assessed as a result of the application of the heterologous human protein.
Summary/Conclusion: The toxicological program demonstrated that CSL889 has a favorable safety profile and supports the clinical development of hemopexin for the treatment of acute VOC in sickle cell disease.

EP1216 ATTITUDES TOWARD THE MANAGEMENT OF SICKLE CELL DISEASE: RESULTS FROM TURKISH REGISTRY

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Background: Sickle cell disease (SCD) is a significant health problem for Turkey. The official register of the Ministry of Health includes 1200 patients with SCD residents in Turkey. However, there has been no data including the demographic and clinical features of this cohort
Aims: The National Hemoglobinopathy Register of the Turkish Society of Hematology (TSH) aims, to evaluate the geographic distribution and disease characteristics of patients with SCD and the need for delivering a standard of care to the patients.
Methods: Thirty-five hemoglobinopathy centers entered a total of 656 patients' data, 627 of whom were alive, into the web-based system from the hospital records. The database was composed of 480 SCD (75%), 160 (25%) HbSB patients, and only 16 HbS with other abnormal beta-globin chain variants. The 640 of 656 registered patients were born in Turkey, and 80% were born in only three provinces (Adana, Hatay, and Mersin).
Results: The patients (305 males, 335 females) were 32 ± 15 years-old. The mean age of diagnosis was 11±10.7 months (HbSS; 10±8.2, HbSB; 23±14). The physicians prescribed penicillin prophylaxis for 46.5% of patients at the mean age of 15±14 months. The pneumococcal, meningococcal, and Hib vaccination was administered to 91.7%, 66.8%, and 54.6%, respectively, and 48.5% of those received booster dose of pneumococcal vaccine. 75% of patients were receiving hydroxyurea, the last amount used was mean 15 ± 6.7 mg/kg/day, the physician reported compliance with the treatment was 69%.
The 33% of patients received simple transfusions for anemia (63%) or controlling painful crises (20%) in the last year. The 8.4% of the patients were on chronic exchange programs. Erythrocytapheresis was the method of choice in the majority of those (81.4%). The rate of transfusion with ABO, Rh(CcDEe), Kell compatible products was 23%. Iron chelation therapy (ICT) has been initiated in 22% of the patients at the mean age of 7.7±11.2 years, with a median serum ferritin level of 2500±470 ug/L. Deferasirox was the first-line iron chelator in 52.5% of the patients. Deferasirox use increased to 85.6% among patients on ICT over the years. The median serum ferritin decreased to 1400±176 ug/L in the last year. The patients who had at least one acute chest syndrome and stroke were 16% and 9.5%, respectively. At least one painful crisis was recorded in 81% of patients in the last year
Summary/Conclusion: Current treatment options for reducing morbidity and mortality in SCD are limited to adherence to penicillin prophylaxis and recommended vaccination schedule, using hydroxyurea, erythrocyte transfusions, and ICT whenever indicated. The data showed, starting hydroxyurea and providing patients' compliance to the therapy were our positive aspects. However, the physicians should reconsider the adjustment of the hydroxyurea dose. The initiating penicillin prophylaxis, use of ABO, Rh(CcDEe), Kell compatible erythrocyte transfusions, and timely initiation of ICT were the aspects we needed to improve delivering a standard of care to the patients.

EP1217 ASSESSING TRANSITION OUTCOMES IN SICKLE CELL DISEASE (SCD) PRIOR TO IMPLEMENTATION OF A FORMAL TRANSITION PROGRAM

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Background: From newborn screening to vaccinations to disease-modifying therapies, the evolution of medicine has potentiated the livelihood of children and adolescents with Sickle Cell Disease (SCD). Over 90% of children with SCD now survive into adulthood in high resource

countries—however, mortality rates have not improved in young adults. Challenges in continuing care emerge as they transition from a heavily contiguous pediatric healthcare model to an increasingly self-reliant adult healthcare model.
Aims: The goal of this study is to identify potential facilitators and barriers to a successful transition in care.
Methods: The Comprehensive Sickle Cell Center at UAB serves a large area of Alabama, including many surrounding cities. The pediatric program is housed in Birmingham, AL but has outreach clinics in Montgomery, Opelika, and Tuscaloosa, AL. It provides care for approximately 900 children with SCD. The adult program only has one clinic located in Birmingham, AL. With IRB approval, we performed a retrospective medical chart review of all individuals with SCD (all genotypes) aged 18-24 (as of January 31, 2019) who were previously treated by hematology at Children's of Alabama. To be included, patients must have been seen at least twice prior to turning 18 years old and have confirmed SCD. Charts were reviewed for demographics, insurance at last known visit, SCD genotype, use disease-modifying therapy (hydroxyurea or transfusion therapy) at last pediatric visit, location of pediatric SCD clinic, and transition status. Based on these characteristics, analyses were done to determine if there were differences in genotype, pre-transition treatment, or demographics between those who had become lost-to-follow-up and those who had successfully transitioned (defined as coming to an appointment with an adult hematologist at UAB or with a community hematologist-oncologist).
Results: The total sample included 544 individuals. Of this group: 234 were lost-to-follow-up, 189 transitioned to adult care, 36 moved, and 15 died before 18 years of age. Seventy patients have not yet transitioned and thus, were excluded from study. Sixty-eight percent of patients (n=127) that successfully transitioned to an adult provider had their last pediatric visit at the Birmingham clinic, compared to only 32% (n=61) that were followed in outreach (non-Birmingham clinics) (P<.01). Patients were also more likely to have successfully transitioned if they had sickle cell anemia versus those with hbSC/hbSß+ (p<.01) and if they were receiving hydroxyurea or chronic transfusion therapy (p<.01).
Summary/Conclusion: Our results suggest that geography, genotype, and the use of disease-modifying therapy are strong predictors for a successful transition to adult care in SCD. Novel strategies to improve transition of care for patients living outside of Birmingham are clearly needed. Potential care improvements include telehealth and developing relationships with local primary care providers or developing affiliate clinics in more rural areas. People with hbSC and hbSß+ disease (compared to hbSS) often have less severe disease complications as children. It may be necessary to enhance engagement in care for these patients to ensure they do not become lost to follow-up. Further, increasing early discussion about the necessity of lifespan care may help patients and families plan for adult care at earlier ages. Beyond our institution, this information could serve as a potential framework for evidence-based guidelines in SCD Transition Care.

EP1218 CHRONIC COMPLICATIONS OF SICKLE CELL DISEASE PATIENTS IN TURKEY

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Background: With the advances in sickle cell disease (SCD), the patients' life expectancy has increased, and chronic disease complications have become more prominent.
Aims: The National Hemoglobinopathy Register of the Turkish Society of Hematology (TSH) aims to evaulate the frequency of chronic complications and long term outcomes of the patients with SCD in Turkey.
Methods: The physicians from 35 hemoglobinopathy centers registered 480 SCD (75%) and 160 (25%) HbSB patients' hospital records into the web-based system.
Results: The patients (305 males, 335 females) were 32 ± 15 years-old. Musculoskeletal disorders (44%), osteopenia (42%), and avascular necrosis (34%) were the most common complications. Musculoskeletal complications were significantly higher in patients with HbSS (48.5%) than the patients with HBSB (34.8%) (p = 0.006). Infectious complications affected 26.5% of patients, and 3.4% of patients suffered from sepsis. Overall, 3.8% of the patients had transfusion-transmitted infections, and the majority (90%) was Hepatitis-C virus infection. 17% of patients with SCD had liver and gall bladder complications. The biopsy-proven cirrhosis was 1.6%. The cardiovascular complications, including heart failure, thromboembolism, arrhythmia, and pulmonary hypertension, affected 4.9%, 4.4%, 3.2%, 1.5% of the patients, respectively. Each of the urogenital and cerebrovascular complications affected 9.5% of the patients. 2.3% of the patients showed chronic renal failure. Endocrine complications were more prominent in patients with HbSB than SS (14.7% versus 6.5%; p = 0.006). 38% of patients aged >18 years got married at the mean age of 26.7 ± 5.2 years (range 18-48). In 11.3% of these marriages, the couples were the patients with hemoglobinopathy. 85.7% of patients with a healthy partner had at least one child indicating patients' reproductive potential. Three patients had breast cancer, non-Hodgkin lymphoma, and neurofibromatosis type 1, one in each. Twenty-seven patients (4.2%) died of SCD-related complications at the mean age of 38.9± 15.4 years (range 10-67). Among the causes of death, cardiovascular complications were the most common (22%), followed by infections (18.5%) and thromboembolic events (11%). Nine patients aged between 4 and 32 years vof age had bone marrow transplantation (BMT) from a matched sibling (n=7) and unrelated (n=2) donors. All transplanted patients alive, and all but one had BMT from an unrelated donor were disease-free.
Summary/Conclusion: As the data showed, adolescents and young adults are composed of most SCD population in Turkey. It indicates the need for consideration of an effective transitioning program from pediatric to adult care. The organization of specialized centers for patients with SCD and improving access to these centers for regular and comprehensive follow-up should positively impact the patients' survival by controlling the disease's life-threatening complications.

EP1219 A LONGITUDINAL OBSERVATIONAL STUDY TO EVALUATE THE PSYCHOMETRIC PROPERTIES OF A DAILY DIARY FOR ADOLESCENTS AND ADULTS WITH SICKLE CELL DISEASE

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Background: Vaso-occlusive crises (VOCs) are one of the most serious clinical features of sickle cell disease (SCD), impacting mortality, morbidity, and health-related quality of life (HRQoL). Existing patient-reported outcome measures (PROs) aim to assess the overall impact of SCD, and are typically administered at fixed intervals several days or weeks apart. However, such PROs are unable to accurately capture the full impact of VOCs, which occur sporadically and unpredictably. The Sickle Cell Pain Diary – Self Report (SCPD-S) was developed to address this measurement gap, assessing the impact of VOCs in adolescents and adults. Administered daily, the diary was designed with patient input to evaluate the severity of SCD-related pain during and outside of a VOC, and to capture the impact of pain on patient-relevant HRQoL concepts.
Aims: To develop a longitudinal observational study to assess the psychometric properties of the SCPD-S.
Methods: Study plans include enrolling 328 patients from 3 countries with a high burden of SCD: the United States (US), United Kingdom (UK), and Kingdom of Saudi Arabia. Participants with a verified diagnosis of SCD who were ≥12 years old were recruited through participant panels, advocacy groups, and clinician referrals. Participants were asked to complete the SCPD-S every day through a mobile application. On days that a VOC was experienced, participants reported on the impact of the VOC; if a VOC was not experienced, they reported on the

impact of SCD on their daily life. The assessments occurred for at least 3 months, increasing the likelihood that participants would experience at least 1 VOC during the study. Anticipating that participants may not have perfect diary completion, it was determined that to be included in the planned analyses, participants must complete at least 25 of 30 daily assessments for at least one month and experience a VOC during that month. One criterion measure was administered daily (single item global impression of severity), while the remainder were administered the day after a VOC in order to reduce respondent burden during a crisis. Planned analyses include factor analysis to confirm the structure of the SCPD-S, which is hypothesized to assess a unidimensional construct of VOC impact. Multiple scoring systems will be explored to provide users flexibility in evaluating diary responses. Psychometric analyses will be conducted to examine the reliability (test-retest and internal consistency reliability), validity (convergent, divergent, and known-groups validity), and responsiveness of the instrument.

Results: After 11 weeks of recruitment in the UK, 81 participants have been enrolled. After 30 weeks of recruitment in the US, a total of 135 participants have been enrolled in the study. Of these, 9 were lost to follow-up, leaving 126 active participants. Only 1 participant missed more than 5 daily assessments for each month of their participation; 8 participants are still in their first month of the study. One hundred nine (93%) of the 117 remaining participants who have completed at least one month of the study have reported at least 1 VOC throughout their participation.

Summary/Conclusion: This study takes a unique approach to the psychometric validation of an SCD-specific PRO that was designed to collect information on sporadic and unpredictable events. Once the psychometric properties of the SCPD-S have been documented, the diary could be used in clinical practice to describe patients' experiences during VOCs and capture responses to treatment.

EP1220 ECONOMIC BURDEN OF SICKLE CELL DISEASE IN THE MIDDLE EAST

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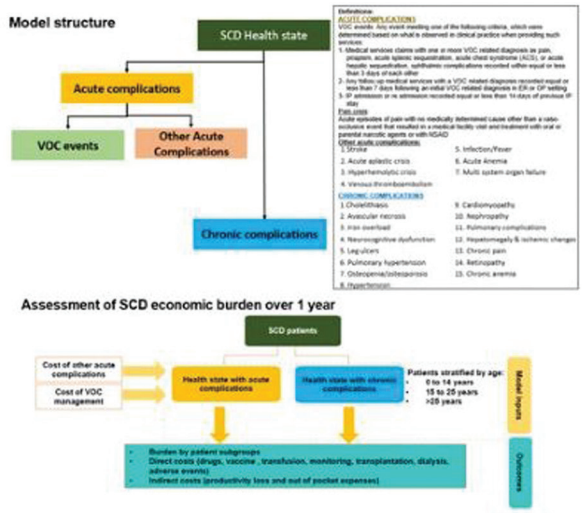
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Background: Sickle cell disease (SCD) is a haematological disorder caused by a mutation in the β-globin gene (HbS) and is characterized by multisystem clinical manifestations, which result in varied acute and chronic SCD-related complications. The most common complication is vaso-occlusive crisis (VOC). In the Middle East (ME), SCD prevalence varies from (0.04%>0.5%) and is localized in certain pockets within countries and is contributed by consanguinity, environmental factors, large sibship size and migration. The increased prevalence together with the complexity in its management, may lead to high utilization of healthcare resources posing a considerable economic burden on the healthcare system, patients, and the society. The paucity of literature on SCD burden, lack of systematic disease registry/databases and structured costs data in the ME challenges the understanding of the scope of the public health concern that SCD poses.

Aims: To estimate the economic burden associated with SCD management in Bahrain, Egypt, Kingdom of Saudi Arabia (KSA), Lebanon, and Oman.

Methods: An excel-based micro-costing analysis was carried out, to estimate the direct and indirect costs associated with SCD management in the countries of interest over a one-year period both from a payer and societal perspective. Data inputs included epidemiology data with health state (defined in model as acute and chronic events consuming resources during the year) and unit costs for SCD management. Data sources included an exhaustive literature review followed by a clinician survey (using Delphi method) which included 41 experts. All findings were further validated by a steering committee of 12 multidisciplinary experts representing the studied countries. The model structure and inputs have been elaborated in the figure. The total annual direct and indirect costs associated with SCD and VOC were calculated. Subgroup analyses were also performed for age groups (paediatrics, adolescents, and adults) and VOC frequencies per year (0, 1-2, 3-4, ≥5 VOCs).

Results: The overall economic SCD burden from Payer's perspectives, across all ages, ranged from USD $1.3 Mn in Egypt to as high as USD $395 Mn in KSA for the management of 1,000 and 94,455 SCD patients, respectively. The model showed that the SCD societal burden in ME ranged from USD $1.79 Mn in Egypt to as high as $1.4 Bn in KSA mostly driven by productivity losses due to SCD. On average and across ME countries, the acute complications represented approximatively 75% of the total SCD burden, of these 58% were attributed to the VOC management costs. In terms of healthcare resources utilization, hospital visits (inpatients, outpatients, and emergency room (ER)) were the main utilized health service contributing, on average, 54% to the total burden. Patients with ≥5 VOC per year incurred the highest annual cost per patient across all countries. The table summarizes the main results per country as well as the overall average.



Total burden	KSA	Oman	Bahrain	Egypt	Lebanon	Average across all countries
Payer's perspective (USD $)	$ 395,141,455	$ 40,305,740	$ 38,416,736	$ 1,289,762	$ 6,211,427	$ 96,273,024
Societal perspective (USD $)	$ 1,443,683,729	$ 68,068,957	$ 55,370,288	$ 1,789,672	$ 6,433,453	$ 3,15,069,216
Number of SCD patients	94,455	7,500	8,800	1,000	850	22,521
Cost of Acute complications as % of total burden (payer's perspective)	93%	89%	73%	68%	47%	74%
Cost of VOC events as % of total burden (payer's perspective)	75%	70%	64%	38%	40%	57%
Cost of hospital visits (inpatients, outpatients and ER) as % of total burden	59%	55%	62%	62%	36%	55%
Average annual cost per patient with ≥5VOC annually (USD $)	$ 14,706	$ 10,390	$ 18,507	$ 5,126	$ 28,654	$ 15,476

Summary/Conclusion: The findings highlighted the extensive utilization of healthcare resources associated with the management of SCD and its substantial impact on patients' work productivity, across the studied countries. Patients with acute complications, primarily VOC events incurred the majority of the economic burden due to the need for hospital visits. The higher the number of VOC events per year the higher the need for medical care hence healthcare resources utilization. This study emphasizes the need for innovative and cost-efficient therapies for the prevention of VOCs and/or reduction of VOCs frequency.

EP1221 THE VALUE OF THE YEARS CLINICAL DECISION ALGORITHM TO RULE OUT PULMONARY EMBOLISM IN PATIENTS WITH SICKLE CELL DISEASE: A RETROSPECTIVE EVALUATION.

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Background: Sickle cell disease (SCD) is recognized as a hypercoagulable state and associated with an increased incidence of thromboembolic events. SCD patients presenting with vaso-occlusive crisis (VOC)

frequently have symptoms also suspected of pulmonary embolism (PE) (i.e. thoracic pain, dyspnea, decreased O2 saturation). To compute the pretest probability of PE, the YEARS decision rule is used. This algorithm uses the presence of three clinical criteria (1. signs of deep venous thrombosis, 2. Hemoptysis, 3. PE most probable diagnosis) in combination with D-dimer cut off values. A D-dimer level of ≥ 0.5 mg/L (and 1 or more positive criteria), or ≥ 1mg/L (and no positive criteria) indicates a high probability of PE and would justify performing a computed tomography pulmonary angiogram (CTPA) for a definitive diagnosis. Being a hypercoagulable disease, SCD is associated with increased D-dimer levels. The YEARS decision rule is not validated for SCD patients.
We questioned whether the use of the YEARS criteria with its current D-dimer cut off values is able to rule out PE in SCD patients.
Aims: To validate the Years criteria with its current D-dimer cut off values to rule out PE in SCD patients.
Methods: We performed a single-center retrospective cohort study in the Amsterdam University Medical Centres, a tertiary hospital in the Netherlands. Consecutive D-dimer samples of patients (≥18y) with a confirmed diagnosis of SCD and sickle cell trait (HbAS) were eligible for inclusion if D-dimers were measured to exclude suspected PE. D-dimer samples that were measured to exclude deep venous thrombosis or in other settings were excluded. Laboratory values including D-dimer levels, medical history, the proportion of indicated CTPA examinations based on the YEARS decision rule, the incidence of PE and other diagnoses were documented and compared between groups.
Results: A total of 76 patients with 94 D-dimer samples were eligible for inclusion. Sixty (79%) participants had SCD, while 16 (21%) had HbAS. Plasma D-dimer levels were significantly higher in SCD patients compared to individuals with HbAS (2.88 mg/L [1.56-4.43] vs. 1.01 mg/L [0.49-4.03]; *P*=0.004). Sixty-seven (89%) of SCD patients and 10 (53%) of individuals with HbAS had D-dimer levels in excess of 1,0 mg/L. In patients with the severe genotype (HbSS and HbS-β^0-thalassemia), 94% had D-dimer levels ≥ 1.0 mg/L. CTPA was performed in 88% of SCD patients and 69% of individuals with HbAS. PE was confirmed in 8 (9%) patients without significant differences between patients with SCD and those with HbAS (n=5 (7%) vs n=3 (16%); *P*=0.203, respectively). No differences in D-dimer levels were found in SCD patients with PE compared to those without PE (3.62 mg/L [2.54-8.59] vs 2.76 mg/L [1.52-4.39), *P*=0.293).

Table 2. Hospital characteristics of SCD patients and HbAS patients

	SCD (n=75)		P[1]	HbAS (n=19)	P[2]
	Severe (n=51)	Mild (n=24)			
D-dimer, mg/L	2.88 (1.99-4.02)*	2.86 (1.18-10.98)*	0.654[4]	1.01 (0.49-4.03)*	0.004[4]
D-dimer ≥ 1,0 mg/L	48 (94)	19 (79)	0.050[3]	10 (53)	0.000[3]
CTPA	49 (96)	17 (71)	0.002[3]	13 (69)	0.037[3]
Diagnosis					
PE	3 (6)	2 (8)	0.691[3]	3 (16)	0.203[3]
Pneumonia/ACS	13 (26)	2 (8)	0.083[3]	2 (11)	0.338[3]
Pleural effusion	5 (10)	1 (4)	0.401[3]	0	0.203[3]

Abbreviations: SCD, Sickle cell disease; CTPA, computed tomography pulmonary angiogram; PE, pulmonary embolism; ACS, acute chest syndrome
**Median and inter quartile range; [3] Pearson's Chi Square; [4] Mann-Whitney-U test*
[1] Statistical analysis between severe and mild genotypes [2] Statistical analysis between all SCD patients and HbAS patients

Summary/Conclusion: In this study, 89% of analyzed D-dimer values in SCD patients were > 1 mg/L. This was 94% for the severe genotypes. This translated into a high percentage of CTPA that then had a low yield (7%) of PE in SCD patients. The rate of indication for CTPA for SCD patients in this study was much higher than the 20-30% previously reported for the YEARS algorithm. These data indicate that the specificity of the YEARS algorithm is very low in SCD patients and might lead to over imaging in this patient group.

EP1222 FACTORS ASSOCIATED WITH HOSPITAL ADMISSION DUE TO VASO-OCCLUSIVE CRISIS IN PATIENTS WITH SICKLE CELL DISEASE: RETROSPECTIVE ANALYSIS OF 3-YEAR OBSERVATIONAL STUDY DATA

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Background: Sickle cell disease (SCD) is a global health burden that has been largely neglected. Despite improvements in diagnosis, treatment and management over the past few decades, SCD morbidity including vaso-occlusive crises (VOCs) remains high. VOCs, the hallmark of SCD, are the primary cause of hospitalization for SCD patients, and are associated with significant morbidity and mortality. Evidence regarding potential risk factors for hospitalization due to VOC (H-VOC) including commonly measured blood markers is limited.
Aims: To assess whether selected factors are associated with the rate of H-VOC and hospital length of stay by performing a retrospective analysis of data collected prospectively during a 3-year, multicenter, observational US study (NCT01220115) that aimed to better understand disease burden and management of SCD in patients aged ≥2 years.
Methods: Out of a total of 498 recruited patients, 202 aged ≥16 years and for whom patient-reported hospital admission data were available were included in this analysis. Negative binomial regression (adjusted for age, sex, and SCD genotype) was used to examine the association of selected baseline characteristics (ie body mass index, hemoglobin, ferritin, transaminases, and any history [received in the preceding 12 months] of opioids, hydroxyurea, transfusion, and H-VOC) with the frequency and length of stay of H-VOC in SCD patients.
Results: Overall, 71% of patients had a HbSS genotype, 98% were Black or African American and 51% were female. The median age of the cohort was 31 years (interquartile range [IQR] 22–41). At baseline, 36% of patients had received opioids, 14% had received hydroxyurea and 51% had received transfusions in the previous 12 months, comprising 30% who had received 1–5 transfusions and 21% who had received ≥6 transfusions. During the 3-year follow-up period, 55% of patients experienced at least one H-VOC with a median length of stay of 16 (IQR 6–45) days. History of H-VOC was significantly associated with a higher rate of subsequent H-VOC (incidence rate ratio [IRR] 4.32, 95% confidence interval [CI] 2.86 to 6.61, *P*<0.001) and a longer stay (IRR 5.37, 95% CI 3.00 to 9.77, *P*<0.001; Table). Transfusion history was also significantly associated with a higher rate of subsequent H-VOC (IRR 1.58, 95% CI 1.05 to 2.38, *P*=0.030) and a longer stay (IRR 3.79, 95% CI 2.03 to 7.06, *P*<0.001; Table). However, further analysis to investigate the effect of transfusion frequency (ie chronic versus rescue transfusions) is needed. Secondary analysis, including hospitalized patients only (n=112), found a HbSC or HbSβ-thalassemia genotype, a body mass index of <18.5 kg/m^2 (ie underweight), a higher aspartate aminotransferase level and transfusion history were associated with a longer stay. Older age, males, and history of opioid use were associated with a shorter stay (Table).

Table: Selected baseline factors assessed for association with rate and duration of H-VOC

Factors	Multivariable analysis* IRR (95% CI)	Stepwise regression† IRR (95% CI)	*P* value
H-VOC rate (n=202)			
Age (per 1-year increase)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.01)	0.760
Sex (male)	1.22 (0.79 to 1.90)	1.04 (0.69 to 1.55)	0.864
Genotype (HbSC or HbSβ-thalassemia)‡	0.90 (0.56 to 1.46)	1.18 (0.75 to 1.85)	0.478
History of H-VOC (in preceding 12 months)	4.56 (3.03 to 6.97)	4.32 (2.86 to 6.61)	<0.001
History of blood transfusion (in preceding 12 months)	1.88 (1.22 to 2.93)	1.58 (1.05 to 2.38)	0.030
H-VOC duration (n=202)			
Age (per 1-year increase)	0.99 (0.97 to 1.02)	1.00 (0.97 to 1.02)	0.731
Sex (male)	1.56 (0.82 to 2.99)	1.27 (0.70 to 2.28)	0.411
Genotype (HbSC or HbSβ-thalassemia)‡	0.62 (0.32 to 1.30)	1.55 (0.83 to 3.01)	0.165
History of H-VOC (in preceding 12 months)	6.16 (3.12 to 12.71)	5.37 (3.00 to 9.77)	<0.001
History of blood transfusion (in preceding 12 months)	5.41 (2.92 to 9.98)	3.79 (2.03 to 7.06)	<0.001
Initial H-VOC duration, hospitalized patients only (n=112)			
Age (per 1-year increase)	0.99 (0.97 to 1.00)	0.98 (0.97 to 0.99)	0.008
Sex (male)	0.80 (0.56 to 1.16)	0.69 (0.49 to 0.97)	0.030
Genotype (HbSC or HbSβ-thalassemia)‡	1.55 (1.04 to 2.34)	1.72 (1.18 to 2.51)	0.006
BMI (<18.5 kg/m^2)	3.27 (1.65 to 7.22)	2.46 (1.29 to 5.06)	0.013
AST (per 1-unit increase)	1.01 (1.00 to 1.01)	1.01 1.00 to 1.01)	0.011
History of opioids (in preceding 12 months)	0.60 (0.43 to 0.84)	0.73 (0.53 to 1.00)	0.045
History of blood transfusion (in preceding 12 months)	2.24 (1.60 to 3.14)	1.95 (1.39 to 2.73)	<0.001

*Adjusted for age, sex and genotype.
†Only factors significantly associated with rate or duration of H-VOC in the multivariable analysis were included in the stepwise regression.
‡Versus HbSS.
AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; H-VOC, hospitalization related to vaso-occlusive crisis; IRR, incidence rate ratio; NA, not applicable.

Summary/Conclusion: Our results demonstrate that history of H-VOC within the preceding 12 months was significantly associated with a higher rate of subsequent H-VOC and increased length of stay in our cohort, independently of age, sex and genotype. Our data have limited statistical power and generalizability. Therefore, future studies in larger cohorts and/or different geographical populations are needed. However, in combination with the widely accepted impact that VOCs have on morbidity and mortality, these findings further support the need to reduce/prevent VOCs in SCD patients.

Stem cell transplantation - Clinical

EP1223 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR REFRACTORY/RELAPSED T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA AFTER ALLOGENEIC CD7-CART CELL THERAPY

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Background: The prognosis of refractory/relapsed T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) was extremely poor. In our previous clinical study (unpublished data), more than 90% complete remission (CR) has been obtained with allogeneic CD7-CART therapy in refractory/relapsed T-ALL/T-LBL, but hematopoiesis reconstitution is crucial for long-term disease-free survival (DFS) in this setting.
Aims: A clinical trial was designed to examine the safety and efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) after allogeneic CD7-CART for refractory/relapsed T-ALL/T-LBL.
Methods: From October 2020 to January 2021, 7 patients with refractory/relapsed T-ALL/T-LBL (refractory in 1, relapsed in 6; with extramedullary disease (EMD) in 4) after allogeneic CD7-CART therapy followed by allo-HSCT from the same donor were enrolled. The median age was 12 (3-44) years old. The median blasts in bone marrow (BM) were 35 (15-90) % before CD7-CART. Before allo-HSCT, minimal residual disease (MRD) in BM and cerebrospinal fluid was negative in all cases, and EMDs were detectable in 3 patients but with much smaller sizes. Pancytopenia was seen in all cases before HSCT. The median time from CART cell infusion to allo-HSCT was 32 (29-36) days. The types of HSCT were haploidentical in 5 cases and identical sibling in 2 cases. Conditioning regimens were busulfan/fludarabine-based (6 cases) or TBI/fludarabine-based (1 case). ATG (rabbit anti-human T-lymphocyte immunoglobulin 10mg/kg in 4, rabbit anti-human Thymocyte globulin 6mg/kg in 1) was applied in haploidentical transplants. Cyclosporine, MMF and short-term MTX were employed for GVHD prophylaxis. Chimerism was analyzed by STR. MRD was detected by flow cytometry (FCM) and PCR, and EMD was evaluated by PET-CT. CART cells were monitored by FCM and PCR.
Results: Before HSCT, all patients were with mixed chimerism. The median percentage of chimerism in BM and peripheral blood were 58.05 (1.57-73.42) %, 92.34 (35.11-98) %, respectively. The median time of neutrophil engraftment was 19 (12-21) days. The median time of platelet engraftment was 21 (6-100) days. At one month post-transplant, all patients achieved MRD^- CR without EMD, and full donor chimerism in $CD3^+$ lymphocytes and BM was detected in all cases. Acute graft-versus-host disease (aGVHD) was mild with only grade I in 2 patients, and no chronic GVHD was noted. Bacterial infections occurred in some patients (perianal infection in 1, sepsis in 1, intestinal infections in 3). Four cases developed CMV viremia and 1 patient had CMV retinitis. Hemorrhagic cystitis occurred in 2 patients. One case had post-transplant lymphoproliferative disease and resolved with rituximab and chemotherapy. One patient died from multi-organ failure on days 14 after HSCT. With the median follow-up 61 (25-151) days, no recurrence was found, 6/7 cases have been survived free of diseases. The median time of CART cell detectable was 39 (28-60) days post-HSCT. The median CART cell percentage was 0.52 (0.17-3.62) %.
Summary/Conclusion: With our protocol, hematopoiesis reconstitution has been achieved in all patients. Allogeneic CD7-CART combined with allo-HSCT has shown powerful anti-T-ALL/T-LBL effects and good safety profile. The existence of CD7-CART early after transplant had no influence on engraftment and may contribute to prolonged anti-tumor effect. Infections are main complications in this setting, therefore, appropriate dosages of immunosuppressants and the timing bridge to allo-HSCT need to be further investigated. This trial is still ongoing.

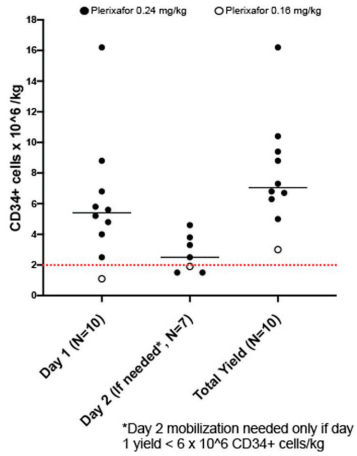
EP1224 PHASE 2 STUDY OF MGTA-145 + PLERIXAFOR FOR RAPID AND RELIABLE HEMATOPOIETIC STEM CELL (HSC) MOBILIZATION FOR AUTOLOGOUS STEM CELL TRANSPLANT IN MULTIPLE MYELOMA

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Background: MGTA-145 (GroβT), a CXCR2 agonist, has shown promising activity for HSC mobilization with plerixafor in pre-clinical models & healthy volunteers. It has the potential to become a GCSF free regimen for reliable, same day stem cell mobilization/apheresis in preparation for transplant, with fewer side effects, better patient experience and optimal resource utilization.
Aims: This phase 2 single center study evaluates HSC mobilization with MGTA-145 + plerixafor and same day apheresis in patients with multiple myeloma (NCT04552743). Primary endpoint is collection of 2 x 10^6 CD34+ cells/kg in 2 days of mobilization/apheresis. Secondary endpoints are collection of 4 and 6 x 10^6 CD34+ cells/kg and engraftment after transplant.
Methods: Patients with myeloma 18-70 years of age, within 1 year of treatment start and creatinine clearance ≥ 30 ml/min were eligible. Patients received plerixafor 0.24 mg/kg (0.16 mg/kg if renal dysfunction) SQ, followed 2 hours later by MGTA-145 (0.03 mg/kg) IV over 3-10 minutes and apheresis within 30 minutes. Mobilization was repeated for a second day if day 1 yield was < 6 x 10^6 CD34+ cells/kg. This interim analysis reports on mobilization in 10 patients (of 25 planned), including safety cohort of first 6 patients completing transplant.
Results: Median age was 63 years (range: 46-68), 50% were female, 22% had ISS stage 3 & 50% had high-risk FISH. Induction therapy was VRD in 7 and daratumumab + VRD in 3 patients; median induction duration: 4 months (3-6) & median lenalidomide exposure: 6 cycles (4-6), with ≥ VGPR in 70%.
Plerixafor 0.24 mg/kg was used in 9 patients and 0.16 mg/kg in 1 (renal dosing). Median total stem cell yield (CD34+ cells/kg x 10^6) was 7.1 (3-16.2), day 1 yield was 5.4 (1.1-16.2) & yield per apheresis session was 4 (1.1-16.2) **(Fig).** 100% patients met the primary endpoint of collecting sufficient HSCs in ≤ 2 days of mobilization + apheresis to proceed to transplant, 90% in 1 day (2 x 10^6 CD34+ cells/kg). Secondary endpoints of 4 and 6 x 10^6 CD34+ cells/kg in ≤ 2 days were met in 90% & 80% patients. Overall, 30% patients underwent 1 apheresis, while 70% underwent 2 sessions (if day 1 yield < 6x10^6 CD34+ cells/kg).
MGTA-145 was well tolerated. At least 1 adverse event (AE) was seen in 90% of patients, 20% had grade 2 AEs (anemia, hypokalemia) and 20% had grade 3 AEs (worsening of baseline grade 3 anemia; hypocalcemia); all resolved. Acute & transient bone pain was seen in 40% of patients (back-2, hip-1, sternum-1), all grade 1, all on day 1, & resolved without intervention after 6 minutes (3-10).
All 6 patients in the safety cohort have completed transplant with melphalan 200 mg/m^2. Median of 4.1 (3.4-5.6) x 10^6 CD34+ cells/kg were infused. All patients have engrafted timely (DiPersio Blood 2009); median time to neutrophil engraftment: 12 days (11-13) & platelet engraftment: 17 days (16-19). Apheresis graft analysis is available in these 6 patients. Grafts with MGTA-145+plerixafor showed high enrichment for CD90+CD45RA- among CD34+ cells, a CD34 subset of long term engrafting HSCs (median: 31% of CD34+ cells, 27-52), higher than seen with G-CSF (6%, Goncalves TCT 2021). 67% of grafts were minimal residual disease negative with next generation flow cytometry.

Figure: Stem Cell Yields with Same Day MGTA-145 and Plerixafor Mobilization in Multiple Myeloma



Summary/Conclusion:
This is the first study to evaluate the novel regimen of MGTA-145 + plerixafor for same day stem cell mobilization & collection in myeloma/hematologic malignancies, with 100% efficacy in interim analysis and the first to demonstrate successful engraftment in patients with cells collected with this GCSF free regimen.

EP1225 FIRST-IN-HUMAN CLINICAL TRIALOF BCMA-CD19 COMPOUND CAR IN THE REDUCTION OF DONOR-SPECIFIC ANTIBODY IN HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Donor-specific anti-HLA antibodies (DSAs) are antibodies in the recipient directed against donor class I/II HLA antigens. The existence of DSAs before HLA mismatched allogenic hematopoietic stem cell transplantation (allo-HCT) are known to cause primary graft failure. Currently, there is no established method of desensitization for DSAs due to the long half-life of plasma cells.
Aims: To evaluate the toxicity and efficacy of the BCMA-CD19 cCAR in the reduction of Donor-Specific Antibody (DSA) in haploidentical hematopoietic stem cell transplantation(haplo-HCT).
Methods: We have generated a BCMA-CD19 cCAR bearing 2 complete CAR constructs connected by a cleavable linker, P2A. CAR T cells were manufactured in a cGMP facility. The in vitro and in vivo activity of the cCAR were detected by co-culture assays and in mouse model studies. Between May 2019 and Sep 2020, 4 haploidentical HCT candidates with high titers of DSA were enrolled. All patients received conditioning (fludarabine 30 mg/m^2/d and cyclophosphamide 300 mg/m^2/d for 3 days). CAR-T cells were given by a dose escalation at 2~4.5×10^6/kg with a single dose. Study endpoints include the safety of the CAR, the reduction of DSA and engraftment after haplo-HCT.
Results: In co-culture assays, BCMA-CD19 CAR-T cells exhibited robust cytotoxic activity against the K562 cells engineered to express either CD19 or BCMA. In mouse model studies, cCAR-T cells were able to eliminate tumor in mice injected with MM.1S cells and REH cells, indicating the ability of the cCAR to specifically lyse both BCMA and CD19 expressing target cells in vitro and in vivo.
Of the 4 patients who have received CAR-T cell infusion, 1 was acute lymphoblastic leukemia(ALL), 2 were acute myeloid leukemia(AML), 1 was aplastic anemia-paroxysmal nocturnal hemoglobinuria (AA-PNH) syndrome. The age was from 21 to 48 years old, all patients had high DSA levels (MFI >5,000). CAR-T dose were from 2-4.5×10^6/kg.
Cytokine release syndrome (CRS) occurred in 3 patients (1 grade I, 2 grade II). No Neurotoxicity and other severe organ toxicity occurred in all the patients.
Bone marrow B cells and plasma cells were depleted at 4 weeks post CAR-T therapy in all patients. DSA dropped to low levels (MFI <5,000) for all patients, of them, plasma exchange was combined in 2 patients due to the emergency of HCT. The reduction percent ranged from 62.3% to 100%. All patients received a haplo-HCT 49-135 days post CAR-T therapy, and were successfully engrafted with a persistent full chimerism. (Figure 1)

	Age/sex Dx	CAR-T Dose (x10^6/kg)	B/plasma cells% in BM at 4 weeks	Days of HSCT	MFI of DSA before CAR	MFI of DSA before HCT	Combined methods
P1	48/F B-ALL	2	0/0	102	7820	1573	No
P2	21/F AA/PNH	2.7	0/0	135	12492/ 9663	0	No
P3	35/F AML	4.5	0/0	49	11547/ 11477	4343/ 2310	PE×3
P4	34/F AML	2	0/0	90	19180	3756	PE×1

	DSA reduction % before HCT	Donor HLA compatibility	Neutrophil engraftment	Platelet engraftment	Donor chimerism	Months post HCT	Status
P1	79.8%	6/12	d11	d10	full	17	alive
P2	100%	6/12	d16	d23	full	5	alive
P3	62.3%/ 79.8%	8/12	d12	d13	full	7	alive
P4	80.4%	6/12	d10	d11	full	1	alive

Summary/Conclusion: Our first in human clinical trial on BCMA-CD19 cCAR demonstrated profound efficacy in reducing DSA levels in an allo-HCT candidate. There was strong clinical evidence of depletion of antibody-producing roots, B-cells and plasma cells in the patients. Our results further suggested that BCMA-CD19 cCAR has the potential to benefit patients receiving solid organ transplants or those with other antibody-mediated diseases.

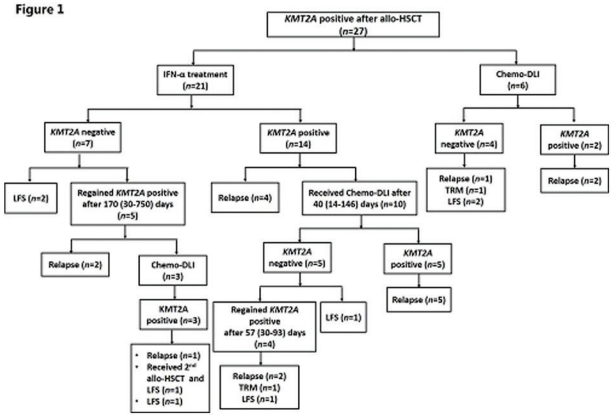
EP1226 MINIMAL RESIDUAL DISEASE MONITORING AND PREEMPTIVE IMMUNOTHERAPIES FOR FREQUENT 11Q23 REARRANGED ACUTE LEUKEMIA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: The prognosis of *11q23/KMT2A* rearranged (*KMT2A*-r) acute leukemia (AL) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) was poor. Minimal residual disease (MRD) was an important prognostic factor for relapse.MRD directed preemptive immunotherapy was effective to prevent relapse after allo-HSCT in AL. However, no study had identified the efficacy of these methods in a disease-specific population of patients with *KMT2A*-r AL, and whether commonly used preemptive immunotherapies could clear the MRD in these patients was unknown.
Aims: We aimed to identify the evolution of *KMT2A* before and after allo-HSCT and the efficacy of preemptive immunotherapies for *KMT2A*-r AL patients receiving allo-HSCT.
Methods: *KMT2A* expression was determined through TaqMan-based RQ-PCR technology. Preemptive immunotherapies included interferon-α and donor lymphocyte infusion. We collected 1751 bone marrow samples from 177 consecutive *KMT2A*-r AL patients.The SPSS 23 and the R software package were used for data analyses.
Results: Pre-HSCT *KMT2A* positive was correlated with post-HSCT *KMT2A* positive (correlation coefficient=0.371, P<0.001). The rates of *KMT2A* achieving negative after allo-HSCT were 96.6%, 92.9%, and 68.8% in the pre-HSCT low (>0, <0.1%)-, intermediate (≥ 0.1%, <1%)-, and high-level (≥1%) groups, respectively. The rates of regaining *KMT2A* positive after allo-HSCT were 7.7%, 35.7%, 38.5%, and 45.5%, respectively, for pre-HSCT *KMT2A* negative, low-, intermediate-, and high-level groups (P<0.001). The 4-year cumulative incidence of relapse after allo-HSCT was as high as 53.7% in pre-HSCT *KMT2A* expression ≥ 0.1% group, which was comparable between the *KMT2A* negative (15.1%) and *KMT2A* <0.1% group (31.2%). The clinical outcomes of patients with post-HSCT *KMT2A* positive were poorer than those with persistent *KMT2A* negative.
Thirty patients showed *KMT2A* positive after allo-HSCT, and the detail of *KMT2A*-directed immunotherapies were showed in Figure 1. In total, 27 KMT2A patients (25 AML and 2 ALL) received preemptive immunotherapies. Twenty-one patients received preemptive IFN-α treatment. Seven patients (33.3%) achieved *KMT2A* negative; however, 5 of them regained *KMT2A* positive, and only 2 patients (9.5%) achieved persistent LFS after IFN-α treatment. Nineteen patients received preemptive Chemo-DLI. Nine patients (47.4%) achieved *KMT2A* negative. In addition, only the patients with very low-level *KMT2A* gene expression might benefit from this treatment (rate of *KMT2A* achieving negative: *KMT2A* <0.01% vs. ≥ 0.01% before IFN-α treatment, 75.0% vs. 23.5%, P=0.088). Thirteen patients (68.4%) experienced relapsed and 5 patients (26.3%) achieved persistent LFS. The level of *KMT2A* gene expression before Chemo-DLI did not influence the rate of *KMT2A* achieving negative (<0.1% vs. ≥ 0.1% before Chemo-DLI, 75.0% vs. 46.2%, P=0.576).

Figure 1



Summary/Conclusion: Pre-HSCT *KMT2A* positive were significantly associated with post-HSCT *KMT2A* positive. The clinical outcomes of patients with post-HSCT *KMT2A* positive was poor. Although post-HSCT preemptive immunotherapies might help to achieve *KMT2A* negative, the long-term efficacy was unsatisfactory.

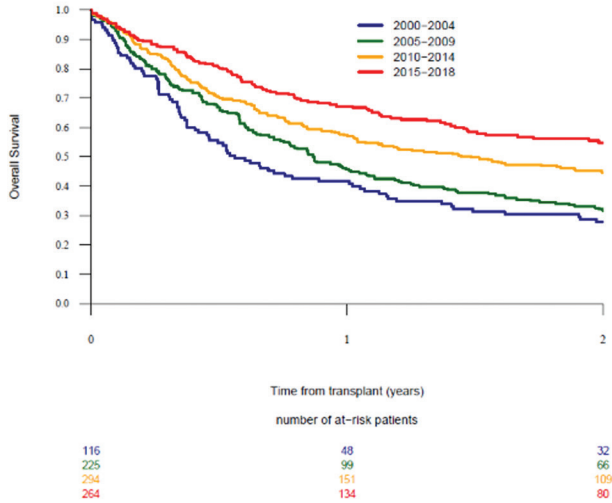
EP1228 SURVIVAL TRENDS OF ADULT PATIENTS WITH RELAPSED PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA POST ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION OVER 20 YEARS: AN ALWP-EBMT ANALYSIS

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) in patients with Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL) in first complete remission (CR1) has improved survival outcomes, even after the advent of tyrosine kinase inhibitors (TKI). However, relapses post allo-HCT still occur in up to 30% of transplanted patients, and pose a real challenge. While historically, available treatment options involved reduction/withdrawal of immunosuppression, cytotoxic chemotherapy, donor lymphocyte infusion, and a second allo-HCT, currently there is an increased use of newer generation TKI, monoclonal antibodies such blinatumomab and inotuzumab, as well as CAR T cell therapy.
Aims: The aim of this study was to assess the impact of the post-transplant relapse therapeutic evolution on survival outcomes over the years.
Methods: We selected all adult patients from the EBMT database with a diagnosis of Ph+ ALL who had morphologic relapse between 2000 and 2019 after allo-HCT performed in CR1, regardless of type of conditioning, donor type, stem cell source and prior TKI treatment. We analyzed survival outcomes using the Kaplan Meier method, and predictive factors by univariate and multivariate analysis. Median follow up for alive patients was 56 months.
Results: We identified 899 patients with a median age at transplant and at relapse of 44 and 45.4 years, respectively. Overall, 116 patients relapsed between 2000-2004, 225 between 2005-2009, 294 between 2010-2014, and 264 between 2015-2019. Patient and transplant characteristics were similar over the 4 time periods except for a progressive increase in the use of matched unrelated donor (from 34.5% between 2000-2004 to 55.7% between 2015-2019; p=0.0002), peripheral blood stem cells (from 60.3% to 84.5%; p<0.0001), reduced intensity conditioning (RIC) (from 16.4% to 34.5%; p=0.004), and *in vivo* T cell depletion (TCD) (from 27.9% to 62.4%; p=0.0001) as well as a progressive decrease in the use of total body irradiation (TBI) (from 73.3% to 53%; p=0.0002), respectively. The 2-year overall survival (OS) after relapse was 41.5 % (95% CI: 38 - 44.9). Original disease was the cause of death in 68.5% of patients. Importantly, the 2-year OS after relapse increased from 27.8% for patients relapsing between 2000-2004 to 31.7% for 2005-2009, 44.5% for 2010-2014 and 54.8% for 2015-2019 (p=0.001) (Figure 1). A second allo-HCT within 2 years after relapse was performed in 13.9% of patients resulting in a 2-year OS of 35.9%. The incidence of second allo-HCT was 21.7%, 12.8%, 9.9% and 15.7% for the same time periods (p=0.027). In multivariate analysis, factors that influenced positively the OS were a longer time from transplant to relapse (>median:7.1 months; hazard ratio [HR] 0.71, p=0.0007) and the year of relapse (reference 2000-2004; HR 0.68, p<0.013 for patients relapsing from 2005-2009; HR 0.72; p<0.008 for patients relapsing from 2010-2014, and HR=0.72; p=0.016 for patients relapsing from 2015-2019). Other patient, donor and transplant characteristics had no significant effect on outcomes.

OS after relapse – Ph–pos B ALL



Summary/Conclusion: We observe a major progressive improvement in OS from post-transplant relapse for patients with Ph+ ALL, likely reflecting the efficacy of post-transplant therapeutic strategies. This large-scale real-world data can serve as a reference for future studies investigating novel agents in this setting.

EP1229 COMPARISON OF OUTCOMES OF SINGLE CORD BLOOD TRANSPLANTATION AND HLA 1-3 ANTIGEN-MISMATCHED RELATED STEM CELL TRANSPLANTATION USING LOW-DOSE ANTITHYMOCYTE GLOBULIN FOR HEMATOLOGICAL MALIGNANCIES

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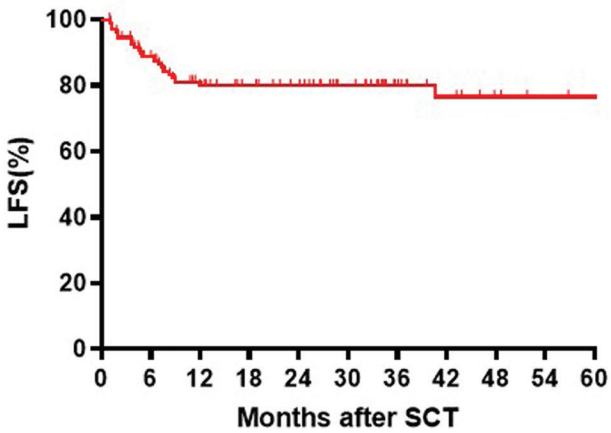
Background: Cord blood transplantation (CBT) and HLA-mismatched transplantation has become established alternative stem cell sources for patients with hematological malignancies. HLA-mismatched transplantation with post-transplant cyclophosphamide has spread rapidly and demonstrated favorable outcomes. Likewise, several studies indicated the potential of HLA-haploidentical transplantation with low-dose antithymocyte globulin, especially for high-risk diseases. On the other hand, significant progress in the management of CBT has led to comparable outcomes of HLA-matched and mismatched unrelated transplantation, showing better outcomes for patients with minimal residual disease.
Aims: To compare the outcomes of CBT and HLA-mismatched transplantation using low-dose ATG, we performed a retrospective study using data from the Japanese registry.
Methods: A total of 7899 patients aged 0-70 years with hematological malignancies who received their first allogeneic hematopoietic cell transplantation between 2009-2018 were eligible. A total of 7034 and 865 patients who underwent single CBT and HLA 1-3 antigen-mismatched related stem cell transplantation using ATG (mismatched-ATG) were included. The primary endpoint was overall survival (OS) and secondary endpoints were relapse-free survival (RFS), GVHD-relapse-free survival (GRFS), non-relapse mortality (NRM), relapse, neutrophil engraftment, platelet engraftment, grade II-IV acute GVHD, grade III-IV acute GVHD, chronic GVHD and extensive chronic GVHD.
Results: The median age in the CBT and mismatched-ATG groups were 53 and 47 years, respectively (p<0.001). High risk diseases and reduced-intensity condition were more frequent in the mismatched-ATG group (43.4% vs 66.1% and 36.6% vs 66.2%). In the mismatched-ATG group, the most common combination of GVHD prophylaxis was ATG plus cyclosporine A (CsA) or tacrolimus (TAC), and steroid (66.6%), whereas it was CsA or TAC plus methotrexate (MTX) in the CBT group (66.5%). In the mismatched-ATG group, 1 antigen mismatched transplant was included (16.5%) and median total dose of ATG was 2.5 (0.42-10.0) mg/kg. Median follow-up time in survivors was 3.3 and 3.4 years in the CBT and mismatched-ATG groups, respectively. OS after CBT was significantly higher than that of mismatched-ATG (3-year OS: 47.2%, 32.4%, P<0.001 and adjusted hazard ratio (aHR) 0.76, P<0.001). RFS and GRFS of CBT were also higher than mismatched-ATG (aHR 0.79, p<0.001 and aHR 0.70, p<0.001). Neutrophil and platelet engraftment were significantly lower (85% vs 94.8% and 60.2% vs 65.2%), whereas the incidence of grade III to IV acute GVHD and extensive chronic GVHD was significantly lower in the CBT group (aHR 0.44, p<0.001 and aHR 0.62, p<0.001). In the subgroup analysis, superiority of CBT to mismatched-ATG was observed in each disease group (AML: aHR 0.87, 95% confidence interval (CI) 0.75-1.00, ALL: aHR 0.70, 95% CI 0.55-0.89, MDS: aHR 0.79, 95%CI 0.52-1.19, and lymphoma: aHR 0.64, 95%CI 0.52-0.79). Favorable OS of CBT was confirmed regardless the disease risk (standard risk: aHR 0.63, 95%CI 0.53-0.75, high risk: aHR 0.83, 95%CI 0.73-0.93) and HLA mismatch (0-1: aHR 0.85, 95%CI 0.67-1.08, 2-3: aHR 0.74, 95%CI 0.67-0.83).
Summary/Conclusion: We observed favorable outcomes of CBT compared to mismatched-ATG, consistently the same according to the patient generations, disease, and disease risk. CBT may be the better choice alternative to HLA mismatched related transplant using low-dose ATG.

EP1230 OUTCOMES FOLLOWING UNMANIPULATED HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION AMONG 111 MIXED-PHENOTYPE ACUTE LEUKEMIA PATIENTS AT A SINGLE CENTER

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Background: Mixed phenotype acute leukemia (MPAL) is rare and generally associated with a poor prognosis. Optimal treatment for patients with MPAL and the role of allogeneic hematopoietic stem cell transplant (allo-SCT) remain unclear. Most prior case series included only modest numbers of transplanted patients, among which haploidentical transplant (haplo-SCT) were rarely included.
Aims: We tried to evaluate the safety and efficacy of haplo-SCT for MPAL patients and attempted to define factors that confer high-risk disease.
Methods: We retrospectively analyzed clinical results among MPAL diagnosed patients, defined by the 2017 World Health Organization (WHO) criteria. All patients included underwent a transplant at the Lu Daopei Hospital between July 2012 and December 2020. The latest follow-up date was December 2020.
Results: MPAL accounted for 3.1% (131 out of 4212) of all acute leukemias. Our analysis included the 111 MPAL patients who underwent unmanipulated haplo-HSCT with antithymocyte globulin [AA1] (ATG). Median age at transplant was 15 years (range: 1- 60 years of age). Patients had one of three immunophenotypes: 61 patients had leukemia with B/myeloid marker, 65 with T/myeloid marker, and 5 had B/T/myeloid markers. Fifteen patients harbored a BCR-ABL1 rearrangement and five had KMT2A-rearranged MPAL. Seventy-nine patients were in first complete remission (CR1), 31 in CR2 and 23 were in none remission (NR). Myeloablative regimens were used in all patients, among which 80 cases were body irradiation-based (TBI, 2Gy×5~6) and 41 busulfan-based (3.2 mg/kg/day×4). Cyclosporine, short-term methotrexate, and mycophenolate mofetil were used for graft versus host disease (GVHD) prophylaxis. Median total mononuclear cell count (MNC) and the infused CD34+ cell count was 9.0 $\times10^8$/kg (range: 3.94-19.13 $\times10^8$/kg) and 4.72 $\times10^6$/kg (range: 1.27-12.57$\times10^6$/kg). Except for two patients transplanted in advanced status both of whom died of sepsis on Day 2, all patients received neutrophil engraftment at a median 14 days (range: 9-34 days) post-transplant[AA2]. One hundred and four patients achieved platelet engraftment at a median 13 days post-transplant (6-73 days). Up to the latest follow-up date, the median survival time was 34 months (range: 1 - 93 months). The 3-year relapse rate was 12.1% (95% CI 5.4%>18.8%) and the 3-year non-relapse mortality (NRM) rate was 20.7%
(95% CI 12.7-28.7%). The 3-year overall survival (OS) and 3-year leukemia-free survival (LFS) were 69.5% (95% CI 60.5-78.5%) and 69.6% (95% CI 60.8-78.4%), respectively. The 3-year LFS of patients in CR1 and ≥CR2 and those with advanced disease were 75.4% (95% CI 64.2-86.6%), 70.1% (95% CI 52.7-87.5%), and 52.5% (95% CI 31.1-73.9%), respectively (CR1vs.≥CR2 p=0.416; CR1 vs. advanced disease p=0.024; CR2 vs. advanced disease p=0.213). There were no differences in relapse rate, NRM, OS or LFS among patients in the three different immunophenotype groups (B/myeloid vs. T/myeloid), nor by age (<13 years vs. ≥14years), conditioning regimes (TBI-based vs. Bu-based), or date of transplant (2012-2017 vs. 2018-2020). In multivariate analyses, status before transplant was the only predictor of relapse rate (hazard ratio [HR] 2.151; 95% CI, 1.058-4.375; p=0.034), OS (HR 1.598; 95%CI, 1.048-2.435; p=0.033) and LFS (HR 1.574; 95%CI, 1.044-2.375; p=0.031).



Summary/Conclusion: Haplo-SCT is a promising treatment option for patients with MPAL with encouraging low rates of relapse and long-term survival. Patients who undergo transplantation at an earlier stage of disease may have better safety and efficacy outcomes.

EP1231 CURRENT ROLE OF ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT) IN MANTLE CELL LYMPHOMA (MCL) IN THE ERA OF NEW IMMUNOTHERAPEUTIC AND TARGETED THERAPIES. THE GETH/GELTAMO EXPERIENCE.

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Background: MCL has been associated with poor prognosis, chemorefractoriness and older median age at diagnosis. For transplant-eligible patients, clinical outcome improves using intensive cytarabine-based induction, followed by autologous stem cell transplant (ASCT). Recently, new approaches with anti-CD20 maintenance, new target drugs or new ways of immunotherapy such as CARTs are changing the therapeutic landscape. Allo-SCT is a curative option for selected patients but with significant non-relapse mortality (NRM).
Aims: Our objective was to analyze long-term results in patients receiving allo-SCT in Spain.
Methods: We performed a retrospective multicenter study including patients from centers of GETH/GELTAMO with relapsed/refractory (R/R) MCL treated with allo-SCT from March 1995 to February 2020. The primary endpoints were event-free survival (EFS), overall survival (OS), NRM and cumulative incidence (CI) of relapse and graft versus host disease (GVHD).
Results: We included one-hundred and thirty-five patients with R/R MCL that fulfilled the inclusion criteria (Table 1). Median age was 56 years (27% >60 years); 49% had previous ASCT and median number of previous lines of therapy were 2 (1-8). Disease status at allo-SCT was complete response (CR) in 64%, partial response (PR) in 26% and stable/progressive disease (SD/PD) in 10%. Most patients (85%) received reduced intensity conditioning (RIC). After a median follow-up of 68 months (2-247), 5-year EFS and OS were 47% and 50%. NRM at day 100 and 5 years were 20% and 44%, respectively. Overall and CR rates on day 100 were 86% and 80%, respectively. The main causes of death were secondary to NRM: 32% GVHD, 32% infection, 3% veno-oclussive disease (VOD), 3% thrombotic microangiopathy and 15% others. Progression was the cause of death in only 14%. CI of relapse at 1 and 5 years were 9% and 16%, respectively. CI of grade 3-4 acute GVHD (aGVHD) at day 100 and moderate/severe chronic GVHD at 5 years were 29% and 42%, respectively. In the multivariate analysis we found the following independent factors: ECOG PS > 1 (HR 3.2; p=0.017) and donor mismatch (HR 2.2; p=0.007) for EFS; ECOG PS>1 (HR 3.1; p=0.018) and previous ASCT (HR 2.1; p=0.004) for OS; and grade 3-4 aGVHD (RR 7.1; p<0.001) for NRM.

Table 1. Characteristics of patients

Median age at allo-SCT (range)	56 (32-70)
Donor type:	
- HLA-id sibling	74 (55%)
- Matched unrelated	29 (21%)
- Mismatch unrelated	14 (10%)
- Haploidentical	18 (13%)
Median donor age (range)	46 (19-72)
ECOG at allo-SCT:	
- 0	74 (60%)
- 1	43 (35%)
- 2-4	6 (5%)
HCT-CI:	
- 0-1	70 (56%)
- 2	28 (23%)
- 3 or more	26 (21%)
Status at allo-SCT:	
- CR	86 (64%)
- PR	35 (26%)
- SD/PD	13 (10%)
Conditioning type:	
- Myeloablative	20 (15%)
- Reduced intensity conditioning	115 (85%)
Median months from diagnosis to allo-SCT (range)	33 (3-164)
Previous ibrutinib	19 (14%)
Previous rituximab maintenance	6 (4%)

Summary/Conclusion: Our data confirmed that allo-SCT may be a curative option in R/R MCL with low CI of relapse, although NRM is still high, mainly secondary to aGVHD. Results are better for fit patients, using HLA-identical donor (related or unrelated) and without previous ASCT. However, in the era of new immunotherapy and target drugs, allo-SCT should only be considered in selected patients failing these new approaches.

EP1232 DYNAMIC ASSESSMENT OF PERIPHERAL PERFUSION IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION SURVIVORS

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Background: Allogeneic hematopoietic cell transplantation (alloHCT) survivors have been recently recognized as patients at increased cardiovascular risk. Although impaired microcirculation dynamics are currently considered an important component of the pathophysiology of CV disease, their role has not been studied in alloHCT.
Aims: We hypothesized that microcirculation dynamics are impaired in alloHCT, independently of traditional cardiovascular risk factors.
Methods: We enrolled consecutive adult alloHCT survivors and otherwise healthy control individuals (January 2019-March 2020), matched for traditional cardiovascular risk factors. Microvascular dysfunction was dynamically assessed by Laser Speckle Contrast Analysis (LASCA); pulse-wave velocity (PWV) and intima media thickness (IMT) were assessed as surrogate markers of cardiovascular disease.
Results: We studied 75 alloHCT survivors after a median of 3.2 (range 2.1-4.9) years from alloHCT, who had suffered from grade 2-3 acute (20%) and/or moderate/severe chronic GVHD (42%), and 75 controls. Although traditional cardiovascular risk factors and surrogate markers of cardiovascular disease did not differ between groups, alloHCT survivors showed significantly impaired microvascular response (Table). Among them, occlusion flux and baseline to occlusion change independently predicted alloHCT status in the multivariate model.
Baseline, occlusion, time to peak, and base to peak change were also significantly impaired in patients with a hypertension diagnosis. Baseline flux was associated with age (r^2=0.191, p=0.020), office DBP (r^2=0.225, p=0.009), and PWV (r^2=0.034, p=0.050). Time to peak had an association with BMI (r^2=-0.189, p=0.034), office systolic BP (r^2=-0.186, p=0.038), heart rate (r^2=-0.375, p<0.001), and PWV (r^2=-0.314, p=0.014). Baseline to occlusion change was associated with office DBP (r^2=0.225, p=0.009), and PWV (r^2=0.335, p=0.001). Baseline to peak change was associated only with office DBP (r^2=-0.299, p=0.009). No significant associations were observed in LASCA indices and studied transplant characteristics.
Taking into account the univariate associations of LASCA indices, we further performed multivariate analyses to determine independent predictors. Only factors with significant univariate associations with the dependent variable were included in the multivariate model. The only independent predictor of baseline flux and baseline to occlusion change was the history of alloHCT (p=0.002 and p=0.022 respectively). Regarding time to peak change, heart rate and history of alloHCT independently predicted time to peak change in the multivariate model (p=0.044 and p=0.037 respectively).

Table . Markers of vascular dysfunction in alloHCT survivors and matched controls

	alloHCT (n=75)	Controls (n=75)	p-value
Surrogate markers of cardiovascular disease			
Pulse-wave velocity (m/s)	5.8 (3.3)	5.9 (1.6)	0.715
Left Carotid IMT (mm)	0.57 (0.18)	0.59 (0.16)	0.694
Right Carotid IMT (mm)	0.55 (0.15)	0.54 (0.12)	0.397
Laser Speckle Contrast Analysis			
Baseline flux (PU)	47.7 (16.0)	42.9 (13.0)	**0.031**
Occlusion flux (PU)	12.4±8.0	3.8±6.1	**<0.001**
Peak flux (PU)	116.1±29.6	114.2±20.8	0.693
Time to peak (sec)	9.3 (6.1)	11.8 (6.0)	**0.004**
Base to peak (%change)	76.8±65.8	130.8±80.4	**<0.001**
Baseline to occlusion (%change)	74.2 (15.6)	70.8 (166.1)	**<0.001**
PORH amplitude	0.75±0.33	0.78±0.24	0.675

alloHCT: allogeneic hematopoietic cell transplantation; IMT: intima media thickness; CVC: Cutaneous Vascular Conductance; PORH: post-occlusive reactive hyperemia. Continuous variables are presented as means±SD or median (interquartile range) according to normality tests.

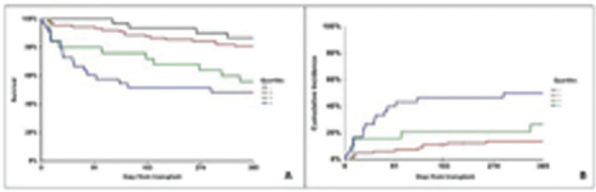
Summary/Conclusion: Our study shows for the first time impaired indices of dynamic microcirculation assessment in adult alloHCT survivors, as this is reflected by LASCA, independently of traditional CV risk factors. Furthermore, we were able to identify occlusion flux and baseline to occlusion change as the most significant predictors. Lastly, our findings confirm that patients with hypertension are at higher risk of microvascular dysfunction. Additional studies are needed to address the role of novel markers in cardiovascular risk prediction, as well as the effects of disease type, phase, and pre-transplant treatments.

EP1233 DAY 0 EASIX SCORE MIGHT PREDICT OVERALL SURVIVAL AND TRANSPLANT RELATED MORTALITY AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: SINGLE CENTRE EXPERIENCE.

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Background: Recently, Endothelial Activation and Stress Index (EASIX), calculated at the onset of acute GvHD, was reported as reliable predictor of survival in patients receiving reduced intensity conditioning at transplant. We wondered if an early evaluation of the EASIX score might be able to predict survival regardless of GvHD development.
Aims: We evaluate EASIX score at day 0 in a cohort of three consecutive years patients submitted to allogeneic stem cell transplantation in our department matching data with pot-transplant outcomes.
Methods: We enrolled 179 patients consecutively submitted to allogeneic stem cell transplantation (HSCT) in our centre from January 2017 to November 2019. The most frequent diagnosis was leukemia (n=104), followed by myeloproliferative disease (n=32), myelodysplastic syndrome (n=19), lymphoma (n=22) and SAA (n=2). Median age was of 53 years (range, 14-72). Twenty patients received a mismatched donor, 72 a haploidentical donor and 87 a matched donor. Donor was unrelated in 60 patients and a relative in the others. Stem cell source was cord blood in 7 patients, bone marrow in 76 patients and peripheral blood in the other 96. Seventy-nine patients received a myeloablative conditioning and 100 a reduced intensity conditioning. EASIX score (lactate dehydrogenase U/L x creatinine mg/dl / platelets x 10^9/L) was calculated at day 0 before stem cell infusion (EASIX-0). No log transformation was applied.
Results: Median level of EASIX-0 was of 1.67 (95% CI 1.39-1.96) for surviving patients and 4.64 (95% CI 2.36-8.59) for patients dying after HSCT (p<0.0001). Multivariate analysis for survival confirmed EASIX-0 (HR 1.01, 95% CI 1.00-1.02, p=0.01) as predictive factor for mortality together with relapse occurrence (HR 2.92, 95% CI 1.3-4.92, p=0.0001). One-year overall survival (OS) according to EASIX-0 was as follows: <25th quartile (n=31) 86.9% (95% CI 74.9-98.9), 25th-50th quartile (n=90) 80.9% (95% CI 72.8-89.1), 50th-75th quartile (n=25) 56% (95% CI 36.2-75.5) and >75th quartile (n=33) 48.5% (95% CI 31.4-65.5) (p<0.0001, Figure 1A). Moreover, EASIX-0 was significantly associated to the cumulative incidence of transplant related mortality (TRM): HR 1.01 (95% CI 1.00-1.02) (p=0.004). Multivariate analysis confirmed EASIX-0 (HR 1.06, 95% CI 1.01-1.12, p=0.01) as predictive factor for TRM together with grade 2-4 acute GvHD occurrence (HR 8.05, 95% CI 1.92-33.80, p=0.004). One-years cumulative incidence of TRM was as follows: <25th quartile 0%, 25th-50th quartile 13.6% (95% CI 7.9-23.6), 50th-75th quartile 26.3% (95% CI 12.4-55.8) and >75th quartile 50% (95% CI 35-71.5) (p<0.0001, Figure 1B). No association was found for relapse incidence.
Figure 1. A) One-year OS survival according to Day 0 EASIX score quartiles; B) One-year TRM according to Day 0 EASIX score quartiles.



Summary/Conclusion: Early EASIX score, calculated at day 0 of transplant, appeared to be a reliable prognostic score of survival after allogeneic stem cell transplantation. We plan to enlarge the study cohort to confirm our data.

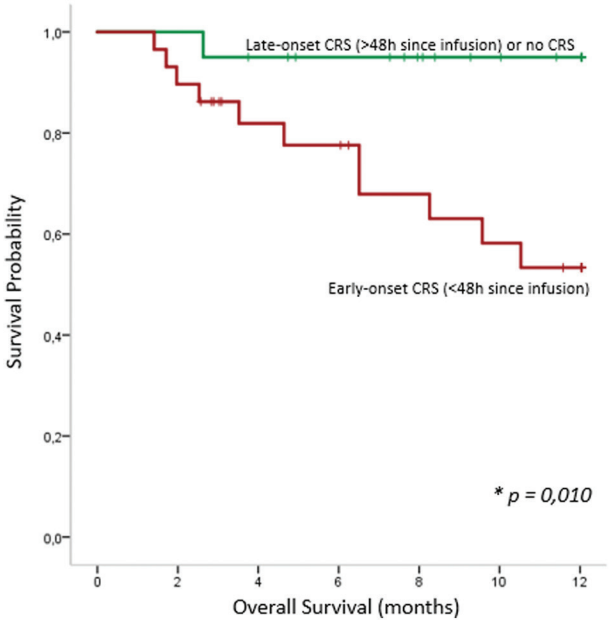
EP1234 EARLY-ONSET CYTOKINE RELEASE SYNDROME FOLLOWING ALLOGENEIC HAPLOIDENTICAL PERIPHERAL BLOOD STEM CELL TRANSPLANTATION MIGHT DECREASE OVERALL SURVIVAL

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Background: Haploidentical HLA stem cell transplantation (haplo-HSCT) is increasingly being used as part of the treatment of hematological malignancies lacking a suitable HLA-matched donor. Cytokine release syndrome (CRS) is a systemic inflammatory response with aberrant immune activation and hyperstimulation which has been described in a number of clinical settings, including haplo-HSCT. However, clinical impact of CRS on these patients is controversial.
During COVID-19 pandemic, graft cryopreservation in haplo-HSCT has increased in our centre. As a result, we clinically noticed a change in CRS onset in these patients.
Aims: To identify novel CRS features that might have a prognostic impact on haplo-HSCT, as well as to determine if graft cryopreservation might influence any of those features.
Methods: A cohort of 154 patients undergoing allogeneic stem cell transplantation in 2019 and 2020 in our centre, from which 51 patients receiving peripheral blood haplo-HSCT from 1st February 2019 to 31st December 2020 were selected. Two of them were excluded for the CRS analysis due to relevant microbiological isolation close to the infusion date and impossibility to distinguish between infectious and CRS fever. CRS was graded according to the ASBMT consensus.
Results: The median age was 51 years (range 17-72), 59% were male. Median follow-up was 359 days for alive patients. Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was low risk in 45%, intermediate risk in 22% and high risk in 33%. Most patients (71%) had an intermediate Disease Risk Index (DRI). Conditioning regimen was myeloablative in 12 (24%). 84% of the patients presented with CRS after haplo-HSCT (71% of them occurred in the first 48 hours after infusion). CRS was mild in most patients (grade 1 in 29 (71%) and grade 2 in 12 (29%); no grade 3 CRS or further occurred. Graft cryopreservation accounted for 13 (25%) patients.
Early-onset CRS (<48h since stem cell infusion) **was associated with lower overall survival** (Figure 1, p=0,01), **as well as lower event free survival** (relapse or death, p=0,03) when compared with the remaining patients in a univariate analysis. Non-myeloablative conditioning was associated with a higher proportion of early-onset CRS (74% vs 9%, p<0,001) as well as age >60 years (80% vs 45% p=0,014). It should be noted that age >60 years did not impact on overall survival in the first year following haplo-HSCT in our patients (p=0,485). We also found an **interesting trend between graft cryopreservation and early-onset CRS** (only 38% of patients with graft cryopreservation presented early-onset CRS, whereas 67% of patients with fresh graft did so, p=0,075).
Cryopreservation was related to less proportion of CRS grade ≥2 (0% vs 33%, p=0,014) and it did not impact on engraftment, overall survival nor graft versus receptor disease rate or severity in our patients. Patients with refractory disease prior to transplantation presented higher rates of CRS grade ≥2 (75% vs 20%, p=0,041). Moreover, a trend was observed for mononucleated cell count >8 x 10^8 (37% vs 14%, p=0,067). However, CRS grade ≥2 did not impact on overall survival in our patients (p=0,251).

Figure 1. Early-onset CRS is associated with less overall survival after allogeneic haploidentical peripheral blood stem cell transplantation



Summary/Conclusion: Early-onset CRS is associated with less overall survival and less event-free survival following the first year after haplo-HSCT. Cryopreservation is associated with less CRS grade ≥2 probability and might also reduce the chance of developing early-onset CRS.

EP1235 TRIAL OF AB-205 (E-CEL® CELLS) IN ADULTS WITH SYSTEMIC LYMPHOMA UNDERGOING HIGH-DOSE THERAPY AND AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HDT-AHCT) RESULTS OF AB-205-001 BY AGE SUBGROUP

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Background: Improvements in supportive care and HCT practices have led to increasing use of HDT-AHCT for patients with chemosensitive lymphomas, with a growing interest of treating older patients (pts). However, HDT is associated with high rates of severe regimen-related toxicities (SRRT), especially in older adults, (Dahi 2018) and the risk of life-threatening SRRT may preclude older pts or pts with co-morbidities from this potentially curative treatment.
SRRT is thought to result from diffuse injury to the microvasculature forming the organ vascular stem cell niches caused by off-target cytotoxic effects of HDT. SRRT involves virtually all organ systems, but is most evident in organs with high cell turnover such as oral-gastrointestinal (oral/GI) tract and bone marrow. While the hematopoietic system is rescued by AHCT, there are no effective therapies to repair damage to other organs.
AB-205 is a novel experimental engineered-cell therapy. AB-205 contains E-CEL® cells: allogeneic *E4*$^{+}$ human cord endothelial cells. E-CEL cells express multiple angiocrine factors in a dynamic, paracrine manner.
Aims: AB-205-001 objectives included assessing initial safety and efficacy.
Methods: Subjects with chemosensitive lymphomas eligible for HDT-AHCT were enrolled. AB-205 was administered IV after AHCT in dose-escalated cohorts: 5, 10 and 20x10^{6} cells/kg, either as single or divided (D0, D2) dose. Supportive care therapies were administered as per site institutional guidelines. Oral/GI SRRT was defined as NCI-CTCAEv5.0 grade (G)≥3 oral mucositis, nausea, vomiting or diarrhea. A retrospective chart review (n=45) at a participating site served as a contemporary control.
Results: Overall results have been presented previously [ASH 2020, TCT 2021, EBMT 2021]. Here we present data from pts treated with 20x10^{6} cells/kg by age.
29 systemic lymphoma subjects were treated with AB-205 with a median (range) follow up of 271 (179, 566) days. MTD was not reached. AEs were generally mild/moderate and as expected with HDT-AHCT.
AB-205 therapy demonstrated dose-dependent reduction of oral/GI SRRT. No (0%) oral/GI SRRT were reported for any subjects (n=18) receiving the recommended AB-205 dose, including the subjects ≥60 yo (n=7). In contrast, the control cohort reported 16/25 (64%) oral/GI SRRT rate ≥60 yo, while those <60 yo had 9/20 (45%).
Median time to neutrophil engraftment, platelet engraftment and number of hospitalization days (from AHCT) were numerically lower with AB-205 than in the control cohort by approximately 2, 7 and 3 days respectively (Table). The benefits with AB-205 treatment were consistent across age subgroups.
As of the cutoff date, there have been no reports of SRRT affecting the pulmonary, cardiac, renal or hepatic systems. No detrimental effect on PFS or OS was observed. There were no deaths by day 100.

	Age <60		Age ≥60	
	AB-205	Control	AB-205	Control
N	11	20	7	25
Age, Median (range), years	47 (25, 59)	40 (21, 59)	66 (61, 73)	66 (60, 73)
Male (%)	55	65	57	80
Diagnosis HL/NHL (%)	27/73	55/40	29/71	8/92
Lines of Therapy, median (range)	2 (1, 4)	2 (1, 3)	2 (2, 2)	2 (1,4)
HDT BEAM/BeEAM (%)	91/9	95/5	86/14	96/4
CD34+ cells x10^{6}/kg, median (range)	4.2 (2.8, 16.7)	5.3 (3.2, 7.9)	6.3 (4.5, 8.4)	3.2 (2.0, 7.2)
Oral/GI SRRT, n (%)	0	9 (45)	0	16 (64)
Neutrophil engraftment, median, days	10	12	10	13
Platelet engraftment, median, days	11	21	11	18
Number of hospitalization days from AHCT, median, days	13	16	12	16

Summary/Conclusion: 20x10^{6} cells/kg of AB-205 eliminated the occurrence of oral/GI SRRT including in subjects 60 yo. In contrast, 64% event rates were seen in pts ≥60 yo in a contemporary control cohort. AB-205 has potential to make HDT-AHCT substantially safer for older pts and may enable physicians to consider this potentially curative therapy for high-risk patients currently considered ineligible for HCT.

EP1236 DEMOGRAPHIC, CLINICAL CHARACTERISTICS AND MORTALITY OF ADULT HEMATOLOGICAL CANCER PATIENTS WITH VENO-OCCLUSIVE DISEASE IN ENGLAND, 2010 TO 2020

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Background: Veno-occlusive disease (VOD), or sinusoidal obstruction syndrome, is a rare liver disorder which is associated with high morbidity and mortality. Patients with hematological malignancies are at particularly high risk of developing VOD following antineoplastic treatment, especially among those who had hemopoietic stem cell transplantation (HSCT).
Aims: To apply an adapted algorithm based on the Seattle/Baltimore diagnostic criteria to identify VOD patients among adult hematological cancer patients and a subcohort of patients with leukemia in England, and to describe their demographic, clinical characteristics, and mortality.
Methods: This retrospective observational study utilized the Hospital Episode Statistics (HES) inpatients, outpatients, and critical care 'pseudonymized' datasets (NHS Digital, England) as its source of adult hematological cancer patients, including a subcohort with leukemia, identified between 1/1/2010 and 31/3/2020. An algorithm to identify VOD was applied based on the Baltimore/Seattle diagnostic criteria and other clinical features of the disease (with a breakdown of its components shown in Table 1); adults with chronic graft-versus-host disease (GVHD) or total parenteral nutrition (TPN) cholestasis were not included. Patients with VOD were followed up from diagnosis of VOD (index date) until the earliest occurrence of death or end of study period.
Results: A total of 386,174 adults with hematological cancers (mean age: 67.9; males: 57.9%), including a subcohort of 80,081 patients with

leukemia (mean age: 70.7; males: 60.4%), were identified within the HES datasets during study period. Overall, the adapted algorithm identified 323 (8 per 10,000; mean age: 51.0; males: 55.1%) patients with VOD in the hematological cancer cohort, and 68 (8 per 10,000; mean age: 53.9; males: 50.0%) in the leukemia subcohort (Table 1). The majority (~41%) developed VOD between 45 and 64 years of age. Overall, prior systemic antineoplastic therapies (inc. chemotherapy), radiotherapy and HSCT were received by 79.3%, 11.2% and 67.5% of hematological cancer patients and 89.7%, 20.6% and 73.5% of leukemia patients, respectively. Antineoplastic treatments were received by 282 hematological cancer patients who developed VOD and among them 218 (77.3%) had prior HSCT. Within the leukemia subcohort, 50 of 64 (78.1%) VOD patients had prior HSCT. Among patients with VOD, 56.7% (hematological cancer patients) and 55.9% (leukemia patients) died within 100 days of developing the disease. The mortality rates following VOD were 68.8 and 94.0 per 100 person-years, among hematological cancer patients and leukemia subcohort, respectively.

Table 1. Characteristics of hematological and leukemia patients with VOD

	Hematological cancer patients (N=386,174)	Among patients with leukemia (N=80,081)
	VOD (n=323)	VOD (n=68)
All VOD[£], n (%)[^]	323 (100.0)	68 (100.0)
K76.5 or K71.8	128 (39.6)	23 (33.8)
Hepatic VOD (ICD 10 K76.5)	108 (33.4)	20 (29.4)
Toxic liver disease with other liver disorders (ICD 10 K71.8)	21 (6.5)	3 (4.4)
Symptoms of VOD within 60 days of HSCT	9 (2.8)	0 (0.00)
Multi-organ failure with liver failure within 60 days of HSCT	147 (45.5)	35 (51.5)
Other hepatic vein occlusion or necrosis within 60 days of HSCT	72 (22.3)	14 (20.6)
Male n (%)	178 (55.1)	34 (50.0)
Age at first VOD event in years, n (%)		
Mean (SE)	51.0 (16.3)	53.9 (16.3)
Median (IQR)	54.1 (36.7, 64.6)	56.7 (42.3, 65.8)
Age[#] group at first VOD event in years, n (%)	312 (100.0)	68 (100.0)
18 to 34	73 (23.4)	10 (14.7)
35 to 44	35 (11.2)	9 (13.2)
45 to 64	128 (41.0)	28 (41.2)
65 and over	76 (24.4)	21 (30.9)
Charlson Comorbidity Score at first VOD event, median (IQR)	2 (2, 4)	3 (2, 4)
Length of follow-up, years		
Mean (SE)	1.0 (1.90)	0.8 (1.6)
Median (IQR)	0.2 (0.0, 0.9)	0.2 (0.1, 0.7)
Treatment, n (%)		
Systemic therapies (including chemotherapy)*	256 (79.3)	61 (89.7)
Radiotherapy*	36 (11.2)	14 (20.6)
HSCT*	218 (67.5)	50 (73.5)
VOD according to antineoplastic treatment received, n (%)	n = 282	n = 64
Chemotherapy and/or radiotherapy	64 (22.7)	14 (21.9)
Chemotherapy and/or radiotherapy and HSCT	218 (77.3)	50 (78.1)
Mortality from VOD diagnosis		
Number of deaths within 100 days, n (%)	183 (56.7)	38 (55.9)
Mortality rate per 100 person-years during entire follow up	68.8	94.0

[£] after applying selection criteria (patients with graft-versus-host disease or total parental nutrition cholestasis removed) and categorized into components as per adapted algorithm. To note, use of defibrotide could not be identified in order to use as proxy to define VOD
[^] unique number of patients after accounting those who were under more than one criterion
*Some patients may have received more than one treatment modality (e.g. chemotherapy, radiotherapy or HSCT)
[#]Data request to NHS Digital was for adult patients only
HSCT, hemopoietic stem cell transplant; ICD, international classification of diseases; IQR, inter-quartile range; n/a, not applicable; SE, standard error; VOD, veno-occlusive disease

Summary/Conclusion: This study identified a similar proportion of VOD patients (8 per 10,000) in the overall hematological cancer cohort as in the leukemia subcohort. It should be noted that the incidence of VOD is representative of the calculations that were based on this study's adapted algorithm. Among patients who were treated for their hematological cancers and subsequently developed VOD, this particular algorithm identified that three quarters had prior HSCT in their treatment strategies. The high mortality rate among patients with VOD in England suggests a clear need to focus research and clinical efforts to identify the disease promptly, develop risk-profiling methodology and improve patients' survival.

EP1237 PHASE II CLINICAL TRIAL (EMN-ALLORIC 2010) OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR HIGH RISK (HR) MULTIPLE MYELOMA (MM) FOLLOWED BY MAINTENANCE WITH BORTEZOMIB AND LENALIDOMIDE. UPDATED ANALYSIS.

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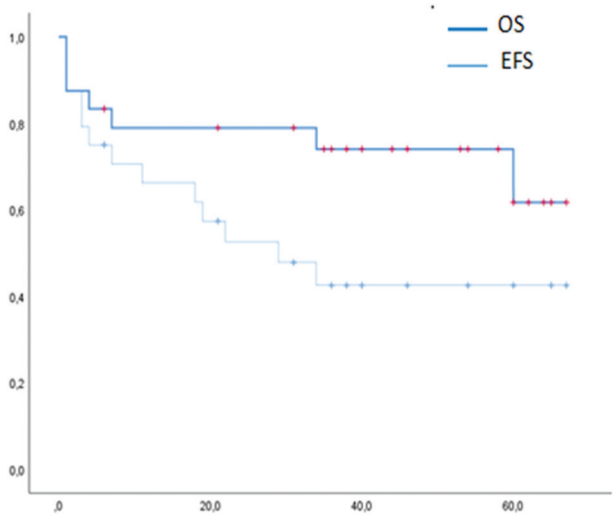
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Background: Maintenance treatment with lenalidomide (Len) after autologous SCT in MM patients has demonstrated 2.5 years improvement in overall survival(OS). Its role after alloSCT is controversial because of an increased risk of graft versus host disease (GVHD), and prospective trials are lacking. AlloSCT can be a curative option in MM patients, but relapse is the main cause of treatment failure, especially after reduced intensity conditioning regimens (RIC), although they are the preferred option due to lower non-relapse mortality (NRM). The use of Bz within the conditioning regimen was demonstrated to be safe and allowed to obtain a high response rate after RIC alloSCT in a previous phase I trial. In an attempt to decrease the risk of relapse, this phase II was planned adding maintenance with Bz and Len.

Aims: Evaluate the toxicity and efficacy of a RIC with Bz and postransplant maintenance with Bz and Len in HR MM patients. Updated analysis of relapse rate (RR), acute and chronic GVHD, event free survival (EFS) and OS. To analyse inmune subpopulations and the effect of Len in immune recovery.

Methods: Multicenter, phase II trial. All patients provided written informed consent. RIC included Bz 1.3 mg/m2 iv on days -9 and -2; fludarabine 30 mg/m2 iv on days –6 to –4 and melphalan 140 mg/m2 iv on d –3. GvHD prophylaxis was based on Bz 1.3 mg/m2 iv on d +1, +4 and +7 plus methotrexate 15 mg/m2 on d+1 and 10 mg/m2 on d +3, +6 and +11 and tacrolimus. For maintenance therapy, all patients received Bz 1,3 mg/m2 iv on d 1, 8 and 15 in 28 days cycles starting on d+70 postransplant. Based on disease status at d +100, patients received six cycles of Bz (1.3 mg/m2 iv on d 1, 8, 15) every 56 days (if complete response(CR) or nCR) or four cycles of Bz (1.3 mg/m2 iv on d 1, 8, 15), Len (15 mg on days 1 to 21) and dex (10 mg on d 1 to 4 and 8 to 11) followed by same treatment regimen specified for patients in CR. Len was started on day +180 (5 mg pd until relapse or toxicity).Different subpopulations of the immune system were evaluated on peripheral blood by flow cytometry (FC) on days +100, +180, +270, and +365.

Results: 24 patients were included. All had previously received treatment with proteasome inhibitors and immunomodulatory drugs, 87% had received a previous autoSCT. Cumulative incidence (CI) of grade 2-4 and 3-4 aGvHD at 100d was 39% (CI 95%: 15.5%>56.1%) and 21.7% (CI 95%: 7.7%>40.4%). CI of overall cGVHD at 1y was 22.7% (CI 95%: 7.9%>42%) and moderate-severe 18.1% (CI 95%: 5.4%>36.8%). 7 patients died (5 due to aGvHD), CI NRM was 21.1% (95% CI 0.074-0.394) at 1y. With a median follow up of 39m (range 1-67), median EFS was 29m (95% CI 8.1%>49.8) (not reached for patients with at least VGPR at d100 postransplant); median OS was not reached. EFS and OS at 3y were 42,48% (95% CI 21.9%>61.7%) and 74% (95% CI 50.8%>87.45%). CI of relapse was 13.6% (95% CI: 3.2%>31.3%) at 1y. Out of 20 patients evaluable for maintenance therapy, 15 patients stopped it before relapse or death due to GvHD (9), infection (1), citopenia (1), neuropathy (2) and patient/physician´s choice (2). Upon comparing inmune recovery between patients included in the phase II or the phase I trial (who did not received maintenance), several differences emerged in different immune cell sub-populations (non classical monocytes, lymphocytes).



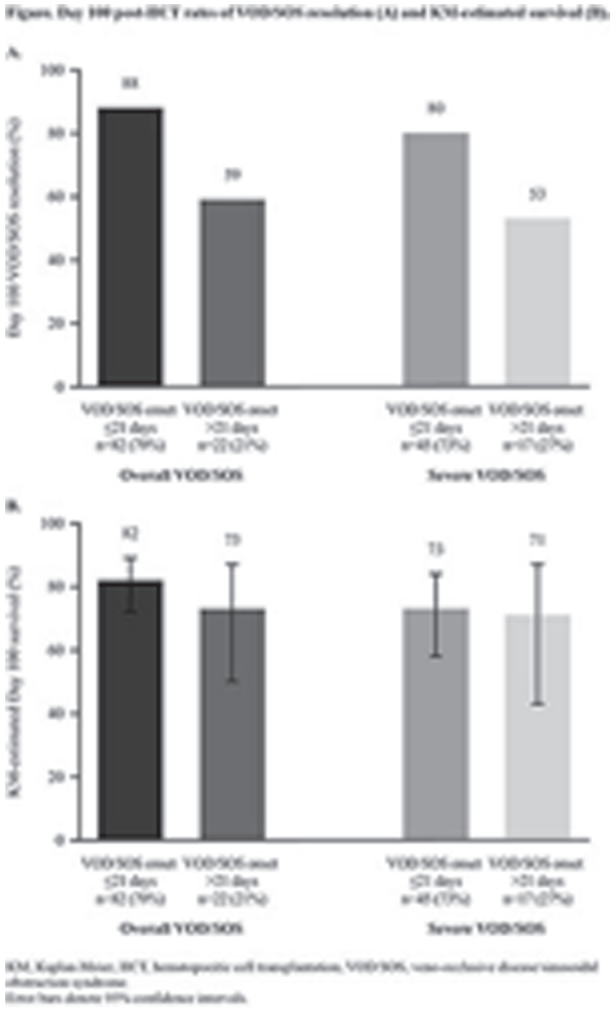
Summary/Conclusion: Combination of alloSCT with novel drugs could improve the efficacy of the procedure in MM.
Maintenance treatment with Len and Bz leads to a low risk of relapse. Although the risk of cGVHD did not increase, Len was stopped in a significant proportion of patients.

EP1238 LATE-ONSET VENO-OCCLUSIVE DISEASE/ SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) AFTER HEMATOPOIETIC CELL TRANSPLANTATION (HCT): OUTCOMES OF DEFIBROTIDE-TREATED PATIENTS FROM THE EBMT PASS REGISTRY STUDY

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Background: Severe hepatic VOD/SOS is a potentially fatal complication of HCT conditioning. Signs and symptoms of VOD/SOS often peak within 14 days of HCT but in a large, prospective study, late-onset (beyond Day 21) VOD/SOS occurred in 26% of patients and was more common in adults than pediatric patients. Defibrotide is approved for severe hepatic VOD/SOS post-HCT in patients aged >1 month in the European Union.
Aims: This subgroup analysis of defibrotide-treated patients from the EBMT PASS evaluated outcomes in patients with VOD/SOS onset ≤21 days or >21 days post-HCT.
Methods: This multicenter, multinational, prospective, observational study (NCT03032016; EBMT PASS), enrolled defibrotide-treated patients from April 2015 to July 2018. Investigators diagnosed VOD/SOS using classical/standard criteria (including, but not limited to, hyperbilirubinemia, hepatomegaly, ascites, and weight gain >5%). Severity grading criteria were not predefined in the protocol; investigators graded VOD/SOS severity based on clinical expertise. Multiorgan dysfunction/failure (MOD/MOF) was diagnosed by the investigator based on renal, pulmonary, or cerebral dysfunction/failure.
Results: Of 104 defibrotide-treated patients with VOD/SOS post-HCT, 82 (79%) had onset ≤21 days (41% were adults) and 22 (21%) had onset >21 days post-HCT (50% were adults). Median time to VOD/SOS onset was 10.5 (range: 1, 21) days in patients with onset ≤21 days and 32.0 (range: 22, 122) days in those with onset >21 days. Median age was 14.0 (range: 0, 69) years and 19.0 (range: 1, 65) years in patients with onset ≤21 days and >21 days, respectively. Severe VOD/SOS occurred in 62 of the 104 patients with VOD/SOS post-HCT; in patients with severe VOD/SOS, 45 (73%) and 17 (27%) patients had VOD/SOS onset ≤21 days and >21 days, respectively. Among patients with severe VOD/SOS, MOD/MOF at baseline was observed in 25 (56%) patients with onset ≤21 days and 11 (65%) patients with onset >21 days.
In the overall population, the rates of VOD/SOS resolution (**Figure [A]**) and Kaplan-Meier–estimated survival (**Figure [B]**) at Day 100 were numerically lower in patients with late-onset VOD/SOS. Overall, the Kaplan-Meier–estimated survival rate at 1 year post-HCT was 65% in patients with onset ≤21 days and 41% in those with onset >21 days; among patients with severe VOD/SOS, 1-year post-HCT survival rates were 53% and 41%, respectively. In patients with severe VOD/SOS, the MOD/MOF resolution rate was 56% in patients with onset ≤21 days and 46% in those with onset >21 days.
Serious adverse events (SAEs) of interest occurred in 29% of patients with onset ≤21 days and 23% of those with onset >21 days; among patients with severe VOD/SOS, incidence of SAEs was 33% and 29%, respectively. The most common categories of SAEs in the overall population were infections (onset ≤21 days: 22%; onset >21 days: 14%) and bleeding events (onset ≤21 days: 11%; onset >21 days: 14%); corresponding values among patients with severe VOD/SOS were 27% and 18% for infections and 11% and 18% for bleeding events.



Summary/Conclusion: In this analysis of post-HCT VOD/SOS patients, approximately 20% developed VOD/SOS >21 days post-HCT, highlighting the need for continued vigilance for VOD/SOS beyond the usual window of development. Given that patients with late-onset VOD/SOS are likely to begin treatment later post-HCT than those with onset ≤21 days, caution must be taken when interpreting rates of Day 100 post-HCT VOD/SOS resolution and survival. The safety of defibrotide in this real-world setting was consistent with previous studies.

EP1239 OPTIMOB STUDY: INTERIM ANALYSIS OF THIS NON-INTERVENTIONAL TRIAL IN GERMANY TO EVALUATE THE MOBILIZATION AND COLLECTION OF HEMATOPOIETIC STEM CELLS IN POOR MOBILIZERS

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Background: Although most of the patients with multiple myeloma (MM) or lymphoma eligible for autologous stem cell transplantation (ASCT) mobilize enough hematopoietic stem cells (HSCs), there are also

patients in which mobilization is more difficult and several apheresis (aph) sessions are needed. For those poor mobilizers (PMs), data will be collected across Germany and adequate mobilization strategies will be established.
Aims: Aim of the OPTIMOB study is to assess the current approach of HSC mobilization and collection, and ASCT in PM patients in Germany to eventually improve mobilization and transplantation strategies, especially in PM patients.
Methods: The OPTIMOB study is an ongoing, prospective, non-interventional study including patients having MM or lymphoma who are eligible for ASCT. PMs are categorized as follows: (1) patient never achieved ≥ 20 $CD34^+$ cells / µL before 1st aph (PM-A), (2) patient received plerixafor (PLX) at any time point of mobilization (PM-B), (3) the initially planned HSC yield had to be reduced (PM-C), or (4) patients have not received aph due to low $CD34^+$ count in peripheral blood (PM-D).
Results: Until data cut-off in November 2020, 461 patients participated in the study, of whom 37.6% were classified as PMs. Most patients (67%) suffered from MM. Notable, the share of PMs was nearly the same in both entities, MM and lymphoma. In general, PMs were older, mostly male and had a poorer Karnofsky score. 68.2% of the PMs received plerixafor during mobilization, mainly in combination with chemotherapy and/or G-CSF (granulocyte-colony stimulating factor). PLX administration led to a notably increase of $CD34^+$ cells in peripheral blood in PM patients (at least two-fold). Until data cut-off, 84.4% of the PMs were able to undergo aph. In general, patients with PLX supported mobilization had a higher mean total $CD34^+$ collection result than PM patients without PLX administration (7.5 x10^6 cells/kg body weight (BW) [SD: ± 7.46] vs 5.2 x10^6 cells/kg BW [SD: ± 3.70]). Further, 72% of the PM patients treated with PLX (n=104) reached the total planned $CD34^+$ collection target (median 6.0 x10^6 cells/kg BW) during aph whereas in patients without PLX administration, only 45.5% of the patients achieved this goal. ASCT was feasible in 66.5% of the PM patients until data cut-off.
Summary/Conclusion: The ongoing OPTIMOB study provides comprehensive data of the current situation of MM and lymphoma patients classified as PMs in Germany. Data support that additive administration of PLX to established mobilization strategies leads to a sufficient mobilization and collection of HSCs PM patients.
This non-interventional study is sponsored by Sanofi.

EP1240 CO-REACTIVATION OF CYTOMEGALOVIRUS AND EPSTEIN-BARR VIRUS WAS ASSOCIATED WITH POOR PROGNOSIS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: Reactivation of cytomegalovirus (CMV) or Epstein-Barr virus (EBV) is common after hematopoietic stem cell transplantation (HSCT). Previous researches have demonstrated that either CMV or EBV reactivation is associated with poor outcomes of HSCT. However, few studies investigate the impact of CMV and EBV co-reactivation after HSCT.
Aims: Our aim was to described clinical characteristics of patients with co-reactivation of CMV and EBV (defined as CMV and EBV viremia occur at the same period of time), research the impact of such co-reactivation on prognosis and identify associated risk factors.
Methods: We conducted a longitudinal study of 247 patients who underwent first HSCT in our center between July 2015 and June 2016. Of these 247 patients, different conditioning regimen were performed according to their different underlying disease. They received uniform CMV and EBV monitoring and therapy, as well as graft-versus-host disease (GVHD) prophylaxis. Peripheral blood samples were collected from the recipients at 30, 60 and 90 days after HSCT for immunophenotyping. Co-reactivation of CMV and EBV was defined as the detection of EBV or CMV viremia during CMV or EBV viremia, respectively. The time of co-reactivation was defined as the day when viremia of the first virus was identified. Univariate and multivariate analysis and survival analysis were performed to elucidate the impact of such co-reactivation on prognosis and identify associated risk factors.
Results: A total of 24 (9.7%) patients had CMV and EBV co-reactivation of these 247 patients. These patients showed higher incidence of viral pneumonitis (P=0.005). Patients with CMV and EBV co-reactivation had significant lower 1-year overall survival (OS) (P=0.004) and lower 1-year leukemia free survival (LFS) (P=0.016). Our further analysis suggested that duration of CMV (P=0.014), EBV (P<0.001), and CD4+CD25+ T cell counts at day 30 post-transplantation (P=0.05) are independent risk factors of virus co-reactivation.

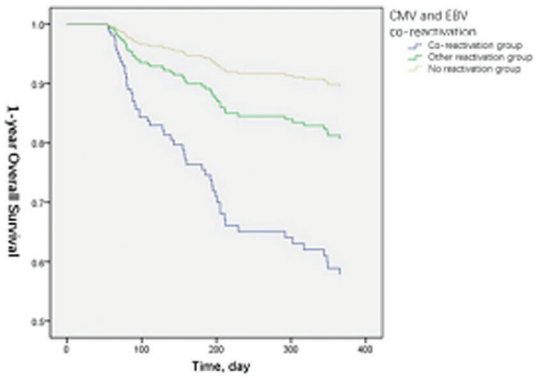


Figure 1 CMV and EBV co-reactivation was identified as one of the independent risk factors for 1-year overall survival. (P=0.004)

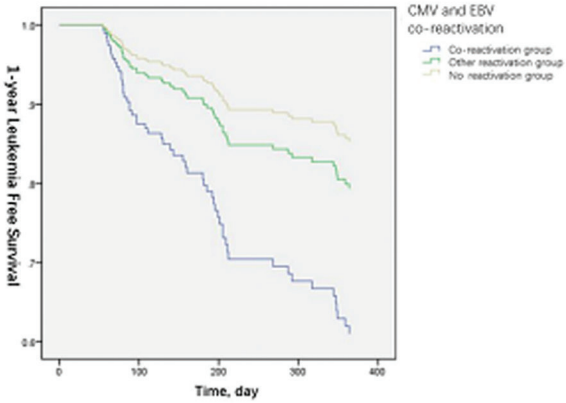


Figure 2 CMV and EBV co-reactivation was identified as one of the independent risk factors for 1-year leukemia free survival. (P=0.016)

Summary/Conclusion: Patients who developed co-reactivation of CMV and EBV had poor prognosis in terms of lower 1-year OS and LFS, and the CMV and EBV co-reactivation was associated with prolonged CMV or EBV duration and poor CD4+CD25+ T cell reconstitution at day 30 post-transplantation, which may provide an alternative way to prevent CMV and EBV reactivation in HSCT patients.

EP1241 IMPACT OF IMMUNE STATUS ON HOSPITAL READMISSION AFTER ALLO-HSCT

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Background: Allo-HSCT is accompanied by different complications including infections, graft-versus-host disease (GVHD) that require constant follow-up. Increased rate of HLA-mismatched allo-HSCT may be associated with higher hospital readmissions rate.
Aims: We studied the impact of immune status (T-, B- and natural killer lymphocytes, or NK-cells) in patients (pts) after allo-HSCT within the period from +6 to +12 months (mths) after transplantation for assessment of hospital readmission risk.
Methods: 51 pts were included in the study (male=23, female=28). Median age 41 (min – 20, max – 70). Pts had diagnosis: AMLs (n=28), ALLs (n=10), NHLs (n=5), CLL (n=1), primary myelofibrosis (n=2), MDS (n=3), aplastic anemia (n=2). 8 pts (16%) had mismatched unrelated donors, 19 pts (37%) had mismatched related donors, 6 pts (12%) had haploidentical, 18 pts (35%) had matched related donors. 24 pts were transplanted with PBSC, 27 - with bone marrow. Myeloablative or reduced-intensity conditioning regimens were performed in 14 (27%) and 37 (73%) pts, respectively. Flow cytometry analysis was performed on BD FACS Canto II device (Becton Dickinson, USA) with BD Multitest™ 6-color TBNK kit to define T-cells, T-helpers, cytotoxic T-lymphocytes, NK-cells and B-cells on +6, +9, +12 mths. The two-platform method was used to determine an absolute lymphocytic subpopulation count. Mann–Whitney U test used for nonparametric data analysis. A p-value was less than cutoff 0.05 was considered significant. ROC-analysis was performed to determine parameters, which affect readmission rate. Multivariate analysis (MVA) was used to determine the relating probability of readmission with gender, age of pts, type of donors, type of grafts, GVHDs, numbers of T-helpers, B-cells, NKs.
Results: From +6 to +9 mths 11 pts (29.7%) were hospitalized due to GVHD, 4 pts (10.8%) were hospitalized due to infections and 22 pts (59.5%) due to other reasons. From +9 to +12 mths hospital readmissions causes were: chronic GVHD (n=13, 41.9%), infections (n=2, 6.5%), relapses (n=4, 12.9%) and other reasons (n=12, 38.7%).
According to thresholds determined by ROC analysis pts were divided into two groups. The probability of readmissions in the period from +6 to +9 mths were: 55% for pts with the absolute number of T-helpers less than 180/μL and 23% for pts with the absolute number of T-helpers more than 180/μL (p=0.0144); 58% for pts with B-cells less than 50/μL and 27% for pts with B-cells more than 50/μL (p=0.0079). The probability of readmissions in the period from +9 to +12 mths were: 72% for pts with the absolute number of T-helpers less than 225/μL and 16% for pts with the absolute number of T-helpers more than 225/μL (p<0.0001); 52% for pts with NKs less than 175/μL and 18% for pts with NKs less than 175/μL (p=0.0033) (figure 1).

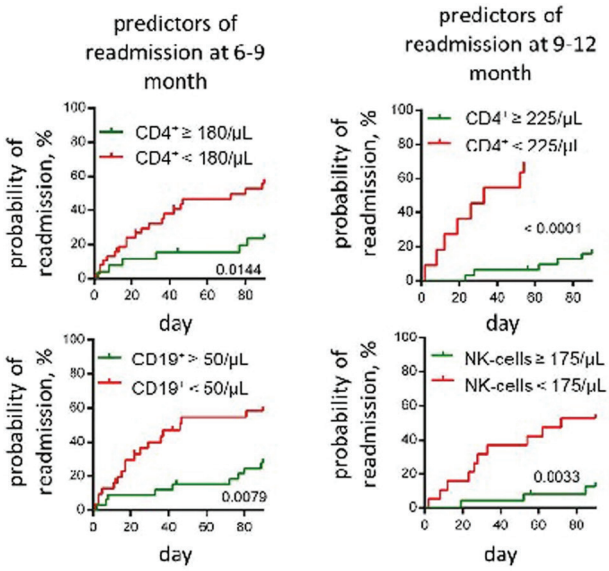


figure 1. The probability of hospital readmission depending on some parameters of the lymphocytes subpopulation

In MVA probability of readmissions weren't related to gender, age of pts, donor's type, graft type, GVHD. But probability of readmissions at +9 mths was significantly associated with the absolute number of T-helpers (for pts with the absolute number of CD4<180/μL at +6 mths (p=0.0435) and for pts with the absolute number of CD4<180/μL at +9 mths (p=0.0157)) and B-cells (p = 0.0184 for pts with the absolute number of CD19<50/μL at +9 mths).
Summary/Conclusion: The absolute number of NK cells, B-cells and T-helpers can reflect the quality of immune reconstitution after allo-HSCT. The low level of these cells may predict high readmission risk in the post-engraftment period after allo-HSCT at different time points disregarding gender, age of pts, donor's type, graft type, GVHD.

EP1242 ASSOCIATION OF TRAVEL TIME TO TRANSPLANT CENTER AND POST-TRANSPLANT CARE MODEL WITH OUTCOME PARAMETERS AFTER ALLOGENEIC TRANSPLANTATION

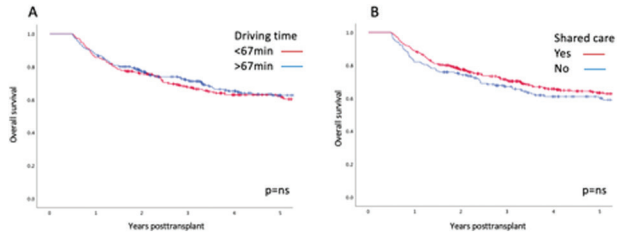
R. Peter [1,*], J. Halter [2], D. Heim [2], M. Medinger [2], T. Pabst [3], G. Stussi [4], J. Passweg [2], S. Gerull [2]

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Background: Allogeneic hematopoietic cell transplantation is a well-established treatment modality for multiple hematological diseases, however a significant risk of complications remains. It is performed only in specialized centers and patients necessitate intense follow-up care posttransplant which is usually performed at the transplant center, in turn leading to long travel times for patients. It is conceivable that travel burden could impair the quality of posttransplant care, as has been shown in other healthcare settings. Previous retrospective studies conducted in North America have shown contrasting results regarding the impact of travel distance on outcome. To reduce the burden of travel time to our center, whenever possible we offer shared care posttransplant meaning that patients can receive some or in selected cases all follow-up visits with other health care providers with which we have an established collaboration.
Aims: Due to the situation at our center with long travel times on the one hand and an established shared care model posttransplant on the other hand, we were interested in analyzing the impact of distance and posttransplant care model on outcome parameters.
Methods: We conducted a retrospective analysis of 678 patients who received a first allogeneic transplantation at the University Hospital of Basel between January 2008 and December 2017. Pediatric patients were excluded. All study participants gave written informed consent. Since the intention to provide shared care posttransplant was not collected prospectively, patients who did not receive shared care presumably also included those that died before they could continue to outpatient care or were considered too sick. For this reason, we performed selected analyses in a landmark population of patients alive at day 180.
Results: Median age at transplant was 53y (range 19-75), 416 (61%) were male. The most common disease was acute leukemia (n=329, 49%). The majority of patients had an unrelated donor (n=379, 56%) and a myeloablative conditioning regimen (n=467, 69%). The median follow-up of survivors was 1750 days while 57% of the patients were still alive after 3 years.
Median travel time by car and public transport to the transplant center was 67min and 112min respectively, and 56% and 78% of patients had a travel time of over 1h by car and public transport respectively.
Of the patients in the landmark population alive at day 180 (n=553), 375 (68%) received shared care, and 277 (91%) of those with a driving time >1h. There was no difference in overall survival (OS) for patients with driving time over or under the median or for those

receiving shared care posttransplant versus not (Figure 1). A multivariable analysis including patient and transplant characteristics confirmed the lack of association between driving time and receiving shared care with OS in the landmark population. Patients alive at one year receiving shared care had significantly less visits at the transplant center with a median of 12 versus 22 visits (p<0.001) between day 100 and day 365.

Figure 1



Summary/Conclusion: Our study demonstrates that within the framework of shared care, increasing distance to the transplant center does not negatively impact outcome and that the burden of prolonged travel time for patients can be significantly reduced. While acknowledging the limits of a retrospective analysis, to our knowledge, this is the first such study performed in Europe, and we believe it will help optimize post-transplant follow-up and is an important contribution to the growing field of health services research.

EP1243 THE ADDITION OF ATG TO NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION WITH FLUDARABINE AND CYCLOPHOSPHAMIDE REDUCES GVHD AT THE EXPENSE OF HIGHER RELAPSE RATES AND POORER OVERALL SURVIVAL.

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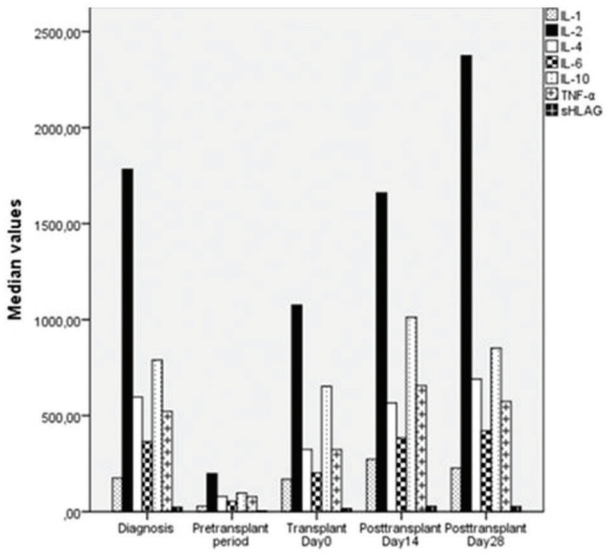
Background: The use of anti-thymocyte globulin (ATG) for graft versus host disease (GVHD) prophylaxis has been demonstrated to reduce acute GVHD (aGVHD) and chronic GVHD (cGVHD) following myeloablative HLA matched related and unrelated allogeneic stem cell transplantation (alloSCT). However, its use in non-myeloablative (NMA) alloSCT is less well described with concerns for graft loss or poor donor chimerism due to prolonged lymphocyte depleting effects.
Aims: To analyse the impact of ATG on post-transplant outcomes following unrelated donor alloSCT using NMA conditioning with fludarabine and cyclophosphamide
Methods: We reviewed patients treated at our centre that received alloSCT from an unrelated donor (n=58) between 2000 and 2020 with (n=35) or without ATG (n= 23) for the treatment of haematological malignancies. All patients received either fludarabine (90mg/m2) and low-dose cyclophosphamide (2250mg/m2) or fludarabine (125mg/m2) and high dose cyclophosphamide (120mg/kg). The primary outcomes were the incidence and severity of aGVHD, cGVHD and T-cell chimerism within the first 100 days following transplantation. Secondary outcomes included rates of non-engraftment, overall survival (OS), and GVHD-free relapse free survival (GRFS).
Results: The ATG cohort was older (median 59 vs 55 years) with more female participants (48.6% vs 30.4%) but had similar disease characteristics and conditioning to the non-ATG group. All patients engrafted with faster neutrophil and platelet engraftment in the ATG cohort with a median recovery time of 16 days (range: 8-23) vs 19 days (range: 9-34) [P = 0.03] and 18 days (range: 10-35) vs 20 days (range: 8-33) [P = 0.47] respectively. There was no difference in median T-cell chimerism at day 30, 60 or 100 for either group although more patients in the ATG cohort had chimerism less than 50% (37.1 vs 17.4%, p = 0.080) at day 100. At 80 months follow-up post-transplant, the cumulative incidence (CI) of cGVHD (0.20 vs 0.52; P = 0.0076) and moderate to severe cGVHD (0.11 vs 0.35; P = 0.048) was lower in the ATG cohort however there was a higher incidence of relapse (0.60 vs 0.17; P = 0.015). There were no significant differences in the incidence of aGVHD (0.20 vs 0.26; P = 0.53) or non-relapse mortality (0.14 vs 0.087; P = 0.50). OS for the ATG group was significantly lower (42.9% vs 82.6%; P = 0.0026), with a lower relapse free survival (25.7% vs 73.9%, P = 0.12) and GRFS (20% vs 48.9%, P = 0.69).
Summary/Conclusion: The addition of ATG to NMA conditioning alloSCT with fludarabine and cyclophosphamide was associated with a reduced incidence of GVHD but with no significant difference in T-cell chimerism or engraftment. There was a greater likelihood of disease relapse leading to inferior OS with the use of ATG.

EP1244 EVALUATION OF SOLUBL HLA-G AND CYTOKINE LEVELS IN CHILDREN WITH ACUTE LEUKEMIA UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION.

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Background: There are few studies about cytokines and soluble human leukocyte antigen-G (sHLA-G) levels in patients with acute leukemia undergoing allogeneic stem cell transplantation (allo-SCT). Proinflammatory and antiinflammatory cytokines maintain a balance between hematopoietic stem cell and lineage spesific cell in a healthy marrow; however, this balance is disrupted in case of leukemic transformation. In addition, HLA-G expressed in leukemic cells contributes to the uncontrolled proliferation of the leukemic cell by protecting the leukemic cell from NK-mediated lysis and apoptosis. Few studies have been reported that the balance of inflammation during allo-SCT is also mediated by cytokines, which stimulate inflammation by proinflammatory cytokines as well as suppress inflammation by anti-inflammatory cytokines and sHLA-G.
Aims: The aim of the present study was to investigate the role of cytokines and sHLA-G levels measured at five different time points in children with acute leukemia undergoing allo-SCT.
Methods: This was a prospective longitudinal cohort study. A total of 41 patients with acute leukemia were recruited in this study. Among them, 26 consecutive patients were examined during the diagnosis of acute leukemia and in the remission period before transplantation (PreTx). The remaining 15 patients were included on the day of transplantation (Tx_0). A total of 41 patients with acute leukemia were also examined on the 14th ($PostTx_{14}$) and 28th ($PostTx_{28}$) days after transplantation. Serum levels of pro-inflammatory (IL-1, IL-2, IL-6, TNF-α), anti-inflammatory (IL-4, IL-10) cytokines and sHLA-G were measured by ELISA (Bioassay Technology, China). This study was approved by the Institutional Review Board. All statistical analyses were performed using SPSS 15.0 program.
Results: The median cytokine and sHLA-G levels in leukemia diagnosis and post-transplantation periods (Tx_0, $PostTx_{14}$, $PostTx_{28}$) were found



to be significantly higher than the cytokine and sHLA-G levels in the pre-transplantation period (p<0.05). Serum IL-1, IL-4, IL-10, and sHLA-G levels at diagnosis were significantly higher in children with relapse acute lymphoblastic leukemia (ALL) than in children without relapse ALL (p<0.05). Compared with patients who had pre-B-ALL and acute myeloblastic leukemia, median serum IL-2, IL-10, and sHLA-G levels were significantly higher in patients with T-ALL (p<0.05 for all). The sHLA-G serum level was strongly correlated with serum IL-4 (r=0.94) and IL-10 (r=0.92) levels (p<0.05). In the Tx_0 and $PostTx_{14}$ days, transplantation related complications, relapse, and mortality risk were found to be approximately 2.5 times higher in patients with elevated cytokines and sHLA-G levels.
Summary/Conclusion: Our results indicate that elevated anti-inflammatory cytokines and sHLA-G levels at diagnosis can be associated with relapse in pediatric ALL, and also elevated cytokines and sHLA-G levels during transplantation have a negative effect on survival in leukemia.

EP1245 SUBMYELOABLATIVE TBI-BASED CONDITIONING AND ALLOGENEIC HEMATOPOETIC CELL TRANSPLANTATION IN HIGH-RISK MYELOMA WITH EARLY PROGRESSION POST AUTOLOGOUS TRANSPLANTATION

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Background: Allogeneic stem cell transplantation (alloSCT) in multiple myeloma (MM) is considered a treatment option in relapsed MM, especially in the presence of high-risk disease as indicated by early progression post upfront autologous transplantation (ASCT) or adverse cytogenetics.
Aims: There is no standard conditioning regimen, especially in patients considered to be melphalan-refractory and data on alloSCT in relapsed MM consist of heterogenous patient populations. We aimed to study a TBI-based submyeloablative conditioing regimen in relapsed high-risk MM.
Methods: Between September 2009 and December 2017, we investigated a submyeloablative conditioning regimen consisting of 8 Gy total body irradiation (TBI) and cyclophosphamide (total 80mg/kg bodyweight) followed by alloSCT in 32 consecutive patients with early progression post upfront ASCT.
Results: 90.6% of patients initially received novel agent-based induction therapy prior to ASCT. 58.3% had adverse cytogenetics (deletion17p, t(4;14), t(14;16) or gain 1q21 > 3 copies) and 79.2% had high-risk MM disease as defined by either International Staging System stage III, elevated LDH (above upper limit of the normal) or adverse cytogenetics and all patients had early disease progression (<24 months) post ASCT (median time to progression post ASCT: 300 days, range 52–664). Median lines of therapy prior to alloSCT reinduction was 1 (range 1-8) with a rate of very good partial response or better (≥VGPR) of 37.5%. Median time of hospitalization for conditioning and alloSCT was 29 days (range: 21 – 64 days). Toxicity of alloSCT during hospitalization was low and acceptable with only one early death (febrile neutropenia with multi-organ failure). Median days to engraftment of neutrophils and platelets of 14 days (range: 11 – 27 days) and 11 days (range: 8 – 34 days), respectively. Acute graft-versus-host disease (GvHD) occurred in 15 patients (20.0% ≥3 grade) and chronic GvHD in 18 patients (mild: 44.4%, moderate: 38.9%, severe: 16.7%). Response rates post alloSCT (between days 100-180) were ≥VGPR in 41.4% of patients. Maintenance therapy post alloSCT was applied in only 10.7% of patients. After a median follow-up of 76.7 months, median progression-free (PFS) and overall survival (OS) from alloSCT were 9.4 (95% CI: 5.2 – 13.7 months) and 28.8 months (95% CI: 8.0 - 49.5 months), 3- and 5-year OS rates were 50% and 30%, respectively. Non-relapse mortality (NRM) was 12.5% at 1 and 3 years (95% CIs: 4 - 27% each).
Summary/Conclusion: Our study demonstrated an acceptable toxicity profile, low NRM and a small fraction of high-risk patients achieving long-term disease control with 8 Gy TBI / cyclophosphamide conditioning prior to alloSCT in a homogenous cohort of MM with early relapse post upfront ASCT. The role of alloSCT in high-risk, relapsed MM deserves further investigation with optimized reinduction, conditioning and maintenance therapies.

EP1246 G-CSF-PRIMED PERIPHERAL BLOOD STEM CELL HAPLOIDENTICAL TRANSPLANTATION COULD ACHIEVE SATISFACTORY CLINICAL OUTCOMES FOR ACUTE LEUKEMIA PATIENTS IN THE FIRST COMPLETE REMISSION: A REGISTERED STUDY

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Background: G-CSF-mobilized peripheral blood (G-PB) harvest is the predominant graft for identical sibling donor and unrelated donor allogeneic hematopoietic stem cell transplantation (HSCT) recipients, but it was controversial in haploidentical related donor (HID) HSCT.
Aims: In this registry study, we aimed to identify the efficacy of HID G-PB HSCT (HID-PBSCT) for acute leukemia (AL) patients in first complete remission (CR1). Also, we reported the outcomes for the use of G-PB grafts in comparison with the combination of G-BM and G-PB grafts in HID HSCT recipients.
Methods: Sixty-seven AL patients in CR1 who received HID-PBSCT were recruited at Institute of Hematology, Peking University. Patients who received haploidentical HSCT using the combination of G-BM and G-PB harvests in the same period were enrolled as controls (n=392).
Results: The median time from HSCT to neutrophil and platelet engraftment was 12 days (range, 9-19 days) and 12 days (range, 8-171 days), respectively. The 28-day cumulative incidence of neutrophil and platelet engraftment after HSCT was 98.5% and 95.5%, respectively. The cumulative incidences of grade II-IV and grade III-IV acute graft-versus-host disease (GVHD) were 29.9% (95%CI 18.8%>40.9%) and 7.5% (95%CI 1.1%>13.8%), respectively. The cumulative incidences of total and moderate-severe chronic GVHD were 54.9% (95%CI 40.9%>68.8%) and 17.4% (95%CI 6.7%>28.0%), respectively. The cumulative incidences of relapse and non-relapse mortality were 13.9% (95%CI 5.4%>22.5%) and 3.4% (95%CI 0-8.1%), respectively. The probabilities of overall survival (OS) and leukemia-free survival (LFS) were 84.7% (95%CI 74.7%>94.7%) and 82.7% (95%CI 73.3%>92.1%) respectively. Compared with the HID HSCT recipients using the combination of G-BM and G-PB grafts, the engraftments of neutrophil and platelet were both significantly faster for the G-PB group, and the other clinical outcomes were all comparable between the groups. In multivariate analysis, graft types did not influence the clinical outcomes.
Summary/Conclusion: Overall, for the patients with AL CR1, G-PB graft could be considered an acceptable graft for HID HSCT recipients.

EP1247 MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC TRANSPLANT FOR ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Allogeneic hematopoietic stem cell transplant (HSCT) is a standard therapy for patients with acute myeloid leukemia (AML), when the risk for relapse overweighs projected transplant related morbidity and mortality. Disease relapse remains the most common reason for transplant failure and patient death, and treatment of relapse remains extremely challenging. Reducing the risk of post-transplant relapse without unwanted toxicity by means of post-transplant maintenance therapy has recently been studied in several prospective studies.
Aims: We aimed to evaluate the efficacy and safety of maintenance therapy for AML after allogeneic HSCT.
Methods: Systematic review and meta-analysis of randomized controlled trials which compared maintenance therapy with observation or placebo in AML patients after allogeneic HSCT. The Cochrane Library, Pubmed, conference proceedings and references were searched until February 2021. Two reviewers appraised the quality of trials and extracted data. Primary outcome was overall survival (OS). Secondary outcomes

included relapse free survival (RFS), relapse rate and safety (including adverse events and GVHD).
Results: Our search yielded five trials conducted between the years 2009 and 2018, including 736 patients, all published in peer-reviewed journals. Maintenance therapy was comprised of tyrosine kinase inhibitors (TKI): sorafenib - 2 studies; midostaurin - 1 study, and hypomethylating agents (HMAs): decitabine and azacytidine - one study each. Characteristics of included trials are presented in Table 1. Data from four trials were available for analysis of OS. Maintenance after allogeneic HSCT was associated with an improved OS, HR=0.61 (95% CI 0.47-0.80, I^2=2%, 547 patients). Subgroup analyses by type of maintenance therapy also revealed advantage in OS with either TKI or HMA maintenance [HR=0.50 (95% CI 0.33-0.77, 3 trials, 345 patients) and HR=0.69 (95% CI 0.49-0.98, 2 trials, 391 patients), respectively]. Data from five trials were available for RFS analysis and showed improved RFS in the maintenance group compared with the control arm HR=0.51 [95% CI 0.40 - 0.66]. Relapse rate was significantly decreased in the maintenance arm compared to the control arm, RR=0.41 (95% CI 0.20-0.88, 4 trials, 668 patients).
Regarding safety, three trials reported grade 3 or 4 adverse events. The risk of any grade 3 or 4 adverse events did not increase with the addition of maintenance after allogeneic HSCT, RR=1.0 (95% CI 0.83-1.20, 464 patients). There was no difference between the maintenance and control arms in the rate of all infections or grade 3 or 4 infections [(RR=0.98 (95% CI 0.83-1.16, I2=0%, 3 trials, 585 patients) and (RR=0.96 (95% CI 0.68-1.36, 3 trials, 464 patients), respectively]. There was no difference between the two arms in grade 3 or 4 thrombocytopenia or in grade 3 or 4 neutropenia. No difference was noted between the two arms regarding grade 2-4 acute GVHD, mild-moderate chronic GVHD or severe chronic GVHD.

Table 1. Characteristics of included trials

Study	AML type eligibility criteria	Start of maintenance post transplant (days)	Primary endpoint	Length of follow up (months)	Treatment regimen	Num. of patients included	Age (Median, range)	Sex (male, %)
Burchert 2020	Flt3-ITD mutated AML	60-100	RFS	42	sorafenib	43	54 (24-75)	42%
					placebo	40	54 (19-76)	58%
Maziarz 2020	Flt3-ITD mutated AML	28-60	RFS	24	midostaurin	30	48 (20-61)	53%
					SOC	30	6 (20-68)5	60%
Xuan 2020	Flt3-ITD mutated AML	30-60	relapse rate	21	sorafenib	100	35 (26-42)	50%
					SOC	102	35 (26-43)	51%
Gao 2020	High risk AML	60-100	relapse rate	28	decitabine + GCSF	102	30 (3-62)	56%
					SOC	102	28 (2-52)	60%
Oran 2020	High risk AML/MDS	42-100	RFS	52	azacitidine	93	57 (19-72)	59%
					SOC	94	58 (20-75)	61%

AML – acute myeloid leukemia; RFS – relapse free survival; GCSF - granulocyte colony stimulating factor; SOC – standard of care; MDS – myelodysplatic syndrome.

Summary/Conclusion: Our meta-analysis shows that post-transplant maintenance therapy in AML patients is effective in decreasing relapse rate and improving RFS and OS, with a satisfactory safety profile.

EP1248 OUTCOME OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR AML PATIENTS WITH 11P15/NUP98 REARRANGEMENT

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Background: Patients with acute myeloid leukemia and 11p15/NUP98 gene rearrangement (NUP98-r AML) treated with chemotherapy alone generally show poor overall survival (OS) and prognosis, with less than 50% OS and leukemia-free survival; some reports with median OS of less than 1 year. In cases of NUP98-r AML with co-existing FLT3 mutation, treatment with chemotherapy alone has demonstrated poor prognosis, with only 28% of 3-year OS.
Aims: To study clinical outcome of patients with NUP98-r AML after allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: We conducted retrospective assessment and outcome analysis in a cohort of 34 patients with NUP98-r AML treated with allogeneic HSCT at the Hebei Yanda Lu Daopei Hospital (from July 1, 2019 to February 1, 2021). Six types of NUP98 fusion gene partners were identified by PCR/FISH as follows: NSD1 (n=23), HOXA9 (n=5), KDM5A (n=4), HOXD13 (n=1), and LNP1 (n=1); 18 cases were identified with FT3 mutation. Median age was 16 years old (range from 1 to 61 years). Majority of patients underwent haplo-identical HSCT (n=31), while the rest received matched sibling donor HSCT (n=3). The conditioning regimens were based on Bu/Cy (n=31) and TBI/Cy (n=3). Patients received antithymocyte globulin, cyclosporine, mycophenolate mofetil, or methotrexate for graft-versus-host disease (GVHD) prophylaxis. Dosage of infused mononuclear cells and CD34+ cells were 10.5±3.2x10^8 /Kg and 5.5±2.3 x10^6 /Kg, respectively.
Results: In this study, the median follow-up time was 9 months (3-30). All 34 patients in this cohort achieved myeloid engraftment with median time for ANC above 0.5x10^9 /L on Day 14 (10-23). The median time for platelet count to exceed 20x10^9 /L was Day 13 (7-58) in 32 patients, with 2 patients remained thrombocytopenic. The incidence of acute GVHD (n=9) and chronic GVHD (n=7) was 26% and 20.5%, respectively. The average survival rate was 24±2 months (95% CI=19-27 months). Two-year OS and LFS were 75.9+7.5% and 75.6± 7.6%, respectively. In this cohort of NUP98-r AML patients, the subgroup with co-existing FLT3 mutation (n=18) has demonstrated an OS of 71.3 ± 10.9%, as compared to 81.3±9.8% in the subgroup without FLT3-mutation (n=16). Our data showed better survival of FLT3-positive patients in NUP98-rAML after allogeneic HSCT as compared to anecdotal survival data with chemotherapy alone. The OS of the subgroup without minimal residual disease (MRD negative, n=13) was 84.6±10.0%, versus 70.3±10.3% in the group with positive MRD (n=21). In this cohort of NUP98-r AML patients, the mortality rate within 100 days after HSCT was 11.7% (n=4). The causes of death (total of 8 patients) include relapse of disease (n=4), Grade IV GVHD (n=3), thrombotic microangiopathy (n=1) and subdural hemorrhage (n=1). Among the 5 patients developed relapse of disease, one with molecular relapse and responded well after chemotherapy and second allogeneic HSCT, while the other 4 relapsed patients expired.
Summary/Conclusion: This study has demonstrated encouraging clinical outcomes for NUP98-r AML patients after treatment with allogeneic HSCT, as compared to anecdotal data with chemotherapy alone in the literature, particularly in the clinical setting of coexisting FLT3 mutation. Larger clinical study is required to confirm this result.

EP1249 EFFECT OF HEMATOPOIETIC STEM CELL TRANSPLANTATION(HSCT)IN SEVERE CONGENITAL NEUTROPENIA

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Background: Severe congenital neutropenia(SCN) is a preleukemic bone marrow failure syndrome.Patients are at considerable risk of infections and evolving into leukemia or myelodysplastic syndrome (MDS). According to the reports of international that allogeneic hematopoietic stem cell transplantation (HSCT) is the curative treatment of SCN, but data on outcome about that are scarce in our country.
Aims: The aim of the present study is to clarify the cficacy of HSCT on patients with severe congenital neutropenia(SCN).
Methods: We retrospectively analyzed clinical characteristics about total 11 patients with SCN who underwent HSCT in our hospital from April 2015 to July 2020. ALL patients with EL. ANE-gene mutation. The median age was 3 (1-14) years. Male to female was 7:4.The median discase course from diagnosis to transplant was 37 (8-165) months.Six patients received umbilical cord blood-HSCT,the conditioning regimen was:Fludarabine(40mg/m^2/d×5days)+Ara-c(2g/m^2/d×5days)+Bu(0.8mg-1.2mg/KgQ6h×4days)+cyclophosphamide(1.8g/m^2/d×2days)+ATG(Thymoglobuline,SANOFI,1.25mg/Kg/d×2days).Two patients underwent matched unrelated donor(MUD)-HSCT,two patients underwent Haplo-HSCT,and another one were sibling donor-HSCT,the conditioning regimen was:Ara-c(3g/m^2/d×3days)+Bu(0.8mg-1.2mg/Kg Q6h×4days)+Fludarabine(40mg/m^2/d×4days)+ATG(ATG-Fresenius S,4mg/Kg/d×4days or p-ALG 20mg/Kg/d×2days for sibling donor-HSCT).For GVHD prophylaxis,CsA/tacrolimus plus MTX were used.
Results: All of the 11 patients tolerated pretreatment successfully. the total implantation rate was 100%.The median time of neutrophil sngraftment was 11 (9-16) days;the median time of platelet engraftment was 12(9-36)days.During the median follow-up period of 25 (range,3-70 months) months:the incidence of CMV was 72.7%;EBV DNA load of all patients who infected with EBV were undetectable after transplant. Grade II-IVaGVHD occurred in 4 cases,the probability was 36.3%. Two cases had cGVHD. Two patients died of GVHD,and the rest of the patients survived, with an overall survival rate (OS) were 81.81%.
Summary/Conclusion: Our results have shown that HSCT has higher implantationrate and overall survival rate,and may become a viable therapeutic option. Nevertheless, because of the transplant-related

death, a careful selection of HSCT candidates and the time point for HSCT should be undertaken.

EP1250 OUTPATIENT PROGRAM BASED ON TELEMEDICINE IS A GOOD OPTION TO MANAGE PRE-ENGRAFTMENT PHASE IN MYELOMA MULTIPLE PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: Autologous Hematopoietic Stem Cell Transplantation (ASCT) is a therapeutic procedure used as consolidation therapy in different acute hemopathies, especially Multiple Myeloma (MM) and Lymphomas.
There are centers with experience in home care programs that avoid hospital admission partially (aplasia phase) or total (conditioning and infussion day include). This model of attencion requires the support of visits from health personnel, mainly home nursing.
In our center we have designed a mixed care model based on telemedicine and visits to an outpatient clinic twice a week, named e-outpatient. For monitoring during the stay at home we have developed a mobile app (THAD® app) with different utilities (registry of constants, treatment adherence, videoconference) that allows us to control the patient's condition twentyfour hours/seven days.
Aims: Our main objective is to describe the efficacy and safety of this type of care in MM patients undergoing ASCT included in the e-outpatient program.
Methods: A one center retrospective study, with data obtained from the electronic clinical history, in our center from 2015 to 2020. Statistical analysis has been performed with IBM SPSS.19.
Results: During the study period, 112 patients with a diagnosis of MM underwent ASCT, 43 of them (38.4%) were included in the e-outpatient program. The characteristics of the patients are listed in Table 1.
The median days of hospital admission for the included patients was 5 (0-25). The median neutrophil and platelet engraftment was 13 and 15 days. Median red blood cell and platelet concentrates were 0 and 2 respectively. None of the patients required parenteral nutrition during the procedure. The hospital readmission rate was 27.9%. The causes of readmission were mainly fever (58.3%) and Grade III-IV gastrointestinal toxicity (41.7%).
The incidence of febrile syndrome in our series was 65.1% (28/43). The median number of empirical antibiotics used was 0 (0-3). The infectious syndromes reported were febrile neutropenia without focus (25 episodes), pulmonary aspergillosis (1 episode), Escherichia Coli bacteremia (1 episode) and soft tissue infection (1 episode). No deaths have been registered.

Table 1. Characteristics of patients included in e-outpatient program (n=43)

Gender (Male)	81.8%
Mean age (years)	57.1 (40-69)
Response pre-ASCT	
• Complete Response	12 (27.9%)
• Very Good Partial Response	19 (44.1%)
• Partial Response	9 (20.9%)
• Stable Disease	3 (7.1%)
ISS	
• Stage I	13 (30.2%)
• Stage II	16 (37.2%)
• Stage II	14 (32.6%)
Mean of Cells Infused	3.01(2.02-5.20)
Conditioning	
• MEL200	28 (65.1%)
• MEL140	12 (27.9%)
• BUMEL	3 (7%)

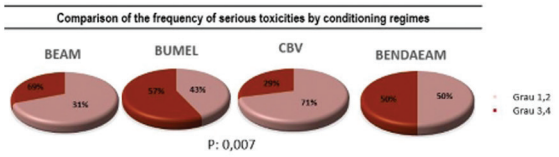
Summary/Conclusion: 1. The use of telemedicine in home care programs is an opportunity to reduce the need for health support resources at home.
2. Our e-outpatient program shows a significant reduction in the days of admission (median 5) compared to conventional hospitalization (3 weeks), allowing less exposure to nosocomial germs, a lower cost associated with admission and a better emotional adaptation to the process of the patient and their caregiver.
3. The safety profile is adequate, with an acceptable incidence of infectious complications, with a transplant-related mortality of 0%.
4. Readmission rate (28.9%) is relatively high compared to similar outpatient programs. The combination of technological tools with home care can be a good option to reduce hospital readmissions.

EP1251 INCIDENCE OF EARLY TOXICITIES AND MORTALITY AFTER 4 TYPES OF CONDITIONING REGIMENS FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH LYMPHOMAS: A RETROSPECTIVE ANALYSIS.

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Background: High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard treatment for relapsed or refractory lymphomas. Until recently, carmustine, etoposide, cytarabine and melphalan (BEAM) was the most used conditioning regimen in this setting, given its acceptable efficacy and tolerability. Recent supply and cost issues for this agent have created an urgent need for alternative conditioning regimens. Toxicity evaluation of alternative conditioning regimens to BEAM may guide the choice of a regimen equally effective and at least equally tolerated, achieving adequate lymphoma control, resulting in similar overall survival.
Aims: To compare toxicities of BEAM (Carmustine, Etoposide, Citarabina, Melphalan), CBV (Carmustine, Etoposide, Cyclophosphamide), BendaEAM (Bendamustine, Etoposide, Citarabina, Melphalan) and BuMel (Busulfan, Melphalan) conditioning regimens used for ASCT in patients with relapsed/refractory non-Hodgkin (NHL) and Hodgkin lymphomas(HL).
Methods: From January 2014 to December 2020, we included patients aged 18 years or older, diagnosed with NHL or HL who underwent ASCT at Hospital das Clinicas da Faculdade de Medicina de Sao Paulo, Brazil. Frequencies of serious toxicities (Grade III-IV CTCAE v4.0) among conditioning schemes were compared using the Fisher's exact test. For the toxicity analysis, a univariate logistic regression model was conducted, and the effect size was presented as odds ratio. Overall survival curves at 100 days and 1 year were determined using the Kaplan Meier method. The assessment of risk factors for mortality was conducted using the multivariate Cox regression method, the effect size on the outcome was presented as a hazard ratio.
Results: Two hundred and thirteen patients were included (BuMel 42, BendaEAM 38, CBV 65 BEAM 68), of which 56% were men, with a median age of 43 years (IQR 19-74), 93% had a KPS> 80%, and 75% had a complete response prior ASCT. Regarding toxicities grade III and IV: Mucositis was frequently observed in the BuMel regimen 50% and BendaEAM 25%, compared to CBV 10% and BEAM 20%. Diarrhea was present in 30% in the BendaEAM, 28% in the CBV and less frequent in the other groups (BEAM 18% and BuMel 11%); renal toxicity was only presented in the BendaEAM (50%). Febril neutropenia was observed in all the regimens, mainly in the BendaEAM (92%) and BEAM (81%) compared with CBV (76%) and BuMel 67%. In the univariate logistic regression, there was an association of grade III- IV toxicities with type of conditioning regimens (p=0.007) In fact, BuMel (OR 2,984 P0.007) and BendaEAM (OR 2.23 P 0.054) were associated with a greater probability of developing grade III-IV toxicity (Figure 1). Median follow-up of the cohort was 27.51 months (0,75-81,40). Estimated overall survival was 95% at 100 days and 79% at 1 year. The following factors were associated with an increased risk of one year mortality: Ann Arbor stage IV at diagnosis (HR 1.81; P=0.028), disease response at transplant (CR>2) or second partial remission (PR) (HR 3.94; P=0.004) and the use of BendaEAM conditioning (HR 2.86; P=0.05).



Univariate logistic regression Any grade 3 and 4 toxicity (oral mucositis, nausea, vomiting, diarrhea, liver and kidney toxicity)

	OR	p-value	IC 95%	Sig
BEAM	1			
BuMel	2.984	0.007	1.342-6.634	***
CBV	0.924	0.836	0.44-1.941	
BendaEAM	2.238	0.054	0.988-5.071	*

*** p<.01, ** p<.05, * p<.1

Summary/Conclusion: BuMel and BendaEAM were associated with higher rate of grade III and IV toxicity however type of conditioning regimen was not ass associated with early mortality Carmustine based conditioning regimens appear to be less toxic and safer. BendaEAM was associated with an increased risk for death at 1 year after autologous transplantation for LNH and LH, but probably related to relapse Longer follow-up is needed to draw definitive conclusions on the use of BendaEAM to control lymphoma relapse.

EP1252 DEVELOPMENT AND VALIDATION OF A RISK SCORE SYSTEM FOR SKIN AND SOFT TISSUE INFECTIONS IN ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

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Background: Skin and soft tissue infections (SSTIs) refer to infections occurring in the skin, subcutaneous tissue, fascia and muscle. As immunocompromised hosts, transplantation patients are more likely to develop SSTIs. According to the Infectious Diseases Society of America (IDSA), SSTIs in immunocompromised patients should all be classified as severe. Several previous studies have analysed the epidemiology and risk factors of SSTIs in solid organ transplantation (OST) recipients. However, to date, no study has focused on SSTIs in haematopoietic stem cell transplantation (HSCT) recipients. The common pathogens, occurrence periods and anatomic sites and clinical outcomes of SSTIs in HSCT population remain unclear.
Aims: This retrospective study investigated the frequency, occurrence time, common anatomic locations, comorbidities and clinical outcomes of allo-HSCT recipients with SSTIs. Moreover, a prognostic model for allo-HSCT recipients with SSTIs was developed.
Methods: Allo-HSCT recipients developing SSTIs from pretreatment to 180 days after transplantation were included in our study. Pathogens including bacterium, fungus and virus were all involved. The patients' baseline characteristics, infection profiles, synchronous comorbidities and clinical outcomes were recorded in. Comorbidity referred to diseases occurring within 7 days before and after the SSTI course. Acute kidney injury was defined as serum creatinine increased 1.5–1.9 times baseline or ≥0.3 mg/dl, or urine output <0.5 ml/kg/h for over 6 hours. Patients involved were divided into two groups according to their outcome: survivors and nonsurvivors at 12 months after HSCT. We compared the differences between the two groups and developed a prognostic model.
Results: Two hundred twelve allo-HSCT recipients with 231 SSTIs were included from January 2005 to December 2019 at the Peking University Institute of Haematology, with a 12-month mortality of 27.4% (58/221). The median onset time of SSTI after transplantation was 10 days (from -9 to 179). Anal infection was the most common (19.4%, 45/231), while maxillofacial infection ranked second (18.6%, 43/231) and infection due to vascular devices ranked third (16.5%, 38/231). Pneumonia was the most common comorbidity of SSTI (23.8%, 55/231). Recipients who had undergone allo-HSCT after January 2014 were grouped as the derivation cohort, while others were grouped as the validation cohort. Failure of platelet engraftment, newly acquired or developed pneumonia and combined acute kidney injury were independent risk factors for 12-month death. According to the modelling coefficient magnitude of each factor, a risk score system was established (Table 1). The risk score was 1×failure of platelet engraftment+1.5×acute kidney injury+1×pneumonia. The patients' 12-month mortality rose with the score increasing. The 12-month mortality rates at 0 points, 1 point and 1.5 points were 12.1%, 44.7% and 77.8%, respectively. The bootstrap internal and external validation showed good discrimination power with AUCs of 0.817 (95CI: 0.692-0.866) and 0.749 (95CI: 0.625-0.855) in the derivation and validation cohorts, respectively. Additionally, the calibration plot demonstrated high agreement between the estimated and observed risks of 12-month death in the study population. Furthermore, decision curve analysis indicated considerable clinical benefit for patients.

Table 1. Coefficients and points for the rate risk score system for SSTIs in allo-HSCT recipients using independent variables in the derivation cohort.

Variables	Multivariable analysis			
	OR (95% CI)	P	Coefficients	Points
Failure of platelet engraftment	4.935 (1.668~14.600)	0.004	1.596	1
Acute kidney injury	12.943 (2.299~72.873)	0.004	2.561	1.5
Newly acquired or developed pneumonia	5.408 (2.023~14.456)	0.001	1.688	1

Summary/Conclusion: SSTIs are common complications in allo-HSCT recipients. Failure of platelet engraftment, combined pneumonia and acute kidney injury can predict the prognosis of patients.

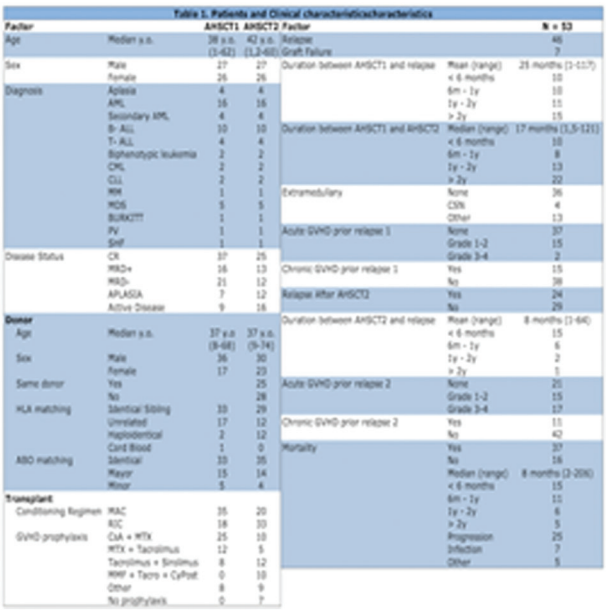
EP1253 SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: SINGLE CENTER EXPERIENCE IN SALAMANCA, SPAIN.

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Background: Allogeneic hematopoietic stem cell transplantation (AHSCT) is a curative option in hematological malignancies. However, relapse is the first cause of transplant failure. Risk of relapse depends on disease and transplant characteristics [1-4].
The best approach after relapse hasn´t been defined and as prognosis is so poor, AHSCT2 is considered for some patients mainly if relapse after 6 months and are fit enough. Many questions remain regarding the best strategy for AHSCT2.
Aims: The aim of this study was to analyze our center´s experience in patients receiving AHSCT2 in order to identify possible factors to improve management and OS in these patients.
Methods: From 1995, 1119 patients have received an AHSCT in our Unit. Of them, 53 (4.7%) received AHSCT2. A retrospective analysis of data included in our Transplant data base was performed. Statistical analysis was performed with SPSS.
Results: Patients' characteristics are summarized in Table 1. Median age at AHSCT2 was 35 years old (range 1 to 65). Mean time between AHSCT1 and relapse was 25 months (range 1 to 117) and median time between AHSCTs was 17 months (range 1.5 to 121) Cause of AHSCT2 was relapse for 46/53 (87%) patients and graft failure for 7/53 (13%), of this latter 6/7 (86%) are still alive with graft recovery.
Most frequent diagnosis was primary acute leukemia (57%) (AML= 30%, B- ALL= 20% and T- ALL= 7%). Disease status at AHSCT2 was CR 25/53 (47%) (12/25 (48%) MRD negative), aplasia 12/53 (23%) and active disease (AD) in 16/53 (30%) respectively. Conditioning regimen was Myeloablative (MAC) in 35/53 (66%) for AHSCT 1 and in 20/53 (38%) of the patients for AHSCT2.
Donor was the same in 25/53 (47%) of the transplants. Donor was HLA identical sibling in 29/53 (55%), unrelated in 12/53 (23%) and haploidentical in 12/53 (23%) respectively.

With a median follow-up of 11 months (range 2 to 253) and 54 months (range 3 to 253) for surviving patients, 37 patients have died and 16 (30%) are still alive, 15/16 (94%) disease free. 12/37 patients die due to causes different from progression with Non relapse mortality of 32%.
The 2- and 4-years OS was 39% (SD ± 0.070) and 34% (SD ± 0.069) and the 2- and 4- years PFS was 35% (SD ± 0.067) and 33% (SD ± 0.066) respectively.
Thirty- two (60%) patients presented acute GVHD (aGVHD), 97% involving skin and/or gut. 11/53 (21%) presented Chronic GVDH after AHSCT2.
In the multivariate analysis, the variables which influenced OS were CR vs AD at AHSCT2 (HR 7.96, 95% CI: 2.67–23.78, p <0.001), MAC vs RIC (HR 7.79, 95% CI: 2.55–23.85, p <0.001) and relapse <25 months vs >25 months after AHSCT1 (HR 18.16, 95% CI: 2.03–162.178, p=0.009). HLA matching had no statistically significant impact on OS Identical sibling vs Haploidentical (HR 2.32, 95% CI: 0.581–9.26, p= 0.234), possibly related with our small sample.



Summary/Conclusion: Our results in more than 1000 transplant demonstrated that AHSCT2 is rarely indicated and confirm the poor prognosis reported by multicenter and single center experiences. Despite new management strategies for allogeneic transplants, mortality and relapse rates after AHSCT2 remain high. However, is a good treatment option for patients with late relapses and for those who achieve CR before second transplant. For earlier relapses and no chemosensitive patients, other options are required. Efforts should be made in identifying new strategies for these patients.

EP1254 THE IMPACT OF MEASURABLE RESIDUAL DISEASE POSITIVITY BEFORE ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH PH(-) ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Background: Measurable Residual Disease (MRD) in Ph negative (-) Acute Lymphoblastic Leukemia (ALL) patients before allogeneic hematopoietic cell transplantation (allo-HCT) has been proposed as a major risk factor for imminent relapse.
Aims: To study the prognostic value of pre-transplantation (pre-HCT) MRD in Ph(-) ALL adjusted to other disease characteristics.
Methods: Sixty-seven consecutive patients who underwent allo-HCT in our JACIE center between 2009-2020 for B- (39), T- (24) ALL or Mixed phenotype acute leukemia (MPAL,4) were evaluated. Eight color flow cytometry (FC) MRD analysis was performed pre-HCT and post-HCT in 3-month intervals. FC-MRD was considered positive if >=0.01%. In case of positive MRD pre-HCT, further treatment, mostly chemotherapy, was administered. In case of post-HCT MRD positivity, immunosuppression was reduced promptly.
Results: Thirty-one out of 67 transplants were matched unrelated, 27 sibling and 9 alternative ones. Most patients received 14,4 Gy total body irradiation (TBI) in conditioning regimen (53/67). Median age was 31 (14-57) years and patients were transplanted in first CR1,44/67 or >CR1, 23/67. Median follow-up was 26 (2-138) months.Overall, 8 presented hematological relapse out of 16 patients with positive MRD post-HCT,successfully reversed by immunotherapeutic intervention. On univariate analysis positive pre-HCT MRD was associated with shorter Time To Progression (TTP) (HR: 8.75 CI95%: 2.06-37.06, p=0.03), shorter Relapse Free Survival (RFS) (HR: 2.33 CI95%: 1.05-5.18, p<0.05) but not Overall Survival (OS). On multivariate analysis adjusted for transplant characteristics only the association with TTP persisted. We also studied the interaction between pre-HCT MRD and other transplant characteristics (age, type of transplant, cytogenetics, disease phase at transplant and conditioning regimen) on TTP, RFS and OS. We found that in the subgroup with disease phase >CR1, patients with positive pre-HCT MRD had shorter TTP (HR: 11.5, CI95%:1.78-74.21%, p=0.01) and shorter RFS (HR: 5.42, CI95%:1.61-18.18%, p=0.006) compared to patients with negative pre-HCT MRD. These associations did not occur in the subgroup transplanted in CR1. Comparing outcome of patients in CR1 vs >CR1, 4-year RFS and OS were: 61.4% [CI95%:44.5-74.5] and 61.4% [CI95%:44.5-74.5%] for CR1 and 44.2% [CI95%:20.6-65.6%] and 56.1% [CI95%:26.3-77.9%] for >CR1 respectively.
Summary/Conclusion: Detectable pre-HCT MRD in patients transplanted in >CR1 is associated to worse outcomes and remains a major failure barrier for transplant. In our small study population, it seems that allo-HCT may overcome the chemo-resistance of residual disease in CR1 performed transplants, as outcome is not related to pre-HCT MRD status. MRD post-HCT is an important tool and its monitoring with sensitive techniques could detect potentially high-risk patients who may benefit from abrupt cessation of immunosuppression. In the current era, the role of novel agents should be defined in large prospective studies in order to optimize the transplant outcome.

EP1255 PERIPHERAL BLOOD STEM CELL APHERESIS IN LOW-WEIGHT HEALTHY DONORS: A SINGLE CENTRE EXPERIENCE

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Background: The peripheral blood stem cells (PBSC) are the source of haematopoietic stem cells (HSC) currently most used in the allograft of malignant and non malignant haematological diseases in our practice. The procedure of mobilization and collection is similar for adult and children. However, many technical sides must be taken into account in the paediatric apheresis because of extracorporal volume related to the weak weight of the donors.
Aims: We report our experience of collection of PBSC in pediatric sibling donors weighing 20 kg or less over one 14 years period for allogeneic stem cell transplantation.
Methods: From January 2005 to December 2018, 29 children donors (17 boys and 12 girls) weighing 20 kg or less had a collection of PBSC by technic of apheresis after parental consent. The median age and weight at the time of apheresis were 5 years (range:3-9) and 18 kg (range: 13-20), respectively. Stem cell mobilization was obtained by once-daily subcutaneous injections of G-CSF (10µg/kg/day) for five consecutive days. PBSC were collected using a continuous flow blood cell separator (Cobe spectra or Optia) at the 5th day and repeated, if necessary, at the 6th and 7th days.
Results: A total of 54 PBSC were performed. Insertion of a femoral catheter was avoided in 58,6% of children. A single apheresis was sufficient to obtain the required cell number in 10 cases (34,4%). Two apheresis were performed on consecutive days in 13 cases (44,8%) and 3 apheresis were performed in 6 cases (20,6%). Five donors (17%) received transfusion of red blood cells before the second or third harvests. Insertion

of a femoral central venous line was necessary in 17 children (58,6%). No child experienced any collection-related occlusion or infection. The median duration of the apheresis per donor, was 223 mn (range: 115-351) with a median blood flow rate of 25 ml/mn (range: 20-50) using a median ACD-A of 375 ml (range: 128-717). The median cell yield per apheresis was 5,9×106 CD34+cells/kg (0,58–24,64) recipient body weight (RBW) of whom 18 donors (62%) achieved the target CD34+ cell dose more than 4.106/kg. Males had a higher mean collected CD34+ cell yields (≥ 4.106/kg) than females (82% vs 33%). The mean ratio between donor and recipient (D/R) body weight was 0,74 (0,25-1,36). Donors with this ratio < 1 failed to reach CD34+ cell dose > 4.106/kg. Morbidity related to PBSC collections was low and 26 children (90%) expressed their willingness to donate again.
Summary/Conclusion: The results suggest that G-CSF mobilization and harvesting of PBSCs are safe and effective in low-weight pediatric donors. An efficient and well-experienced team of physicians and nurses involved in CVC positioning and apheresis is crucial to perform a safe PBSC collection in children donors weighing 20 kg or less. Males and D/R body weight ≥ 1 have a higher mean collected CD34+ cell yields.

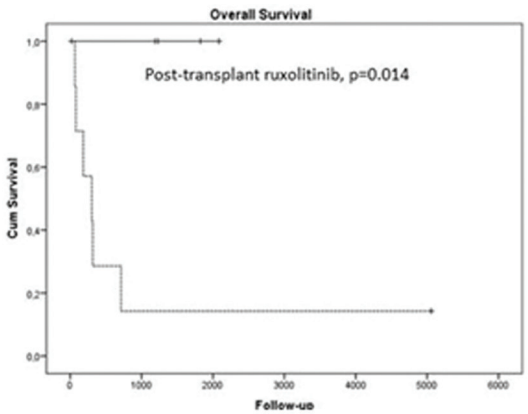
EP1256 IMPROVED SURVIVAL IN MYELOFIBROSIS PATIENTS RECEIVING RUXOLITINIB POST ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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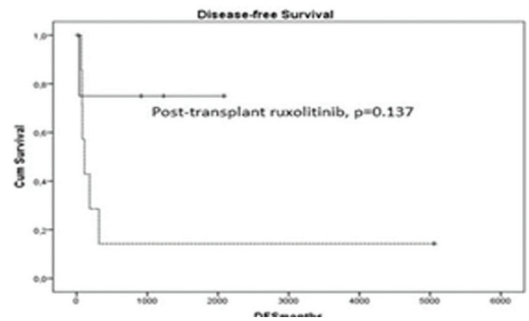
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Background: Allogeneic hematopoietic cell transplantation (alloHCT) remains the only curative option of myelofibrosis. Despite intensified efforts to broaden alloHCT indications with better patient stratification, treating physicians are reluctant to refer patients for alloHCT in the era of JAK2 inihibitors.
Aims: We investigated the long-term safety and efficacy of alloHCT in patients with myelofibrosis
Methods: We retrospectively enrolled consecutive adult alloHCT recipients transplanted for myelofibrosis over the last two decades (2000-2020) at our JACIE-accredited center. We excluded patients transplanted with acute myeloid leukemia progression post myelofibrosis. Factors included in the analysis were: age, type of myelofibrosis (primary or secondary due to polycythemia vera/essential thrombocytosis), dynamic IPSS score, donor (sibling/unrelated), HLA matching, graft failure, acute (grade II-III) and chronic (according to NIH classification) GVHD, relapse, second alloHCT, bacterial, viral or fungal infections, spleen size and ruxolitinib administration before/after alloHCT.
Results: We studied 12 alloHCT recipients aged 53 (31-66) years, after a median of 42.8 (range 4.1-421) months from alloHCT. Median DIPSS was 3 (range 2-4). Seven patients suffered from primary myelofibrosis, while five from secondary. Eight were transplanted from a sibling donor, and 4 from an unrelated (2 matched and 2 mis-matched donors). All patients received peripheral blood stem cells graft, after myeloablative (5) or reduced intensity (7) conditioning regimens. Neutrophil engraftment was achieved in all patients (median 13, range 9-23 days), while platelet engraftment in 11/12 (median 16, range 10-146 days). Two patients developed graft failure and received second alloHCT with reduced intensity regimens.
Splenectomy was performed before alloHCT in 2 patients, and 7 months post-transplant in 1. Incidence of acute GVHD (grade 2-3) was 33% patients, while cumulative incidence of moderate chronic GVHD reached 58%. Two-year cumulative incidence of treatment-related mortality (TRM) was 34.6% Ruxolitinib was administered in patients transplanted after 2015: before alloHCT in 6/6 patients, and after alloHCT in 4/6 (2 for relapsed disease, 1 for splenomegaly and thrombocytopenia despite involved field radiation therapy, and 1 for moderate chronic GVHD). Patients that received ruxolitinib post-transplant did not suffer from TRM. Additionally, 2-year disease-free survival was 75% for patients that received ruxolitinib post-transplant, compared to 14.3% for those that did not (p=0.137, Figure). Importantly, 2-year overall survival was significantly improved in patients with post-transplant ruxolitinib (100% compared to 13.1%, p=0.014, Figure).
Summary/Conclusion: Our real-world cohort indicates that the use of ruxolitinib has optimized outcomes of alloHCT. Especially after alloHCT, our results suggest a significant benefit of a personalized approach in ruxolitinib administration. Given the safety of alloHCT, further studies are needed to guide this personalized approach.

Overall Survival



Disease-free Survival



EP1257 A MODIFIED BUSULFAN/CYCLOPHOSPHAMIDE CONDITIONING REGIMEN INCORPORATING CLADRIBINE FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA

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Background: How to reduce the recurrence of autologous hematopoietic stem cell transplantation in patients with acute myeloid leukemia is very important to improve the efficacy of transplantation.
Aims: To investigate the safety and efficacy of a modified busulfan(Bu)/cyclophosphamide(Cy) conditioning regimen incorporating cladribine(CLAD) for autologous hematopoietic stem cell transplantation(auto-HSCT) in acute myeloid leukemia(AML).
Methods: We retrospectively evaluated the clinical outcomes of patients with AML who had received auto-HSCT with conditioning incorporating CLAD at the Institute of Hematology and Blood Disease Hospital.
Results: Between September 2016 and February 2021, 20 adult patients with AML were enrolled including 13 males and 7 females with a median age of 32(range, 15 to 54) years. The median courses of chemotherapy before auto-HSCT were 4 courses(range, 3 to 9) and all patients were minimal residual disease(MRD) negative before auto-HSCT. Twelve out of the 20 AML patients received myeloablative conditioning regimens including:Bu 3.2 mg/kg/d*3, Cy 40mg/kg/d*2, CLAD 5mg/m^2/d*3, cytarabine(Ara-c) 2g/m^2/d*3 or idarubicin 12mg/m^2/d*3. The other 8 patients with AML received the similar modified conditioning regimens as above mentioned but CLAD and Ara-c were administered for 5 days while Cy was abandoned for its adverse cardiovascular reactions. All the 20 patients received peripheral blood stem cells for auto-HSCT. The median amount of infused mononuclear cell and CD34$^+$ stem cell were 9.05×10^8/kg(range, 2.88 to 20.97) and 1.99×10^6/kg(range, 1.59 to 10.44), respectively. All the 20 patients achieved neutrophil and platelet engraftment with a median time of 13(range, 10 to 34) days and 27(range, 14 to

113) days, respectively. Three patients suffered from septicemia during neutropenia stage, 2 patients suffered from pulmonary infection, the others suffered from mild to moderate infection or gastrointestinal reaction after conditioning and all were relieved by anti-infection and other supportive treatment. None of the patients died of transplant related complications. From 2 months after auto-HSCT, the maintenance therapy with interleukin-2, interferon or azacitidine was performed for 7 patients with FLT3- ITD mutation negative, sorafeni were performed for 2 patient with FLT3 -ITD mutation positive. At a median follow-up of 25.5(range, 2.5 to 52.5) months,four patients relapsed after auto-HSCT at a median time of 8(range, 0.5 to 18.5) months. One patients died due to leukemia relapse at 18 months after auto-HSCT, the other 19 patients were all alive including 16 patients with MRD negative and the other 3 patients achieved MRD negative after allogeneic HSCT or maintenance therapy. The estimated 2-year survival, relapse, and disease-free survival rates were 93.3%, 22.9% and 77.1%, respectively.

Summary/Conclusion: The modified conditioning incorporating CLAD was safe and effective for auto-HSCT in acute myeloid leukemia which might be confirmed by more clinical studies.

EP1258 INCIDENCE OF VENO-OCCLUSIVE DISEASE/ SINUSOIDAL OBSTRUCTION SYNDROME AFTER HEMATOPOIETIC CELL TRANSPLANTATION IN ENGLAND BASED ON HEALTHCARE RESOURCE GROUP CODES AND HOSPITAL EPISODE STATISTICS© DATA

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Background: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication that occurs after hematopoietic cell transplantation (HCT) conditioning or chemotherapy. The most severe form of VOD/SOS is associated with multi-organ dysfunction/failure and a mortality rate of >80% if untreated. Defibrotide is approved in the EU for severe hepatic VOD/SOS post-HCT in patients aged >1 month. Based on the number of patients undergoing HCT reported to the British Society of Bone and Marrow Transplantation (BSBMT) and available commissioned defibrotide use data from National Health Service (NHS) England, the estimated incidence of severe VOD/SOS in patients with first HCT (allogeneic or autologous) in England from 2019-2020 was ~2.5%. Within the NHS Hospital Episode Statistics (HES) database, healthcare resource group (HRG) codes are applied to patient events that have been judged to consume a similar level of resource.

Aims: This analysis used HRG codes to evaluate the incidence of post-HCT VOD/SOS in England and provide details on the effect of HCT and donor type on risk for VOD/SOS.

Methods: In this retrospective analysis, data for patients with first HCT as an inpatient between April 2010 and March 2020 were obtained from the HES database (copyright 2021; reused with the permission of NHS Digital; all rights reserved), a data warehouse containing details of admissions, outpatient appointments, and accident/emergency department attendances at NHS hospitals. Patients were coded for VOD/SOS using ICD-10 diagnostic codes. HRG codes were used to summarize age (≤18 years vs ≥19 years), HCT modality (allogeneic vs autologous) and allogeneic donor type.

Results: Of the 32,147 identified patients who underwent HCT, 31,387 had evaluable HRG data; 330 (1.05%) of these patients were coded for VOD/SOS (any severity) within 100 days post-HCT. Among the 3,679 pediatric patients (≤18 years) who received HCT, 2,582 (70.2%) received allogeneic HCT and 232 (6.3%) were coded for VOD/SOS. Among the 26,886 adult (≥19 years) patients who received HCT, 8,893 (33.1%) received allogeneic HCT and 82 (0.3%) were coded for VOD/SOS. Age was unknown in 822 patients, 16 of whom were coded for VOD/SOS. VOD/SOS in pediatric patients was primarily reported in the autologous setting (56.9%), in contrast to adults where most VOD/SOS cases were reported in the allogeneic setting (90.2%; **Table**). There appeared to be a trend to higher VOD/SOS prevalence in groups with increased allogenicity of the donor source but this was not borne out by statistical analyses (**Table**); among 133 patients with syngeneic HCT, no cases of VOD/SOS were reported.

Table. Incidence of VOD/SOS by HCT modality and donor source.

HCT modality and donor source	Pediatric patients		Adult patients	
	n	VOD/SOS incidence, %* (95% CI)	n	VOD/SOS incidence, %† (95% CI)
All allogeneic	100	43.1 (36.64, 49.75)	74	90.2 (81.68, 95.69)
VUD	25	10.8 (7.1, 15.5)	20	24.4 (15.58, 35.12)
Sibling	24	10.3 (6.74, 15)	6	7.3 (2.73, 15.25)
Cord blood	12	5.2 (2.7, 8.86)	6	7.3 (2.73, 15.25)
Haplo-identical	2	0.9 (0.1, 3.08)	1	1.2 (0.03, 6.61)
Syngeneic	0	0 (0, 1.58)	0	0 (0, 4.4)
Unspecified	37	15.9 (11.48, 21.31)	41	50.0 (38.75, 61.25)
Autologous	132	56.9 (50.25, 63.36)	8	9.8 (4.31, 18.32)

VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation; CI, confidence interval; VUD, volunteer unrelated donor.
*Denominator is the number of pediatric patients coded for VOD/SOS (n=232).
†Denominator is the number of adult patients coded for VOD/SOS (n=82).

Summary/Conclusion: The incidence of VOD/SOS in this analysis of HRG codes was lower (1.05%) than the ~2.5% incidence rate for severe VOD/SOS obtained from NHS England commissioning data, suggesting that VOD/SOS may be undercoded in the HES database. Limitations of the analysis include restriction to the data available in the HES database, underrecording of haplo-identical HCT in the HES database versus BSBMT returns and the small sample size. In this analysis, there appeared to be higher rates of VOD/SOS in pediatric patients versus adults. VOD/SOS was observed more frequently in the autologous setting in pediatric patients and in the allogeneic setting in adults. These observations suggest that, for allogeneic transplants, there may be a possible relationship between allogenicity of the HCT donor source and incidence of VOD/SOS; further investigation is needed to explore this potential relationship.

EP1259 THE EFFECT OF MYELOMA INDUCTION THERAPY TYPE AND DURATION ON PERIPHERAL BLOOD STEM CELL HARVEST FOR AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: Autologous stem cell transplant (ASCT) remains standard of care for eligible newly diagnosed myeloma patients (TE NDMM). Induction prior to ASCT frequently includes lenalidomide, reported to have an adverse effect on peripheal blood stem cell (PBSC) harvest in some studies.

Aims: The UK NCRI Myeloma XI/+ study compared induction combinations including thalidomide or lenalidomide giving the opportunity to compare PBSC harvests between patients treated with different immunomodulatory agents.

Methods: TE NDMM patients were randomised to triplet combinations, thalidomide or lenalidomide plus dexamethasone and cyclophosphamide (Tdc/Rdc) or the quadruplet combination carfilzomib+Rdc (KRdc). Induction was given for a min. of 4 cycles but continued to max. response. Patients who received Tdc/Rdc and achieved a max. response less than VGPR underwent response-adapted intensification therapy.

PBSC harvest was planned to occur after the completion of induction+/-intensification. Stem cell mobilisation and harvest was performed according to local practice with advice to aim for the collection of sufficient cells for at least two transplants.

The median number of CD34+ cells harvested was compared between patients randomised to Tdc, Rdc and KRdc and those who received 4, 5-6 or >6 cycles of induction. Mann-Whitney U Tests were used to compare groups. Only patients achieving >=VGPR to initial induction, completing >=4 cycles and proceeding directly to ASCT were included in this analysis to avoid any impact of response or intensification therapy on harvest outcome.

Results: Of the 1543 patients included, 521 had received Tdc (51.0% of all patients randomised to Tdc), 610 Rdc (59.7%), 412 KRdc (78.3%). Of these patients 88.4% underwent harvest (Tdc 86.9%, Rdc 87.5%, KRdc 91.5%).

The median number of CD34+ cells harvested was lower for those who had received lenalidomide compared to thalidomide. Patients who received Tdc harvested a median 4.6x10^6/kg CD34+ cells, Rdc 4.1, KRdc 4.2 (Rdc vs Tdc p=0.0002, KRdc vs Rdc p=0.1766, KRdc vs Tdc p=0.0210). There was also a reduction in the median CD34+ cells harvested for patients requiring >6 cycles of induction to achieve

maximum response prior to harvest. 4 cycles 4.5 x10^6/kg CD34+ cells, 5-6 cycles 4.2, >6 cycles 4.1 (4 vs 5-6 p=0.1212, 5-6 vs >6 p=0.1839, 4 vs >6 p=0.0262).
The reduction in CD34+ cells with increasing number of induction cycles appeared greater for those patients who received lenalidomide induction. Tdc: 4 cycles 4.9 x10^6/kg CD34+ cells, 5-6 cycles 4.6, >6 cycles 4.6. Rdc: 4 cycles 4.4, 5-6 cycles 4.0, >6 cycles 3.5. KRdc: 4 cycles 4.4, 5-6 cycles 4.1, >6 cycles 3.9. This corresponded to a reduction in the proportion of patients meeting the threshold for two ASCTs both between therapies and with increasing cycles. Tdc: 4 cycles 63.0%, 5-6 cycles 60.2%, >6 cycles 61.4%. Rdc: 4 cycles 54.3%, 5-6 cycles 47.4%, >6 cycles 46.2%. KRdc: 4 cycles 60.9%, 5-6 cycles 49.3%, >6 cycles 41.7%.
Despite these differences, more than 96% of patients in all groups were considered to have enough stem cells and proceeded to first ASCT within the trial, with no differences between treatment groups.
Summary/Conclusion: Lenalidomide-based induction therapy was associated with lower median CD34+ cells harvested than thalidomide-based induction. This had no impact on the proportion of patients able to undergo first ASCT. The reduction in median CD34+ cells with lenalidomide was most marked when >4 cycles were administered. This should be considered when planning the timing of harvests, especially if storage of sufficient cells for two ASCTs is desired.

EP1260 ADVERSE IMPACT OF PRE-TRANSPLANT MINIMAL RESIDUAL DISEASE ON OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LEUKEMIA PATIENTS.

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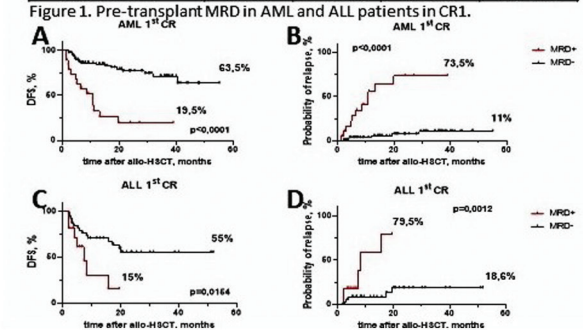
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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for high-risk acute leukemias. But one of the main causes of treatment failure after allo-HSCT for acute leukemia (AL) is still the disease relapse. Currently, minimal residual disease (MRD), detected by multiparameter flow cytometry (MPC), is widely used to identify patients at high risk of relapse due to its availability and the ability to obtain results in a short time frame.
Aims: To assess the predictive value of pre-transplant MRD status.
Methods: We included 207 patients: 122 patients AML and 85 patients with ALL, who underwent allo-HSCT National Research Center for Hematology between September 2015 and December 2020. Patient characteristics are summarized in Table 1. All patients were in complete morphological remission (CR) at the time of allo-HSCT. The median follow-up was 17 (1,5-55) months for AML and 11,7 (1-64) months for ALL. 6-color MFC was performed on bone marrow samples obtained before allo-HSCT. MRD was detected using a combination of the "different-from-normal" and LAIP methods. The probabilities of DFS and relapse were estimated using the Kaplan–Meier method for all patients. The value of $p < 0.05$ was considered as significant. Statistical analysis was performed using SPSS ver. 23 (IBM, Chicago, Ill., USA). Cox proportional hazards model was used to assess the influence of various independent factors on the probability of relapse/death from any cause. The factors included in the model: disease status, donor type, conditioning regimen, source of graft, pre-transplant MRD status, age, acute or chronic graft versus host disease (GVHD).
Results: In univariate analysis, the DFS of MRD+ patients with AL in the 1st CR was significantly worse than MRD- (AML: 19,5% vs 63,5%, p <0.0001 (Fig.1A), ALL: 15% vs 55%, p = 0.0154(Fig.1C)), and the probability of relapse in MRD+ patients was significantly higher (AML: 73,5% vs 11%, p <0,0001 (Fig.1B), ALL: 79,5% vs 18,6%, p = 0,0012 (Fig.1C)). Pre-transplant MRD status was not prognostically significant for AL-patients in the 2nd and 3rd remission. In our study, the presence of MRD before allo-HSCT has been shown to be an independent factor influencing the probability of relapse/death (HR = 3,673 [2,185- 6,174], p<0,0001). In turn, it was noted that the development of chronic GVHD reduces post-transplant mortality if it does not require systemic therapy with glucocorticosteroides (HR = 0,183 [0,065-0,516], p=0,001).

Table 1. Patient's characteristics.

	AML (n=122)		ALL (n=85)	
	MRD+ (n=29)	MRD- (n=93)	MRD+ (n=20)	MRD- (n=65)
Age (median, interval)	36 (21-61)	38 (18-66)	35 (18-61)	30 (19-63)
Disease status, n (%)				
• 1st CR	19 (65,5%)	84 (90,3%)	11 (55%)	41 (63,1%)
• 2nd and 3rd CR	10 (34,5%)	9 (9,7%)	9 (45%)	24 (36,9%)
Donor type, n (%)				
• related matched	8 (27,6%)	33 (35,5%)	5 (25%)	10 (15,4%)
• unrelated matched	9 (31%)	24 (25,8%)	4 (20%)	18 (27,7%)
• unrelated mismatched	7 (24,1%)	16 (17,2%)	4 (20%)	14 (21,5%)
• haplo	5 (17,3%)	20 (21,5%)	7 (35%)	23 (35,4%)
Conditioning regimen, n (%)				
• myeloablative	6 (20,7%)	28 (30,1%)	6 (30%)	25 (38,5%)
• reduced intensity	23 (79,3%)	65 (69,9%)	14 (70%)	40 (61,5%)
Source of stem cells, n (%)				
• bone marrow	9 (31%)	43 (46,2%)	4 (20%)	20 (30,8%)
• peripheral blood	20 (69%)	50 (53,8%)	16 (80%)	45 (69,2%)

Figure 1. Pre-transplant MRD in AML and ALL patients in CR1.



Summary/Conclusion: Pre-transplant MRD is an independent factor of a poor prognosis. Testing for MRD before allo-HSCT is extremely important to stratify the risk of allo-HSCT and identify patients with AML or ALL who need early interventions such as withdrawal of immune suppression, donor lymphocyte infusion or preemptive chemotherapy in order to prevent the disease relapse.

EP1261 RELATIONSHIP OF HLA ALLELES AND THE RISK OF CYTOMEGALOVIRUS (CMV) REACTIVATION FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT)

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Background: Evidence is emerging to support an association between certain HLA alleles, and the risk of CMV reactivation post-allo-HSCT. HLA alleles associated with resistance to CMV reactivation have been referred to as "CMV immunodominant alleles", and are thought to present viral antigen to T lymphocytes more effectively.
Aims: We aimed to identify HLA alleles associated with either resistance or susceptibility to CMV reactivation.
Methods: We studied 586 adults who underwent allo-HSCT. We included patients who had engrafted successfully, and had been typed at HLA-A, B, C, DRB1 and DQB1 loci by next-generation sequencing. Weekly CMV monitoring by PCR was done on whole blood, and anti-viral treatment was initiated for levels more than 200 IU/ml.
The primary outcome measure was the occurrence of CMV reactivation needing treatment, with or without CMV disease. Hazard ratios were calculated by Cox regression analyses, for HLA alleles and other variables significantly associated with CMV reactivation. We analysed only HLA Class I and II alleles that were observed at a frequency of >5% in donor or recipient cohorts, and adjusted for the effect of multiple comparisons.
Results: The median patient age was 57 years. AML was the most common diagnosis (51.5% patients). Donor types were as follows: matched unrelated (MUD; 52.5%); matched related (19%); mismatched unrelated (MMUD; 18%); and haploidentical (11%) donors. Eighty nine percent received a T-cell depleting agent during conditioning.
The cumulative incidence of CMV reactivation in the entire cohort at 6 months was 55% (95%CI 51%>59%).
This was significantly higher in recipients of MMUD and haploidentical grafts, and in those with a pre-transplant CMV IgG serostatus either donor positive/recipient positive or donor negative/recipient positive.

The one-year overall survival in patients with and without CMV reactivation were 54% and 63%
respectively (p=0.01). The univariate analysis indicated that alleles HLA A*01:01 (HR 0.62, 95% CI 0.48-0.83), A*02:01 (HR-0.77, 95% CI 0.59-0.93), and B*07:02 (HR 0.59, 95% CI 0.40-0.83) were associated with protection against CMV (Table 1). Other factors impacting risk of CMV reactivation on univariate analysis were increasing recipient age, use of T-cell depletion, mismatched donor (haploidentical or MMUD), and pre-transplant CMV serostatus. These factors, along with the significantly associated HLA alleles were included in a multivariable model. Mismatched donor (HR 1.23, 95% CI 1.02-1.63) and increasing age (HR 1.09, 95% CI 1.007-1.18) were independently associated with increased risk of CMV reactivation, whereas donor negative/recipient negative
serostatus (HR 0.05, 95% CI 0.02-0.11), donor positive/recipient negative serostatus (HR 0.35, 95% CI 0.20-0.59), and HLA B*07:02 (HR 0.63, 95% CI 0.44-0.88) were independently associated with protection against CMV reactivation.
Patients who developed CMV reactivation had lower overall survival (HR 0.62, 95% CI 0.46-0.82), higher transplant related mortality (TRM; HR 1.72, 95% CI 1.25-2.36), lower relapse (HR 0.58, 95% CI 0.41-0.82) and similar relapse free survival (RFS) when compared to those who did not develop CMV reactivation. The number of CMV reactivations had no effect on TRM.

Variable	Hazard ratio	95% CI	P-value
Associated with decreased risk			
A 0101	0.62	0.48-0.83	0.001
A 0201	0.77	0.59-0.93	0.01
B 0702	0.59	0.40-0.83	0.001
Donor neg/Recipient neg serostatus	0.05	0.02-0.11	<0.001
Donor pos/Recipient neg serostatus	0.35	0.2-0.59	0.001
Associated with increased risk			
Increasing age	1.09	1.007-1.18	0.033
Mis-matched donor (haplo/MMUD)	1.23	1.02-1.63	0.034

Table 1. Key risk factors for CMV infection (n=586)

Summary/Conclusion: HLA B*07:02 was associated with protection against CMV reactivation post-transplant. Although CMV reactivation was associated with increased TRM, it was also associated with decreased relapse rates, resulting in similar RFS post-transplant compared to patients not developing CMV reactivation.

EP1262 SURVIVAL AFTER SEQUENTIAL FLAMSA-BU CONDITIONING REGIMEN IS HIGHLY DEPENDENT ON PRE-HSCT MRD STATUS IN HIGH-RISK MYELOID NEOPLASM

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Background: Historically, sequential transplant regimen using fludarabine/cytosine arabinoside/amsacrine (FLAMSA) cytoreduction followed by busulfan (Bu) based regimen has been associated with improved outcome in high-risk myeloid neoplasms (Schmid et al. J Clin Oncol 2005). Recently, Craddock et al. showed prospectively that FLAMSA-RIC was not associated with survival benefit compared to classical reduced intensity conditioning (RIC) regimens, especially in patients who experienced positive minimal residual disease (MRD) prior hematopoietic stem cell transplantation (HSCT)(Craddock et al. Blood 2020).
Aims: In this monocentric study, we aimed to evaluate retrospectively the outcome of patients receiving FLAMSA-Bu based conditioning regimens for high-risk myeloid neoplasms.

Methods: We analyzed 203 patients who received FLAMSA-Bu based conditioning regiments for high-risk AML (N=165), myelodysplastic syndrome (MDS)(N=32) or MDS/myeloproliferative neoplasms (MPN) (N=6), between October 2011 and June 2020. In AML setting, flow cytometry minimal residual disease (MRD) was available in 151/165 patient prior transplant and based on leukemia associated immunophenotype (LAIP) using ELN recommendations (bulk lyses, and at least 500 000 live cells to achieve a sensitivity of 0.1%). MRD flow was performed in bone marrow samples using 8 color panel.
Results: The median follow-up post HSCT time was 32,2 months (0.0—98 months). At 3 years, overall survival (OS) was 56% and 39.8% in AML and MDS settings respectively. In the AML cohort, ELN 2013 classification was not predictive for survival or cumulative incidence of relapse (CIR). When available, results were similar regarding ELN 2017 classification. For patients in CR1 (1st complete remission) at the time of HSCT, median OS was not reached. For those in > CR1 or refractory at the time of HSCT, median OS was 34.3 and 25.6 months respectively (p=0.56). For AML patients in CR1, pre-HSCT MRD+ (defined positive when ≥ 0.1%) was highly predictive for relapse, which reached 57.3% at 3 years. For pre-HSCT MRD- patients, median OS was not reached either patients where in CR1 or more. However, median OS was not statistically different for pre-HSCT MRD+ patients whatever was the pre-HSCT CR status (refractory excluded) (figure). Finally, MRD- patients receiving myeloablative (Bu4) regimen (MAC) has superior outcome compared to RIC (Bu2). However, neither MAC or RIC abrogated negative impact of pre-HSCT MRD positivity. Post-transplant, neither acute GVHD, chronic GVHD, prophylactic donor lymphocyte infusion or partial chimerism (at day+30, +60 or +90) were associated with survival. Regarding donor type, TRM was 14,1%, 29% and 37.3%, whereas cytologic relapse occurred in 32%, 20.3% and 15.1% cases in HLA-identical, matched-unrelated (MUD) and mismatched unrelated donor (MMUD) respectively. TRM was significantly higher in patients aged over 55 years old (38%) compared to younger ones (age < 45 = 14.9%, age 46-55 = 22%) (p=0.03). In multivariate analysis, only prior HSCT MRD status and age remained of statistical significance regarding survival in AML patients.

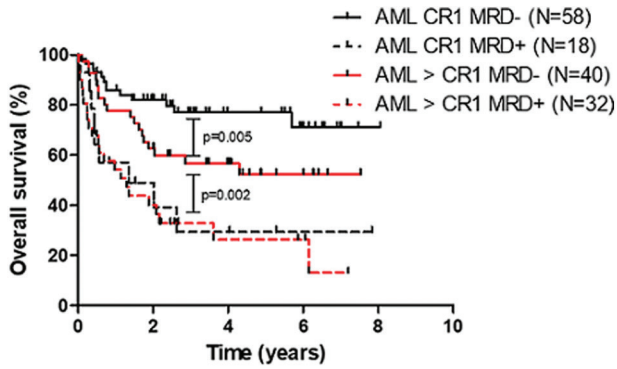


Figure : overall survival among AML patients according to the pre-transplant MRD status (assessed by flow cytometry)

Summary/Conclusion: Our results emphasize that FLAMSA conditioning regimen is an interesting strategy in high-risk myeloid neoplasm, even in refractory AML patients. Despite abrogating the impact of ELN risk groups in AML settings, pre-HSCT MRD status remains the main detrimental factor for relapse probability. Moreover, advanced age was associated with high rate of TRM suggesting that such strategy should be avoided, especially in adults aged over 55 years old.

EP1263 LETERMOVIR FOR CMV PROPHYLAXIS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION - CLINICAL "REAL WORLD" EXPERIENCE

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Background: CMV reactivation continues to be a significant clinical problem after allogeneic stem cell transplantation (allo-HSCT).

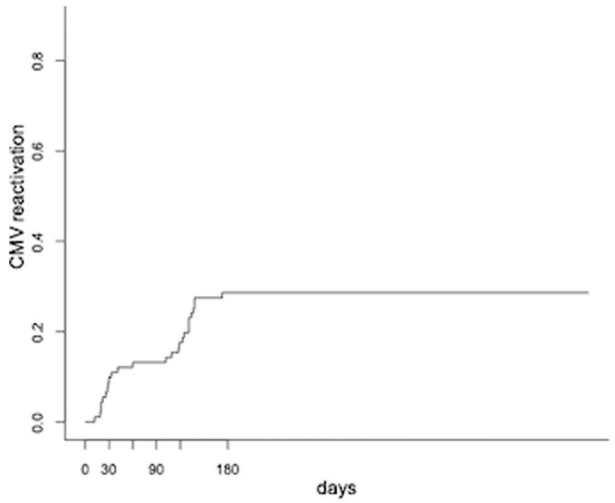
CMV (IgG) seropositivity before allo-HSCT is an important risk factor for CMV reactivation and CMV disease. Without prophylaxis, CMV infections occur in approximately 60-80% patients after allo-HSCT, usually in the early post-transplant period. Any level of CMV viremia is associated with increased non-relapse mortality in the first year post allo-HSCT. In 2019 at UHC Zagreb the preemptive CMV treatment approach was substituted with letermovir prophylaxis

Aims: The aim of this study was to analyse the population of patients who received letermovir, and to compare them with historical controls.

Methods: We retrospectively analysed 90 consecutive patients who underwent allo-HSCT between mid-2019 and mid-2020 in our Center.

Results: Median age of patients was 52.5 years, 49% of them were female and only 8.9% CMV seronegative. The most frequent indication for transplantation was acute leukaemia (53%) with peripheral blood stem cells (88%) from unrelated donor (62%) being the most common source of stem cells. Conditioning was of reduced intensity in most of the cases (86%). The patients received letermovir prophylaxis starting from a median of 18.5 days (range 5-28) after allo-HSCT during 90 or until CMV reactivation. With a median follow-up of 385 days (range 152-636), 26 patients (29%) experienced CMV breakthrough while on letermovir, 12 within 100 days, and 14 after day 100 post allo-HSCT. In 22 patients preemptive treatment was started and two patients developed CMV disease (pneumonitis). In one patient muscle and joint pain occurred, possibly related to letermovir, no other adverse events were noticed.

Cumulative incidence of CMV reactivation at day 180 was lower in letermovir group: 29% (95% CI 20-38; median 105 days, range 12-173) compared to historical group (with similar demographic characteristics): 61% (95% CI 53-68; median 27 days, range 1-131). Patients with detectable virus level <137 IU/ml were also started on letermovir prophylaxis, and were found to have higher cumulative incidence of CMV reactivation 53% (95% CI 26-7), compared to patients who were CMV DNA negative 23% (95% CI 14-33), p=0.002. At day 500 overall survival was 76% (95% CI 65-88) in patients without CMV reactivation compared to 75% (95%CI 53-100) with CMV reactivation.



Summary/Conclusion: Our "real-world" experience confirms the efficacy of letermovir in CMV prophylaxis, its favourable safety profile and lack of negative impact on engraftment. We showed a striking decrease in the incidence of CMV reactivation in patients on letermovir prophylaxis compared to similar patient cohort from the same institution during the "preemptive treatment" era, justifying the prophylactic approach. Given the connection between CMV reactivation and NRM, clinicians should be encouraged to use different anti-CMV options available to prevent or at least delay CMV reactivation and CMV disease in transplanted patients. Patients with low, but detectable CMV levels (<137 IU/mL) and patients with the highest risk of CMV reactivation (such as patients with GvHD receiving corticosteroids, or patients who received ATG) might need a specifically tailored anti-CMV approach. Further studies addressing these questions are warranted.

EP1264 THE PRELIMINARY RESULTS OF EFFICACY OF UPFRONT HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION FOR IV STAGE AND HIGH-INTERMEDIATE/HIGH IPI RISK GROUPS DLBCL.

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Background: Approximately 30% of patients(pts) with high-intermediate/high IPI risk groups (IPI ≥2) diffuse large B-cell lymphoma (DLBCL) have relapsed after the frontline regimens. High-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (auto-HSCT) in the first remission can be an effective option to decrease the relapse rate in these patients.

Aims: Preliminary evaluation of the efficacy of the HDCT with auto-HSCT in the first remission for stage IV DLBCL patients with IPI ≥2.

Methods: 108 pts, which fit the following criteria: DLBCL NOS, age 18-65, stage IV, IPI ≥2, treated by x6 CHOP/EPOCH/H-CVAD + R in frontline from 01.01.2010 to 31.12.2019 at NMRC of Oncology named after N.N.Petrov of MoH of Russia were retrospectively analyzed.

If patients achieved complete response (CR) or partial response (PR) after frontline, they enrolled into upfront HDCT with auto-HSCT group (Group 1, n=38) or follow-up group (Group 2, n=70) based on multidisciplinary team (MDT) decision.

High LDH had 84% (32/38) pts in Group 1 and 81,4% (57/70) pts in Group 2; more than one extranodal involvement had 78,9% (30/38) pts in Group 1 and 75,7% (53/70) pts in Group 2. MYC and BCL-2 coexpression were analyzed in 84% (32/38) pts samples in Group 1 and 65,7% (46/70) in Group 2 and were present in 46,8% (15/32) pts samples in Group 1 and 28,2% (13/46) in Group 2.

An independent two-sample T-test and one-tailed p-value were used to determine the difference in relapse rate between Group 1 and Group 2.

Results: CR after induction was achieved in 61% (23/38) pts in Group 1. After HDCT with auto-HSCT, the CR rate increased to 97% (37/38) and continues for a median of 30 (7-56) months in 87% (33/38) pts. It demonstrates the statistically significant difference - $t\alpha = 4,42$ ($p \leq 0,00001$). Early relapses were diagnosed in 6% (2/38) pts, late relapses in 6% (2/38) pts. HDCT associated mortality (infection) has occurred in 3% (1/38) pts.

Group 2 patients achieved CR in 81% (57/70) cases. CR continues for median 38 (8-73) months in 67% (47/70) pts. Group 2 patients have 14% (14/70) early and 6% (4/70) late relapse rate. No treatment-related deaths occurred.

Early relapse rate was significantly higher in Group 2 if the patient had initially high LDH (Group 1 – 3,1% (1/32), Group 2 – 15,8% (9/57)) - $t\alpha = 2,21$ ($p = 0.014865$); more than one initial extranodal site (Group 1 – 3,3% (1/30), Group 2 – 17,0% (9/53)) - $t\alpha = 2,23$ ($p = 0.014257$). MYC and BCL-2 coexpression was statistically significant in terms of both early (Group 1 – 6,6% (1/15), Group 2 – 38,4% (5/13)) - $t\alpha = 2,13$ ($p = 0.0214$) and all relapses (Group 1 – 6,6% (1/15), Group 2 – 46,1% (6/13)) - $t\alpha = 2,59$ ($p = 0.007761$). The early relapse rate in Group 2 was significantly higher if the combination of initially high LDH, more than 1 extranodal site, MYC and BCL-2 coexpression were present (Group 1 – 12,5% (1/8), Group 2 – 55.5% (5/9)) - $t\alpha = 2,12$ ($p = 0.025547$).

Summary/Conclusion:

1. CR rate significantly increased for DLBCL NOS pts with stage IV, IPI ≥2 treated by upfront HDCT with auto-HSCT.

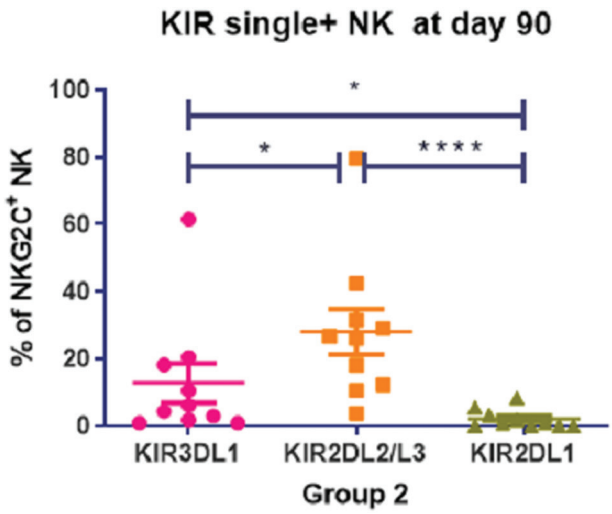
2. Upfront HDCT with auto-HSCT significantly decreases early relapse rate for DLBCL NOS pts with stage IV, IPI ≥2 if high LDH, more than one extranodal site, and MYC and BCL-2 coexpression are present.

EP1265 KIR2DL2/L3 SINGLE POSITIVE/NKG2C+ NK CELLS SIGNIFICANTLY EXPAND IN NKG2C+ NK CELLS DURING EDUCATION AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: NK education plays a vital role in leukemia control and infection prevention after hematopoietic stem cell transplantation (HSCT), which is affected by interaction of human leukocyte antigen (HLA)-I/killer immunoglobulin receptor (KIR). However, different HLA-I/KIR interactions on NK education for intrinsic responsiveness is still conflicting. Recent studies showed that obvious NKG2C+ NK cell expansions are dominated by specific single KIR clones, mainly encoded by the centromeric part of group A haplotypes under cytomegalovirus (CMV) infection. However, the effect of HLA-I/KIR interactions on NKG2C+ NK education post HSCT were still unknown.
Aims: To figure out what KIR/HLA-I interaction has a main effect on the expansion and reactivity of NKG2C+ NK cells in NK education after HSCT.
Methods: We prospectively studied 114 patients with malignant hematologic disease who underwent HSCT at the Peking University People's Hospital between May 2016 and April 2017. All patients and donors provided written informed consent. Patient and donor DNA was prepared from peripheral blood mononuclear cells (PBMCs) for HLA, NKG2C and KIR genotyping test.The expansion, expression of cell surface molecules and function of three single KIR positive/NKG2C+ NK cells (KIR2DL1, KIR2DL2/L3 and KIR3DL1) at day 30, 90 and 180 are tested by flow cytometric analyses and cytotoxicity assays. Statistical analysis was performed by nonparametric test, Pearson correlation test and Chi-squared Test.
Results: It was shown that KIR2DL2/L3 single positive NKG2C+ cells significantly expanded in NKG2C+ NK cells than KIR2DL1 and KIR3DL1, in group1 where donor and recipient were both HLA-C1C1, and group2 where donor and recipient are both HLA -C1BW4, at day 90 (group1:P<0.0001, P=0.0001; group2:P<0.0001, P=0.0232) and 180(group1:P<0.0001; group2:P=0.0003, P=0.2581). In group3, where donor and recipient are both HLA-C1C2BW4, the proportion of KIR2DL2/L3 and KIR2DL1 single positive/NKG2C+ were both higher than KIR3DL1 (Day90:P<0.0001, P=0.0023; Day180:P<0.0001, P=0.0007). MFI of NKp30 expression on KIR2DL2/L3 single positive/NKG2C+ NK cells was significantly higher than KIR2DL1/NKG2C+ and KIR3DL1/NKG2C+, in group1, group2 and group3. Additionally, we found that KIR2DL2/L3 single positive cells showed more significant proliferation in NKG2C+ NK cells than NKG2A- NK cells at day 30, 90 and 180. NKG2C genotype (*NKG2C*$^{wt/del}$ or *NKG2C*$^{wt/wt}$) of donor cells had no effect on the significant expansion of KIR2DL2/L3 single positive/NKG2C+ NK cells at day 30, 90 and 180. Moreover, we observed that KIR CenA/A genotype may induce strong expansion of NKG2C+ NK cells and KIR2DL2/L3 single positive/NKG2C+ NK cells. Besides, it was observed that the frequencies of KIR2DL2/L3 single positive/NKG2C+ NK cells showed significant consistent correlation with the proportion of NKG2C+ NK cells among NK cells only at day 90 (P=0.0417). However, the proportion of KIR2DL2/L3/NKG2C+ was irrelevant with CMV infection type (refractory reactivation or not), clinical outcomes (relapse or not) and duration of viremia. Finally, the data revealed that the number of KIRs and KIR ligands shared by donors and recipients has no effect on NKG2C+ NK cells.
Summary/Conclusion: Interaction between KIR and HLA-C can modulate the education of NKG2C+ NK cells, characterized by KIR2DL2/L3 single positive/NKG2C+ NK cells clonal expansion, with NKp30 increasing expression, dominated by the combination of KIR2DL2/L3 and HLA-C1.



EP1266 DOWN-REGULATION OF HLA EXPRESSION IN ACUTE LEUKEMIA PATIENTS RELAPSED POST TRANSPLANTATION CORRELATED WITH MRD DURATION

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is an important treatment for the hematological malignancies. Relapse is the leading cause after transplantation. The immunological principle of recurrence is different, but HLA down regulation may be important.
Aims: study the change of HLA expression when relapse post allogeneic hematopoietic stem cell transplantation, and the relationship of HLA down regulation with MRD duration.
Methods: A total of 2581 patients received allogeneic hematopoietic stem cell transplantation(allo-HSCT) in Hebei Yanda Ludopei Hospital from 2018 to 2020, of which 32 patients with recurrent acute leukemia after transplantation were selected for HLA antigen expression analysis. Male: female was 23:9, median age was 17 years old (2-51 years old), including 18 cases of AML, 7 cases of B-ALL, 5 cases of T-ALL and 2 cases of MPAL. Among them, there were 23 cases of haplo-identical transplantation, 5 cases of related matched transplantation and 4 cases of unrelated matched transplantation. Bone marrow samples were taken at the time of initial diagnosis and recurrence, and the expression of HLA-II proteins (HLA-DR and/or HLA-DRDPDQ) in tumor cells were detected by multi-parameter flow cytometry. HLA-I proteins HLA-ABC were detected in 6 cases simultaneously. 52 kinds of common fusion genes and 58 kinds of gene mutation were monitored at the same time for all patients by real-time quantitative polymerase chain reaction (RT-PCR) and next generation sequencing (NGS), as well as chromosome examination. 34% (11/32) of the patients were analyzed for HLA gene sites in the HLA region by NGS or PCR according to the proportion of tumor cells at relapse. Median follow-up were 722 days (0-1950 days), and MRDs were detected using multicolor flow cytometry at regular intervals. SPSS 25 software was used to analyze the changes in HLA antigen expression intensity between initial diagnose and relapse after transplantation, as well as the correlation between HLA expression and persistence of MRD.
Results: Among the 32 patients, the median recurrence time was 239 days (30-1290 days). Compared with the initial diagnose, the HLA-II antigen expression was down-regulated in 43.75% of patients after transplantation (P=0.01), which was consistent with the results of NGS. And the down-regulated degree of HLA-II was positively correlated with the duration of MRD (R2=0.9996). 50% (5/10) of AML involved chromosome 3 at initial diagnose, and such patients were more prone to down-regulation of HLA class II protein expression. 77% of patients with relapse after transplantation were associated with new chromosomal abnormalities, but flow cytometry showed no correlation between down-regulation of HLA-II antigen expression and new chromosomal abnormalities after the relapses, and no significant correlation with gene mutation and fusion genes. Due to the small number of cases, no correlation was found between ALL. Three patients showed HLA-loss, including one case of HLA-I (haplo-allo-HSCT), one case of HLA II

(haplo-allo-HSCT), and one case of loss of both HLA II and class I sites (related matched allo-HSCT).

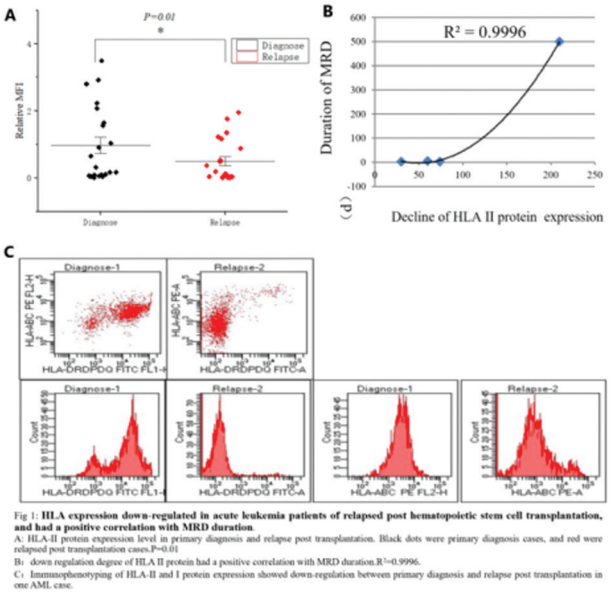


Fig 1: **HLA expression down-regulated in acute leukemia patients of relapsed post hematopoietic stem cell transplantation, and had a positive correlation with MRD duration.**
A: HLA-II protein expression level in primary diagnosis and relapse post transplantation. Black dots were primary diagnosis cases, and red were relapsed post transplantation cases.P=0.01
B: down regulation degree of HLA II protein had a positive correlation with MRD duration.R^2=0.9996.
C: Immunophenotyping of HLA-II and I protein expression showed down-regulation between primary diagnosis and relapse post transplantation in one AML case.

Summary/Conclusion: The HLA-II protein expression is prone to be down-regulated in relapsed patients after transplantation, which may be one of the important immunological reasons for the recurrence of hematologic tumors. The down-regulation degree of HLA II protein level is significantly positively correlated with the duration of MRD. Patients with AML that initially involved chromosome 3 were more likely to have down-regulated HLA class II protein expression.

EP1267 DONOR LYMPHOCYTE INFUSION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: RESULTS FROM A RETROSPECTIVE MULTICENTER STUDY

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Background: Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a curative therapy for several hematological malignancies. However, a major cause of alloHSCT therapeutic failure is represented by the underlying disease relapse. Donor lymphocyte infusion (DLI) is a powerful adoptive immunotherapy that can be used after alloHSCT in patients with high-risk disease (prophylaxis), mixed donor chimerism or minimal residual disease (preemptive), and relapse (therapeutic). DLI exploits donor derived graft versus tumor effects to induce a durable remission.
Aims: To evaluate DLI characteristics, outcomes and adverse events in a series of patients treated in three Bone Marrow Transplant Units of Northern Italy between January 2010 and June 2020.
Methods: Among 938 alloHSCT patients, 119 (12.7%) underwent DLI. Median age was 48.7 years (18-70). Patients were affected by acute myeloid leukemia (AML) (n=56), acute lymphoblastic leukemia (n=18), multiple myeloma (n=10), chronic myeloproliferative disease (n=10), Hodgkin lymphoma (n=7), myelodysplastic syndrome (n=6), non-Hodgkin lymphoma (n=5), chronic lymphocytic leukemia (n=4), mixed phenotype leukemia (n=1), severe aplastic anemia (n=1), and large granular lymphocytic leukemia (n=1). Conditioning was myeloablative in 57 (47.9%) patients, reduced-intensity in 62 (52.1%). Thirty-six (30%) donors were HLA-matched, 13 (11%) haploidentical, 70 (59%) HLA-matched unrelated. DLIs were prophylactic in 18 (15%) patients, preemptive in 43 (36%). Fifty-eight patients (49%) underwent therapeutic DLIs, 35 (60%) in combination with other drugs. DLI was administered in escalated schedule, from $1x10^5$ to $1x10^7$ CD3+ cells/Kg. Disease free survival (DFS) was calculated from the first DLI to relapse or last follow-up.
Results: The median number of DLIs was 4.6 (1-49), the median dose of total CD3+ cells infused was $2.9x10^7$/Kg (0.03-19.7). The median time elapsed between alloHSCT and the first DLI was 19 months (2-122). Complete remission (CR) was maintained in 13/18 (72%) patients undergoing prophylactic DLIs. Patients who received preemptive and therapeutic DLIs achieved CR in 30/43 (70%) and 22/58 (38%) cases, respectively. The median DFS was undefined in patients undergoing prophylactic or preemptive DLIs, 0.5 months (0-187) in those receiving therapeutic DLIs (p=<0.001). In the largest group of patients (i.e., AML), prophylactic, preemptive and therapeutic DLIs maintained or induced CR in 6/8 (75%), 12/20 (60%), and 10/28 (36%) cases, respectively.
Overall, 27/119 patients (23%) developed graft-versus-host-disease (GVHD). No significant differences were observed in terms of number of DLIs and donor type between patients with and without GVHD. Patients with GVHD received a slightly higher total number of CD3+ cells/Kg than those without ($3.31x10^7$ vs $2.74x10^7$, p=ns), though in a lower time frame (4.8 vs 5.2 months). GVHD was associated to a significantly higher CR rate (78% vs 48%, p=0.006), however, 3/27 (11.1%) patients died of GVHD. None of patients experienced bone-marrow aplasia following DLI. Overall, with a median follow-up of 38 months (0.3-189), 56/119 (47%) patients are currently alive in CR.
Summary/Conclusion: Although with the limits of a relatively small and heterogeneous series, our study indicates that DLI is an effective prophylactic and preemptive treatment option in alloHSCT patients. Prospective studies on homogeneous patient cohorts in terms of disease type and drug combination are awaited in order to address and ameliorate the effectiveness of DLI in therapeutic settings.

EP1268 FEASIBILITY OF ALLOGENEIC STEM-CELL TRANSPLANTATION WITH CONDITIONING REGIMEN OF 5-DAY DECITABINE IN MDS AND MDS/MPN : A MULTICENTER PROSPECTIVE COHORT STUDY IN CHINA

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Background: Allogeneic stem-cell transplantation (allo-HSCT) is the only curative treatment in myelodysplastic syndromes (MDS) and MDS/myeloproliferative neoplasm (MPN). Post-HSCT relapse remains a major cause of treatment failure.
Aims: In our retrospective group, the addition of a 5-day schedule of decitabine conditioning regimen was proven to be feasible and effective.
Methods: We conducted a multicenter study to prospectively evaluate the feasibility of allo-HSCT with conditioning regimen of 5-day decitabine in 61 patients with a MDS, 6 with chronic myelomonocytic leukemia (CMML), and 9 with secondary acute myeloid leukemia (sAML) after MDS or CMML. Patients received Dec 20 mg/m^2/day on days -9 to -5, combined with a Bu/Cy/ Flu/ Ara-c modified preparative regimen.
Results: At a median follow-up of 563 (range: 8-1265) days, the overall survival (OS) was 82.9±4.5%, relapse incidence was 7.9±3.4%, and non-relapse mortality was 13.1±4.1%. Transplant related mortality(TRM) was assessed at 13% on the whole cohort. 6.5% has no engraftment for a total of 5 patients. A neutrophil count of >0.5 × 10^9/L was achieved at a median of 12 days (range, 6–21 days) and a platelet count of >20 × 10^9/L within 16 days (10–103 days) post-transplant. The incidence of severe acute (grade III/IV) graft-versus-host disease (GVHD) was 25.0% and that of chronic GVHD was 26.4%. At 2 years, OS was 78.8%,91.7% and 87.5%, respectively, for MDS patients with high risk, very high risk and sAML. Survival was promising in patients with poor-risk mutations, such as TP53 and ASXL1 (76.0%), and in those with ≥3 gene mutations (87.1%).
Summary/Conclusion: This new regimen was associated with a low relapse rate, low incidence and severity of GVHD, and satisfactory survival for allo-HSCT patients with MDS and MDS/MPN.

EP1269 DONOR-DERIVED ACTIVATED NK CELLS IN MANAGEMENT OF RELAPSE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

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Background: Relapse remains the main cause of failure for hematopoietic stem cell transplantation (HSCT) in acute myeloid leukemia (AML). In some cases, leukemia cells may develop HLA loss which would result in poor response to conventional immunotherapy such as donor lymphocyte infusion (DLI) and thus NK cell therapy would be appropriate treatment.
Aims: In present clinical study, the safety and efficacy of donor-derived activated NK cells in management of relapse after allogeneic HSCT in AML were examined.
Methods: Between October 2019 and January 2021, 7 AML patients with hematologic relapse or minimal residual disease (MRD) positive after allogeneic HSCT and then received donor-derived activated NK cell therapy were enrolled. The median age was 10 (3-41) years old. Seven patients were with fusion genes (MLL-AF6 in 1, MLL-PTD in 1, CBFβ-MYH11 in 1, AML1-ETO in 4). The disease status before transplant was CR1 in 2 cases, CR2 in 3 and non-remission in 2. All transplants were from haploientical donors. Conditioning regimen was busulfan/fludarabine-based. Cyclosporine, MMF and short-term MTX were employed for GVHD prophylaxis. Isolated peripheral blood mononuclear cells (PBMCs) from original donors were co-cultured with cryopreserved-thawed irradiated genetically engineered (GE)_K562 feeder cells (a gift of Alex H. Chang, Shanghai YaKe Biotechnology Ltd., China) at a ratio of 2:1 (PBMCs:GE_K562) in SCGM media, with 100ul/ml IL-2 and donor serum for 8-9 days. Escalated dosages of NK cells were infused starting with 1×10^5 cells/kg (recipient's body weight) with or without IL-2 injection. The patients with hematologic relapse received NK cells 3 days later after chemotherapy. The disease status before NK cell therapy was hematologic relapse in 2 and MRD^+ in 5, and 2 cases with hematologic relapse failed to chemotherapy combined with DLI before NK cell therapy.
Results: The purity of donor-derived ex-vivo activated NK cells was 80-90%. Compared with our original culture system, the modified culture system enhanced approximately 20% to 40% of the purity and 3 to 6 fold in number of NK cells by day 8-9. The median NK cells infused were 5 (1-100) $\times10^5$ cells/kg with four-week interval. No transfusion-related side effects were noted. Five cases had response to NK cell therapy. Two cases with hematologic relapse all had response (CR) to NK cell therapy. For 5 cases with MDR^+, 1 case had a complete response, 2 cases had 1 log reduction in fusion gene, and 2 cases had no response. With the median follow-up192 (22-510) days, 7 cases have been survived, 5/7 cases have been survived free of diseases. Two patients relapsed.
Summary/Conclusion: Our preliminary results have demonstrated that donor-derived ex-vivo activated NK cells are safe and effective treatment in relapse after allogeneic HSCT in AML patients who even failed to chemotherapy combined with DLI. Optimal culture system with cryopreserved-thawed irradiated genetically engineered (GE)_K562 feeder cells has improved not only NK cell's purity and number but also clinical efficacy compared with our previous study.

EP1270 RESULTS OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS WITH RENAL FAILURE: A RETROSPECTIVE SINGLE-CENTER STUDY

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Background: According to the Russian register renal impairment at the time of diagnosis was noted in every fifth patient with multiple myeloma (MM). Timely induction therapy followed by autologous stem cell transplantation (ASCT) in some cases contributes to the reversibility of renal failure
Aims: To study the efficacy and safety of high dose therapy followed by ASCT in patients with MM and renal failure
Methods: A retrospective single-center study was performed, including 64 (30 males, 34 females) MM patients with renal failure at the time of diagnosis aged 19 to 65 years (median 54) underwent ASCT during a period from 2013 to 2019. At the time of diagnosis median of serum creatinine level was 462 μmol/L, and median of glomerular filtration rate was 10 ml/min/1.73 m^2 (CKD-EPI). 23 patients (36%) were dialysis-dependent at the time of diagnosis. Induction therapy included bortezomib-containing regimens in all patients, immunomodulatory drugs were used in 20% of cases. Before ASCT the overall response rate (CR, VGPR, PR) was documented in 91% of cases, CR was achieved in 45% of patients. Renal response was achieved in 80% of patients (complete response – 28%). In 13 of 23 cases (57%) dialysis was stopped after induction therapy. 10 patients were dialysis-dependent at the time of ASCT. 47 patients (73%) underwent a single and 17 patients (27%) underwent a tandem ASCT (Mel 140-200 mg/m^2). The analysis of complications, a requirement for transfusion therapy was carried out in 2 subgroups: subgroup A - patients without dialysis at the time of ASCT (n = 54), subgroup B - dialysis-dependent patients at the time of ASCT (n = 10).
Results: Reactivation of a herpesvirus infection was developed significantly more often in the subgroup B patients compared to the subgroup A patients (30% versus 6%, p = 0.04). Reversible toxic encephalopathy was developed significantly more often in the subgroup B patients comparison with the subgroup A patients (20% versus 0, p = 0.02).In subgroup B patients compared to subgroup A patients significant differences were observed in a requirement of the red blood cell transfusions (100% vs 37%, p = 0.001).100 days after ASCT the achievement of the overall response rate increased from 91 to 96%, the percentage of CR increased from 45% to 64%. After auto-HSCT, there was an increase in the rate of achieving complete renal responses - from 28% to 34%, however, the rate of total renal response remained within 80% (fig.1). In one case dialysis was stopped after the transplantation. So, at the time of diagnosis 23 patients were dependent on the renal replacement therapy. As a result of the treatment (induction therapy with auto-HSCT), 14 patients (61%) became hemodialysis-independent. Follow-up of these patients lasts from 1.5 to 7 years. There was no transplant-related mortality. After a median follow-up of 48 months 5-year overall survival (OS) was 70%, and 5-year progression-free survival (PFS) was 42%. We were analyzed OS and PFS depending on the dose of melphalan (140 versus 200), no statistically significant difference was obtained

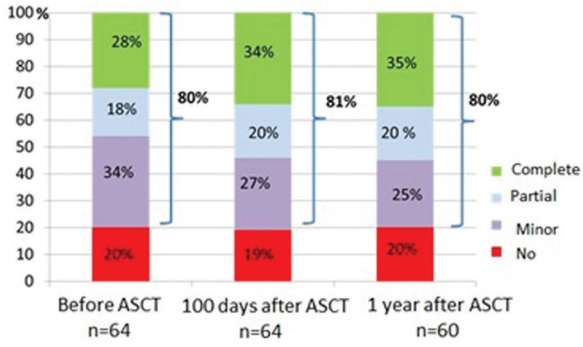


Fig. 1. Renal response in MM patients

Summary/Conclusion: ASCT is feasible, safe and effective method of the treatment in MM patients with severe kidney injury. Induction therapy followed by ASCT allowed reducing a requirement of dialysis from 36% at the time of diagnosis to 14% after ASCT. In our study 14 of 23 patients (61%) became dialysis independent. Overall, this work confirmed dialysis-dependent MM patients should not be excluded from high dose therapy followed by ASCT

EP1271 POST-TRANSPLANTATION FLUDARABINE AND CYCLOPHOSPHAMIDE SELECTED AND PROMOTED UNRELATED UCB IMPLANTATION IN COMBINED TRANSPLANTION OF HALPOID AND UCB STEM CELLS FOR TREATMENT OF PEDIATRIC LEUKEMIA

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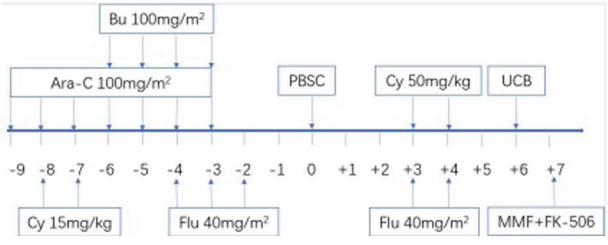
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Background: For patients without HLA matched donor, PTCY in haploid stem cell transplantation has relatively higher risk of relapse and severe GVHD. Umbilical cord blood (UCB) are readily available and has helped expand the donor pool to almost all patients requiring a transplant. Meanwhile UCB transplant improves outcomes in leukaemia with lower risk of relapse and GVHD.However, the clinical application of UCB is limited due to their small cell numbers and lower implantation rate than other sources of hematopoietic stem cells(HSC).

Aims: This clinical study is to explore the feasibility and efficacy of post-transplantation fludarabine and cyclophosphamide to select and promote the unrelated UCB to engraft in combined transplantation of haploid and UCB stem cells for the treatment of childhood and adolescent leukemia.

Methods: Total 27 children and adolescent patients with leukemia in Nanfang Hospital and Shenzhen Children's Hospital enrolled this study from Sept.2019 to Feb.2021. These patients were diagnosed as AML (3 secondary AML, 3 relapsed AML, 11 HR, 3 IR), ALL(2 relapsed, 2 HR),JMML(2) and MDS(1) with a median age of 10 years (range 1-17 years). Only one patient is BM PR before HSCT. The haploid stem cell was 5/10-9/10 mismatched and UCB was selected as 6/10-10/10 HLA matched or mismatched. The condition regimen was busulfan+fludarabine+CY+Ara-C. Haploid PBSC was infused in day0. All received PTCy 50 mg/kg and posttransplantation fludarabine 40mg/m^2 on days 3 and 4 along with tacrolimus or cyclosporine and mycophenolate mofetil for prophylaxis of acute graft-versus-host disease(GVHD). UCB was infused in day6. A median of haploid stem cells of 11.08×10^6/kg(1.51-23.20) of CD34+ cells/kg was infused while a median of UCB cells of 1.80×10^5/kg(0.40-4.80) of CD34+ cells/kg was infused.

Results: At a median follow-up of 6 months (range 2-17), all patients are alive and leukemia free. Among these patients, 25/27(92.6%, *95%CI*: 0.820~1.032)of patients achieved complete chimerism of unrelated UCB cells and 2/27(7.4%, *95%CI*: -0.032~0.180) of patients achieved high-level mixed chimerism of unrelated UCB cells rather than haploid cells. Two recent patients had primary poor graft function around posttransplantation of 70days. Neutrophil reconstitution was achieved in 25/27 patients with a median time of 30 days (range 17-44 days)without G-CSF after transplantation. Platelet recovery was achieved in 25/27 patients with a median time of 39 days (range 8-92 days).The incidence of grade I and grade II GVHD was 37% and 37% respectively (*95%CI*: 0.176~0.565). There was no grade III-IV GVHD and no extensive chronic GVHD. The incidence of chronic limited GVHD was 6/22(27.3%, *95%CI*: 0.071~0.475). Fourteen of 27 (51.9%, *95%CI*: 0.317~0.720) patients experienced clinically significant CMV reactivations or infections. One of 27 (3.7%,*95%CI*: -0.039~0.113) patients experienced EB virus reactivation.



Summary/Conclusion: In our primary clinical study, post-transplantation fludarabine and cyclophosphamide could effectively selecte and promote the unrelated UCB to implant rather than haploid cells in combined transplantion of halpoid and UCB stem cells even if the dose of CD34+ cells of UCB as little as less than 1.00×10^5/kg. Although acute GVHD was common but just milder degree and with lower incidence of EB virus reactivation. This new strategy has the potential to promote the wilder clinical use of unrelated UCB in the treatment of leukemia.

EP1272 RELAPSED/REFRACTORY (R/R) HODGKIN LYMPHOMA (HL): WHO SHOULD RECEIVE CONSOLIDATION TREATMENT AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)? EXPERIENCE OUTSIDE CLINICAL TRIALS.

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Background: Salvage chemotherapy followed by high-dose chemotherapy and ASCT is the standard treatment approach for R/R HL patients. This strategy leads to cure of almost half of the patients. Several HL study groups suggest various prognostic factors that identify patients at high risk for failing ASCT. These patients benefit from brentuximab vedotin (BV) consolidation treatment, as suggested by the AETHERA trial.

Aims: The identification of prognostic factors and the construction of an algorithm, to identify individuals at high-risk for progressing after ASCT from a series of consecutive R/R HL patients, treated in a single Unit.

Methods: A total of 189 patients who received ASCT between 1996 and 2020 were retrospectively analysed with a median follow-up of 106 (range 9-369) months, median age: 32 years, 110 males. The following factors were studied: age, sex, histologic type, stage, number of involved fields, extranodal, bulky disease, B-symptoms at diagnosis and at relapse, anemia at relapse (Hb<13 g/dl (males) and <12 g/dl (females), response to 1st line and salvage chemotherapy regimens, number of therapies before ASCT, use of radiotherapy, and disease status pre-transplant as assessed by computed tomography (CT) and positron emission tomography (PET), as well as by a composite score integrating both CT and PET. The primary endpoint was 5-year freedom from progression (FFP). Univariate Kaplan Meier analysis was conducted, followed by multivariate analysis using the Cox Proportional-Hazards Model.

Results: Univariate Analysis revealed the following significant factors for FFP: Response after 1st line and 1st salvage, Early (including primary refractory) vs late relapse, B-symptoms and anemia at relapse, disease status pre-transplant, as assessed by CT, PET and the composite PET and CT score. The latter was the factor with the highest significance (p<0.001), that could stratify patients into three groups with different outcomes. The 1st group included patients with complete remission (CR) by CT and PET up to Deauville 5-point scale (D5PS) of 4, and those with partial remission (PR) by CT and PET D5PS 1-3; the 2nd group included patients in PR by CT and PET D5PS 4-5, and those with stable disease (SD) by CT regardless of PET; finally the 3rd group included patients with progressive disease (PD) by CT, regardless of PET.

By multivariate Cox Regression analysis 2 factors remained significant: 1. The composite PET and CT score pre-transplant showed that patients of group 2 and 3 are more likely to relapse after ASCT, compared to those of group 1, (p=0.002, <0.001, hazard ratio 3.45 and 9.49, respectively), 2. Anemia at relapse; patients presenting without anemia at relapse had 51% less risk of progression (p= 0.033). PD and PR after 1st line of treatment show almost double, but marginally significant (p= 0.046 and 0.055, respectively) risk for progression, and SD was insignificant(p=0.99), but few cases were included (N=8).

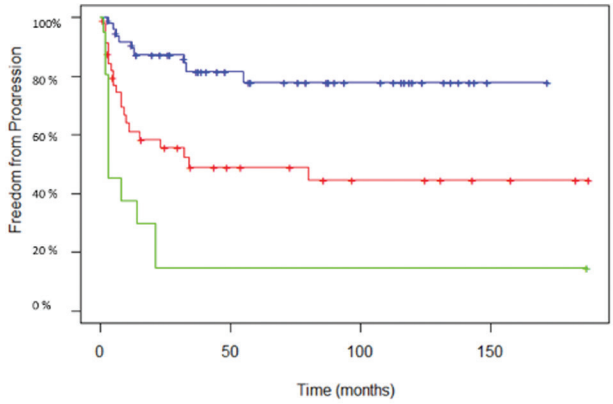


Figure 1: Freedom from Progression Survival Curves for the three groups, adjusted for gender, anemia and response to first line of treatment

Groups	5 year FFP	Total Events/ Number of cases#	Log rank test p value
Group 1: CR by CT and PET D5PS: 1-4, PR by CT and PET D5PS:1-3	78%	9/50	<0.001
Group 2: PR by CT and PET D5PS: 4-5, SD by CT, regardless of PET D5PS*	49.1%	21/40	
Group 3: PD by CT, regardless of PET D5PS	19%	14/15	

*Three patients CR by CT and PET D5PS:5 were also included in Group 2
the number of cases is smaller, as these with missing values were excluded from multivariate analysis

Summary/Conclusion: Analysis of real world data showed that disease status assessment using both CT and PET prior to transplant can direct therapeutic strategy in R/R HL patients undergoing ASCT. Patients with PD do not benefit from the procedure and should be treated with alternative treatment. Patients with CR by CT and PET up to D5PS of 4 or these with PR by CT and PET up to D5PS 3, show excellent prognosis and do not need consolidation treatment post ASCT. The remaining ones representing 25% of the population are those who may benefit from BV maintenance. This strategy is currently adopted by our center.

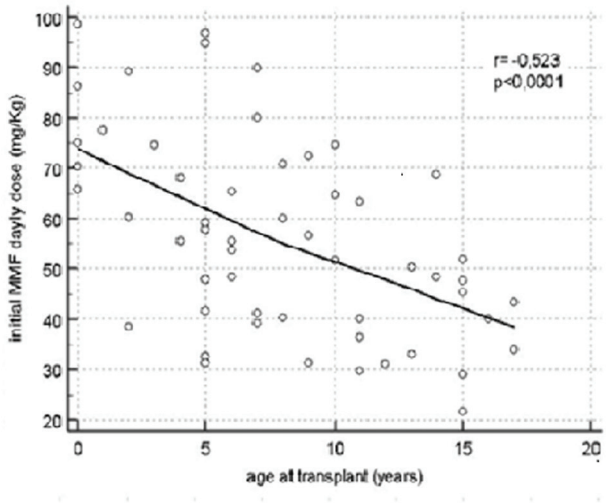
EP1273 AREA UNDER THE CURVE BASED MYCOPHENOLATE MOFETIL DOSAGE REDUCED THE INCIDENCE OF GVHD AFTER ALLOGENIC HSCT IN PEDIATRIC PATIENTS: ONE FACILITY'S EIGHT-YEAR EXPERIENCE

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Background: Use of mycophenolate mofetil (MMF) has been developed with different prophylactic regimens to obtain effective immunosuppression in combination with calcineurin inhibitors (FK506 or cyclosporine (CsA)) and/or serotherapy (anti-thymocyte immunoglobulin or alemtuzumab). However, the drug presents a significant inter and intra-patient variation that could lead to an inadequate GvHD prophylaxis or, on the contrary, excessive immunosuppression.
Aims: Study of the pharmacokinetics of MMF (MPA AUC) may help to correctly adequate dose and efficacy of GvHD prophylaxis but only a few data are available in pediatric population. Our study aims to find the correct balance in drug dosage to maximize the GvhD prophylaxis without impairing the process of immune recostitution.
Methods: We conducted a retrospective single-centre study at IRCCS "Burlo Garofolo". The primary goal was to analyze whether FK506 plus MMF prophylactic regimen, with MMF administered dose based on MPA AUC, reduces the incidence of acute and chronic GvHD in pediatric patients comparing with a control historical cohort. Inclusion criteria were age under 18 years, first HSCT, myeloablative conditioning regimen, and at least twelve-month follow-up after HSCT. Control group consisted of CsA and short-course of MTX or CsA and MMF at a standard daily dose of 30 mg/kg with pre-dose plasma level monitoring. All patients in the study group received FK506 and MMF as GvHD prophylaxis. The initial daily dose of MMF in this group was a minimum of 30 mg/kg and subjected to therapeutic drug monitoring (TDM) through MPA AUC.

Results: The two populations considered were 55 pts (study group) that received HSCT from 01/11 and 12/19 and 57 patients (control group) from 01/02 to 12/10. The demographics, clinical and HSCT features of the two groups were comparable. (table 1) After a twelve-month follow-up period, we observed a statistically significant difference either in overall acute GvHD (13% vs 69% p<0.0001) and overall chronic GvHD (5% vs 18% p<0.05). Comparing the incidence of different grades of GVHD in the study and the control group, we found statistically significant differences of the rate of acute GvHD I-II grade, acute GvHD III-IV grade, and acute GvHD III-IV grade with donor lymphocyte infusion (DLI)-related onset (45% vs 9%p<0.0001; 22% vs 5% p<0.001, 20% vs 2% p<0.0001, respectively). AUC of MMF leads to change drug dosage one time during the 28 days post-transplant prophylaxis with an increase of dosage mainly under six years of age and a strong inverse correlation (r= -0,523, p<0.0001) between initial daily MMF dose and age at transplant. (figure 1) Finally, no difference was shown in term of relapsed disease in the study group versus the control historical group (20% and 21.3%, respectively).



Summary/Conclusion: In our study using a drug monitoring of MMF through the calculation of MPA AUC shows a significant reduction of acute and chronic GvHD incidence. Furthermore, analyzing AUC curves, we saw that patients under six years of age need a significantly higher dose of daily MMF due to greater drug clearance than in older children. Due to the limitation of a retrospective, monocentric study furtherinvestigations are warranted to define efficacy and safety of FK506/MMF prophylaxis.

EP1274 EBMT, RPAM AND EASIX SCORES – IS THERE A BETTER PREDICTOR OF SURVIVAL AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA?

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Background: Several scoring systems have been developed to predict the clinical outcome in hematopoietic stem cell transplantation (HSCT). The score of the European Society for Blood and Marrow Transplantation (EBMT) and the revised Pretransplantation Assessment of Mortality (rPAM) score include clinical characteristics of the patient, donor and disease status. Most recently, the Endothelial Activation and Stress Index (EASIx), a laboratory biomarker-based formula including serum creatinine, lactate dehydrogenase, and platelet count, was developed as a predictor of mortality after allogeneic HSCT (allo-HSCT). Data regarding the comparative performance of these scores are lacking.

Aims: To compare the performance of 3 scoring systems in a cohort of patients (pts) with acute myeloid leukemia (AML) undergoing allo-HSCT.
Methods: Retrospective analysis of 95 adult AML patients (pts) who underwent allo-HSCT between January 2015 and December 2019 in a single institution. EBMT and rPAM scores and EASIx prior to conditioning (EASIx-pre) were calculated for each patient. Using Cox regression, the predictive ability of each score for non-relapse mortality (NRM), relapse free survival (RFS), overall survival (OS), and acute graft versus host disease (aGvHD) was assessed.
Results: The median age at HSCT was 49 years (22-65), and 55% of pts were male. Seventy-five pts (80%) were in first complete remission at the time of allo-HSCT. Fifty-four pts (57%) were treated with myeloablative conditioning (MAC) regimens while the remaining pts received reduced intensity conditioning (RIC). Donors were a matched sibling in 53% of pts, a fully matched unrelated donor in 28%, and a partial matched unrelated donor in 17%. The stem cell source was peripheral blood in the majority of the pts (98%). The incidence of aGvHD was 55%, and the median time to onset of aGvHD was 33 days (8-211). The median OS and RFS for the whole cohort was 26 months and not reached (NR), respectively. NRM rate for the whole cohort was 24%. EASIx-pre predicted OS (HR 1.04; p= 0,021); however, its predictive ability did not remain after adjustment for other variables (age, donor type, conditioning intensity and disease status). RFS, NRM and aGvHD were not predicted by EASIx-pre. Revised PAM score predicted the occurrence of aGvHD (p=0,038); however, this score did not predict OS, RFS and NRM. EBMT score did not predict the assessed outcomes.
Summary/Conclusion: In our cohort, EASIx-pre was the only score predicting OS; however, the association between EASIx-pre and OS lost its significance in multivariate analysis, suggesting that EASIx-pre is not an independent predictor of OS. Neither rPAM nor EBMT score could predict survival outcomes. Interestingly, rPAM had a statistically significant association with aGvHD. Our results suggest that new scoring systems relying on biomarkers may improve predictive ability of survival after allo-HSCT for AML.

EP1275 PREVALENCE OF PURE RED CELL APLASIA AFTER HEMATOPOIETIC TRANSPLANTATION USING MAJOR ABO-INCOMPATIBLE UNMANIPULATED PERIPHERAL BLOOD STEM CELLS

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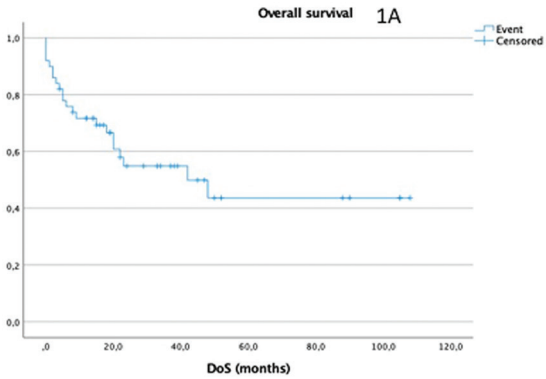
Background: Pure red cell aplasia (PRCA) is considered an uncommon but critical complication after ABO-incompatible allogeneic hematopoietic stem cell transplantation (HSCT). Previous studies have demonstrated several risk factors for post-HSCT PRCA, such as anti-A isohemagglutinins against donor red blood cells (RBC) and reduced-intensity conditioning regimens.
Aims: We intended to evaluate the clinical outcomes in the context of ABO-incompatible transplantation using peripheral blood stem cells.
Methods: We carried out a prospective nested case-control study to determine the prevalence and factors associated with PRCA following major ABO-incompatible peripheral blood stem cell transplantation (PBSCT) between August 1, 2014 and June 30, 2020. A total of 478 patients receiving ABO-incompatible PBSCT were observed and divided into 3 cohorts, including 196 with major grafts, 214 with minor grafts, and 68 with bidirectional grafts. The nested case-control study enrolled 187 patients after major ABO-incompatible PBSCT for the detailed analysis.
Results: A total of 13 out of 187 patients developed PRCA. The factors associated with PRCA were the patient's age, donor type, and the use of anti-T-lymphocyte globulin (ATG). Haploidentical related donor (HRD) was the only independent factor for PRCA after HSCT in the multivariate analysis (HR=0.029, 95%CI 0.004-0.231, P<0.001). The presence of PRCA did not influence overall survival (OS), disease-free survival (DFS), acute or chronic graft-versus-host disease (GVHD), non-relapse mortality (NRM), and relapse rate after HSCT.
Summary/Conclusion: The incidence of PRCA was 7% (95% CI, 3.9%>11.9%) after major ABO-incompatible PBSCT and low dose ATG-based haploidentical transplantation can significantly decrease the development of PRCA post-HSCT.

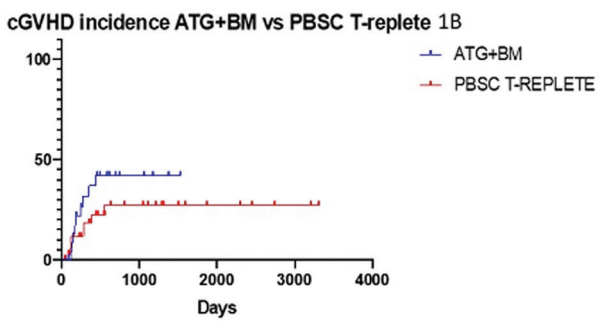
EP1276 EXCELLENT COMPARABLE OUTCOMES OF HAPLO-HSCT IN HIGH RISK MYELOID MALIGNANCIES USING MYELOABLATIVE OR REDUCED INTENSITY CONDITIONING WITH LOW RISK OF CGVHD IN RECIPIENTS OF PERIPHERAL BLOOD STEM CELL

D. Avenoso [1,*], M. Hassanein [1], R. El Fakih [2], P. Krishnamurthy [1], W. Rasheed [2], V. Mehra [1], S. Ahmed [2], H. De Lavallade [1], M. Shaheen [2], A. Kulasekararaj [1], M. Aljurf [3], S. Gandhi [1], M. Altareb [2], A. Pagliuca [1], F. Dazzi [1], M. Kenion [1], S. Ware [1], Y. T. Leung [1], V. Potter [1]

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Background: Haploidentical haematopoietic stem cell transplant (haplo-HSCT) is a potentially curative option for patients with myeloid malignancies lacking an HLA identical donor. Although the original platform was based on bone marrow (BM) as cellular source, many transplant centres now use G-CSF mobilised peripheral blood stem cells (PBSC). Chronic graft versus host disease (cGVHD) is a complication that can jeopardize the transplant outcome; for that reason, some centres still prefer BM or use t-depletion with ATG. Relapse rates are also of concern, and the optimal intensity of conditioning (MA vs RIC) in haplo-HSCT for patient with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) remains unclear.
Aims: The aim of this paper is to compare results of two different haplo-HSCT approaches (BM vs PBSC and MA vs RIC) in patients affected by AML and MDS at King's College Hospital (KCH) in London and King Faisal Hospital (KFH) in Riyadh.
Methods: Between August 2010 and March 2020, 50 patients with a median age of 46 (14-60yrs) and a high-risk myeloid malignancy were identified (AML n=34, MDS n=16). At KCH, haplo-HSCT (n=23) was performed with G-CSF mobilized PBSC with FluCyTBI protocol (Cy 14.5 mg/kg/ days -6, -5, fludarabine 30 mg/m2/ days -6 to -2, and 200 cGy Total Body Irradiation day -1). At KFH 27 patients had t-deplete BM with TBF regimen (thiotepa 5 mg/kg days -8, -7, fludara 50 mg/m2 days -6, -5, -4, busulphan 3.2 mg/kg days -6, -5, -4, rabbit ATG 1 mg/Kg day -3, -2). GVHD prophylaxis was with post-transplant cyclophosphamide





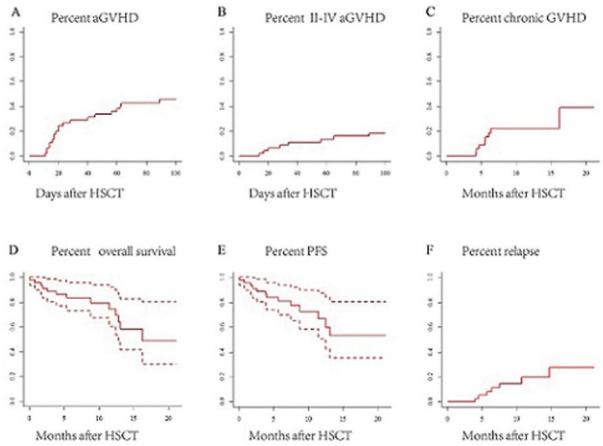
(50 mg/kg day +3 and +4 at KCH; day +3 and +5 at KFH), mycophenolate and tacrolimus. All patients were in morphological complete remission prior to HSCT. A median 4,8x10^6 (1,5-14) CD34+/Kg was infused.
Results: At 24 months 55% of patients were alive and in CR, with median overall survival (OS) not reached (Fig 1A) and no differences between the two cohorts. Two septic deaths before engraftment and 3 primary graft failure were noted. Among 45 evaluable patients, median time to neutrophils □ 1000/□L was 17 days (13-42), and 25 days (14-44) to platelets □ 20.000/□L. Median CD3 and CD 15 chimerism at day 100 was 100%. Overall incidence of acute GVHD was 35% (grade I-II 76%; grade III-IV 24%) with no differences between t-replete PBSC and t-deplete BM. cGVHD rate was 26% (30% mild, 13% moderate, 56% severe) and significantly different between the two cohorts (in the PBSC cohort the incidence was 25% vs 40% in the t-deplete BM population (p 0.05 – Fig 1B)). CMV reactivation occurred in 77% of patients, at a median of 42 days after transplant (10-415); 74% patients of KFH had detectable CMV within 4 weeks whereas 54% of KCH's patients developed CMV reactivation; no cases of CMV disease were noted. The relapse rate at 4 years was 26% for both t-deplete BM and t-replete PBSC (p not significant). Overall, 18 patients (36%) died; cause of death were relapse (57%), GVHD (10%) and sepsis (33%).
Summary/Conclusion: this retrospective analysis demonstrated good OS in AML and MDS. The use of a haploidentical protocol with PBSC resulted in a low rate of cGVHD compared to a MA approach that utilised BM with the addition of ATG. Whilst noting the inherent limitations of retrospective data we conclude that PBSC is a safe and effective cell source for haploidentical transplants. Future strategies directed at relapse prevention either via further optimisation of the conditioning, post-HSCT maintenance or cellular therapy will be important for the optimal delivery of the RIC PSBC haplo-HSCT.

EP1277 CLINICAL EXPERIENCE OF VENETOCLAX THERAPY AS A BRIDGE TO ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES: A MULTI-CENTER RETROSPECTIVE STUDY

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Background: The use of Bcl-2 inhibitor venetoclax (Ven) combined with hypomethylating agents or chemotherapy has shown promising results in treating Acute myeloid leukemia (AML) and other hematologic malignancies as frontline treatment and for relapse. However, studies regarding the effect of Ven therapy on subsequent HSCT are limited.
Aims: Aiming to evaluate the outcome of patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) after Ven therapy, we retrospectively collected data from patients treated at four transplant centers in Zhejiang Province, China.
Methods: Patients who had received ≥1 cycle of Ven combinations prior to undergoing HSCT were included. Conditioning regimens included myeloablative regimens and nonmyeloablative regimens, which were determined by the individual transplant physician based upon disease- and transplant-related considerations.
Results: Forty-five patients who underwent HSCT after Ven therapy were enrolled between November 2018 and November 2020. Thirty-one patients were diagnosed with AML (28 were de novo AML, 3 were secondary for MDS), 6 with MDS, 3 with ALL, 2 with CMML, and 2 others. The majority (75.6%) of patients received Ven for treatment of relapse (40.0%) or induction failure (35.6%), 5(11.1%) were treated as initial treatment, and 6(13.3%) patients who were already in CR received Ven for further consolidation or deep remission before HSCT. Thirty-three (73.3%) patients were in complete remission at the time of HSCT. The median time of neutropenia and platelet engraftment were 12 days and 13 days, respectively. Day +100 cumulative incidences of acute graft-vs-host disease (aGVHD) and grade II-IV aGVHD was 42.9% and 15.9%. Of 39 evaluable patients, 38.9% developed chronic GVHD developed. The 100-day cytomegalovirus (CMV) reactivation occurred in 74.4% of patients; Epstein-Barr virus (EBV) reactivation in 38.1% of patients. With a median follow-up of 9.5 months, one-year overall survival, progression-free survival and relapse incidence were



74.5%, 56.9% and 19.8%, respectively.
Summary/Conclusion: Our multicenter results showed that patients receiving HSCT after Ven therapy had favorable transplant outcomes with low aGVHD and relapse incidence, suggesting the feasibility of Ven proceeding to HSCT. Meanwhile, virus reactivation monitor should be paid attention.

EP1278 INCIDENCE, ETIOLOGY AND PROGNOSTIC IMPACT OF ATYPICAL ELECTROPHORETIC PROFILES IN PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Atypical electrophoretic profiles (AEP) may appear in patients who required allogeneic hematopoietic stem cell transplantation (allo-HSCT). Nevertheless, their clinical significance remains unkown. AEP combine either monoclonal and oligoclonal components, suspected on serum protein electrophoresis and confirmed by immunofixation.
Aims: The purpose of the study is to analyze the incidence, etiology and prognosis of AEP in patients who received allo-HSCT for myeloid malignancies.
Methods: In this retrospective study, we recruited 117 patients with myeloid disease who received an allo-HSCT between 2012 and 2018. We excluded patients with lymphoid malignancies, multiple myeloma, patients with AEP before transplantation, and patients who died within 100 days after transplantation.
Results: AEP occurred in 42.7% of patients. The cumulative incidence of AEP was significantly higher in patients with acute Graft Versus Host Disease (GVHD, p=0.019) and in patients with CMV reactivation (p=0.0017). Noticeably, we showed for the first time that AEP mainly appeared in patients transplanted from a CMV+ donor (p=0.031). CMV reactivation preceded the onset of AEP in most patients. In patients with AEP, we observed a significantly longer time to relapse (486 vs 189 days, p=0.006) and a better overall survival (OS; 33.1 months vs 28.3 months, p=0.049). The presence of an AEP was the only factor that significantly improves OS in both univariate and multivariate analyses.
Summary/Conclusion: The occurrence of an AEP, after allo-HSCT, may result from an adapted post-transplant immune response, as an anti-CMV clonal expansion from pre-immunized donor cells. These atypical profiles could reflect both GVH and GVL activity, leading to favourable outcomes. This study provides new insights for clinicians that monoclonal or

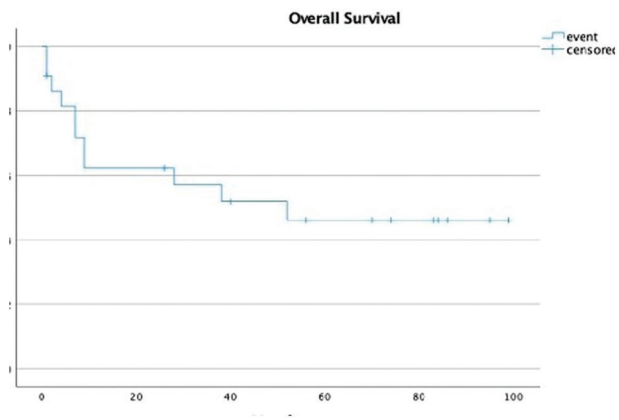
oligoclonal components on protein electrophoresis are common, benign and associated with an improved prognosis after allo-HSCT.

EP1279 GOOD OUTCOME OF HIGH-RISK MYELOFIBROSIS IN ELDERLY RECIPIENTS AFTER FULL INTENSITY T-DEPLETE CONDITIONING WITH FLUDARABINE, BUSULFAN, WITH SINGLE AGENT CICLOSPORIN AS GVHD PROPHYLAXIS.

D. Avenoso [1,*], M. Hassanein [1], M. de Farias [1], P. Krishnamurthy [1], V. Mehra [1], H. De Lavallade [1], A. Kulasekararaj [1], S. Gandhi [1], A. Pagliuca [1], F. Dazzi [1], M. Kenyon [1], S. Ware [1], Y. T. Leung [1], V. Potter [1]

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Background: The expected median survival of intermediate risk and high-risk myelofibrosis (MF) defined by dynamic international prognostic staging system (DIPSS) is of 2.9 and 1.3 years, respectively.
For that reason, allogeneic hematopoietic stem cell transplant (HSCT) is still considered the only curative option for those patients that are eligible for it.
The use of peripheral blood stem cell (PBSC) as graft source is allowing a fast engraftment, but there is still uncertainty among different centres about the most appropriate conditioning regimen in MF and the maximum age limit for myeloablative (MA) conditioning.
Aims: Herein we report the outcome of myeloablative HSCT in patients older than55 with high-risk MF as defined by DIPSS.
Methods: Between April 2012 and December 2018, 22 patients (10 high risk, 12 intermediate-2) with a median age of 61 (range 44-68 years) had full matched allogeneic stem cell transplant. HSCT was performed with GCSF mobilised PBSC. Conditioning protocol was with fludarabine 15 mg/m^2 days -9, -8, -7, -6, -5, busulfan 3.2 mg/Kg days -6, -5, -4, -3; graft versus host disease (GVHD) prophylaxis consisted of thymoglobulin before transplant (ATG 5.5 mg/Kg until January 2015; ATG 5 mg/Kg since March 2016) and single agent ciclosporin 1.5 mg/Kg (therapeutic level of 200) until d+90 and then tapered. A median of 5x10^6 CD34+/Kg was infused (3.2 – 6). Donors were: 10 siblings, 11 unrelated donor, 1 mismatched unrelated donor.
Results: at 24 months 60% of patients were alive and in complete remission, median overall survival was not reached (figure 1). No septic death before engraftment or primary graft failure were noted. Only 1 patient never had platelets engraftment and subsequently developed secondary graft failure four months after HSCT. Median time to neutrophils ^{3} 1000/mL was 13 days (11-56), and 19 days (12-161) to platelets ^{3} 20.000/mL. Median CD3 and CD15 chimerism at day 100 were 97% and 99%, respectively. Overall incidence of acute GVHD was 54% (grade I-II 50%, grade III-IV 50%); chronic GVHD rate was 31% (mild 57%, moderate 28%, severe 15%). CMV reactivation occurred in 40% of patients, at a median of 50 days after transplant (29 - 165). Incidence of venous occlusive disease (VOD) was 13%. Overall, 11 patients died (50%); cause of death were GVHD (3), PTLD (1), sepsis (2), VOD (1), donor derived acute myeloid leukaemia (1), relapse (1), unknown (1).
Summary/Conclusion: In this retrospective study we demonstrated a good



OS for high-risk MF. The use of MA conditioning and PBSC allowed a fast engraftment. Despite the small population, few cases of VOD were recorded as expected. The use of single agent ciclosporin as GVHD prophylaxis was not enough to avoid high rate of GVHD despite the use of in vivo T-cell depletion with ATG. In conclusion, MA HSCT seems a promising and safe curative option for high-risk MF in patients older than 55 years, but more strategies are needed to optimise the GVHD prophylaxis without increasing the rate of opportunistic infection or relapse.

EP1280 THE RELATIONSHIP BETWEEN THE CONCENTRATION OF VITAMIN A, C AND E, CYTOKINES AND THE OCCURRENCE AND SEVERITY OF MUCOSITIS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES UNDERGOING AHSCT

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Background: Hematopoietic stem cell transplantation (HSCT) that is currently the standard treatment for many hematological diseases is associated with high risk of mucositis. Recent studies showed that vitamins A, C and E play critical role in enhancing immune function and their low concentration in serum can be associated with higher frequency of mucositis and poor outcomes in patients with infectious complications. Relationship between antioxidative vitamines concentration and their inhibitory effect on the expression of proinflammatory cytokines were also described.
Aims: The aim of the study was to analyze the relationship between concentration of vitamins A, C and E and cytokines and the frequency and severity of mucositis in patients with hematological malignancies undergoing autologous HSCT (AHSCT).
Methods: The study group consisted of 57 patients aged 18-70 years (52.3 ± 13.4 years) who underwent high dose therapy (HDT) and HSCT. Eleven patients were diagnosed with Hodgkin's lymphoma (HL), 15 with non-Hodgkin lymphoma (NHL), 30 patients with MM (multiple myeloma) and 1 patient with amyloidosis. The severity of mucositis was assessed according to CTCAE v5.0. Serum concentrations of cytokines (IFN-gamma, IL-3, IL-6, IL-10, IL-1β) and vitamins A, C, E were evaluated before HDT/AHSCT and at the time of hematopoietic recovery (10 - 38 days after HDT/AHSCT) using the traditional ELISA method. A commercial was used according to the manufacturer's instructions.
Results: Mucositis was diagnosed in 26 patients, including eleven patients with grade 1, four with grade 2, six with grade 3, and five with grade 4 according to CTCAE v5.0. Frequency of mucositis was higher in the patients with lymphoma than in the MM patients (17 vs. 9 cases; 29.8% vs. 15.8%). The concentration of vitamin C and E was significantly lower ($p < 0.05$) after HDT/AHSCT comparing to the pretreatment values in the whole studied group(14748.4±9262.5 vs. 9875.1±8072.6 and 50.9±524.5 vs. 44.6±20.1, respectively).
There was no correlation between the frequency and severity of mucositis and the concentration of vitamin A, C and E before transplantation ($p>0.05$). After AHSCT concentration of vitamin C was significantly lower (7664.7±6919.5 vs. 12196.1±8701.8) and concentration of vitamin A was significantly higher (0.0025±0.0033 vs. 0.0040±0.0035) in patients with mucositis than in patients without mucositis. Pretreatment concentration of IL-3, IL1β, IL-6 were significant lower in the group of patients with mucositis after HDT/AHSCT: 15.4±45.8 vs. 24.1±65.3, 0.37±0.48 vs. 0.60±0.60 and 5.6±8.6 vs. 6.8±4.9, respectively. There was a positive correlation between the concentration of vitamin A and IL-3 and between the concentration of vitamin C and IL-3, IL-6, IL1β ($p<0.05$) before AHSCT ($p>0.05$).
Summary/Conclusion: Assessment concentrations of cytokines and antioxidative vitamin may allow to determine the factors predisposing to mucositis after HDT/AHSCT. Supplementation of antioxidative vitamins could be also beneficial to the recovery of the immune system in these patients, but further studies are necessary for a larger group of patients and assessing a larger number of parameters.

EP1281 PROGNOSTIC FACTORS AND OUTCOME OF CYTOMEGALOVIRUS INFECTION IN POST-ALLOGENEIC STEM CELL RECIPIENTS. FIVE YEARS RETROSPECTIVE STUDY.

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Background: Cytomegalovirus (CMV) infection is one of the major cause of morbidity and non-relapse mortality in allogeneic hematopoietic stem cell transplantation (aHSCT). There are many recognized risk factors for CMV infection or reactivation after aHSCT, being the most important CMV donor/recipient (D/R) serostatus and ocurrence of acute graft versus host disease (aGvHD). CMV infection can affect almost any organ, however, the most important clinical entities are pneumonia, gastroenteritis and retinitis.
Although some studies have shown that novel antiviral drugs should have a role in a prophylactic strategy, our current strategy is yet preemptive, based on regular pp65 antigenemia assays or qPCR.
Aims: The primary objective was to recognize and characterize prognostic factors related to CMV infection in post-transplant recipients. Moreover, we analyzed the impact of CMV infection in HSCT outcomes, respecting overall survival and non-relapse mortality.
Methods: A retrospective unicenter study was conducted in a cohort of 326 patients with hematological disease who underwent allogeneic stem cell transplant between January 2014 and December 2018. Analysis of survival and statistical comparison was made using the SPSS26® platform
Results: The median follow up time of our study was 26 months. Our cohort showed a male predominance (55% n=178) and a median age of 43 years, with 51 pediatric patients. The primary diseases were hematological malignancies in 89,6% (n=293). There was an almost even distribution of donor type (related 50% n=163, unrelated (MUD) 50% N=163) and conditioning regimen (mieloablative 47% n= 154 and reduced-intensity 53% N=172). Matched HLA donors constituted 73% (n=238) and mismatched donors were 27% (n=83) (26% HLA 9/10 or 8/10 and 1% haploidentical). Recipients were mostly seropositive for CMV infection (87% n=284) as well as donors (66% n=217). In respect to D/R serostatus the most frequent was D+/R+ (60,7%) followed by D-/R+ (26.4%), D+/R- (8.9%) and D-/R- (4%).
The incidence of aGvHD and chronic GvHD in this study was 51% (n=167) (91% with grade ≥ 2) and 32.5% (n=106), respectively.
CMV infection occurred in 46% of our cohort, with a median time to infection of 36 days (3-391d) and a median first infection time of 19 days (3-129d). Prognostic factors that impact the risk of infection were donor type (MUD – odds ratio (OR) 1.3 p=0.014), donor (IgG- OR 1.58 p=0.006) and recipient CMV seropositivity (IgG+ 1.18 p=0.000), D/R status (D-/R+ OR 2.09 p=0.000) and development of aGvHD (OR 1.9 p=0.000).
In our study, relapse was observed in 16% (n=51) of the cohort and 5% (n=17) of the sample died without evaluation of primary disease status. CMV infection has an impact on overall survival (2yOS 46.2% with infection vs 66.1% without, (with infection OR 1.51, p=0.001) and non-relapse mortality (2yOS 56% with infection vs 81.5% without infection (with infection OR 1.82, p=0.000).
Summary/Conclusion: CMV is still a major cause of morbidity and mortality in patients post allogeneic transplant and is of greater importance to recognize prognostic factors that increase the risk of reactivation. Our study confirms the role of classical risk factors in CMV infection. Despite the expected impact of prophylactic therapy in the incidence of CMV infection is still important to search for the best donor available regarding a multiplicity of factors as well CMV D/R status.

EP1282 THE IMPACT OF HEMATOPOIETIC STEM CELLS QUANTITY AND QUALITY ON HEMATOPOIETIC RECOVERY AFTER AUTOLOGOUS OR ALLOGENIC GRAFT: A TWO YEARS MULTICENTRIC RETROSPECTIVE STUDY

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Background: Hematopoietic Stem Cells (HSCs) transplantation is a therapeutic alternative for several malignant blood diseases and hemoglobinopathies. HSCs can be harvested from peripheral blood (PB), bone marrow (BM) or cord blood. The number of transplanted HSCs (CD34+ cells) represents the principal indicator of graft quality [1]. Usually, 2x106 CD34+/kg is the minimal required dose, 4x106 CD34+/kg is the target dose and over 8x106 CD34+/kg the benefice is highly speculative [1]. While autologous HSCs are systematically frozen and cryopreserved for later use, allogeneic HSCs are usually freshly transplanted after a possible manipulation including volume reduction, plasma removal or erythrocyte depletion. These processes may impact HSCs quantity and/or quality.
[1] Carreras et al., *The EBMT Handbook*.
Aims: The aims of our work were to evaluate (i) the correlation between hematopietic recovery and HSCs quantity and/or quality and (ii) the impact of HSCs manipulations on the hematopoietic recovery objectified by the delay of polynuclear neutrophils (PN) and platelet (PLT) engrafment.
Methods: We realized a retrospective multicentric study including 367 autologous HSCs from PB and 450 allogeneic HSCs (312 from PB and 138 from BM), over the period 2018-2019. The PN and PLT recovery were defined as the first day (d) of PN ≥ $0.5x10^9$/L and PLT ≥ 20 $x10^9$/L over 3 consecutive values and at least 7d after the last transfusion [1]. Statistical analyses were performed on GraphPad Prism® V8.4 and results expressed as mean ± standard deviation. Mann-Whitney, Kruskal-Wallis and Spearman's tests were used.
Results: CD34+ cell dose as well as total nucleated cell (TNC) dose were not correlated to PN (r=-0.066; r=-0.016, p>0.05) nor to PLT recovery (r=0.06054; r=0.027, p>0.05) for allogeneic HSCs from PB neither from BM (r=0.073; r=0.080 for PN and r=-0.049; -0.066 for PLT, p>0.05). In addition, hematopoietic recovery was independent of the CD34+ range doses ($x10^6$/kg): < 4, 4 - 8 and > 8 (p>0.05). However, BM volume reduction delayed the PN recovery comparing to the unmanipulated BM (21.9 ± 6.1 d *versus* 18.6 ± 4.0 d, p<0.05). This may be explained by the reduction of HSCs clonogenicity after this process (6.7% *versus* 25.3%, p<0.001).
Analysis of autologous graft showed a significant correlation between CD34+ cell dose and PN (r= -0.3086, p<0.0001) and PLT recovery (r= -0.1617, p<0.01). CD34+ cell dose > $4x10^6$/kg reduced time to PN recovery (13.6 ± 3.5 d *versus* 12.1 ± 2.5 d, p<0.001), whereas dose > $8x10^6$/kg reduced PLT recovery (12.9 ± 5.4 d *versus* 9.2 ± 4.0 d, p<0.001). Interestingly, the TNC dose was correlated to the PLT recovery (r=0.246, p<0.0001).
Summary/Conclusion: Our results showed a significant impact of CD34+ cell dose on the PN and PLT recovery for autografts. CD34+ cell dose > $4x10^6$/kg reduced time to PN recovery whereas dose > $8x10^6$/kg decreased delay to PLT recovery. For allograft, no correlation was found. This difference could be explained by a better quality of HSCs harvested from healthy donors. Indeed, we showed that the decrease of HSCs functionality might delay the hematopoietic recovery. To better understand these mechanisms, we will analyze biological and clinical risk factors of engrafment failure after autologous and allogeneic HSCs transplantation. Finally, it is important to notice that our study was indepedent of pathology and clinical factors. A more specific analysis will be performed.

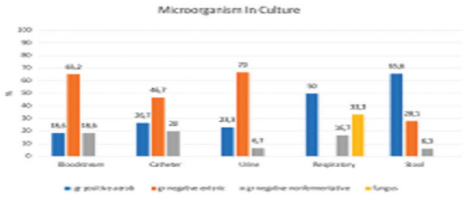
EP1283 THE DURATION OF ANTIBIOTICS WITH DIFFERENT SPECTRUMS ADMINISTERED DURING ALLOGENEIC HEMATOPOEITIC STEM CELL TRANSPLANTATION CAN PREDICT GVHD.

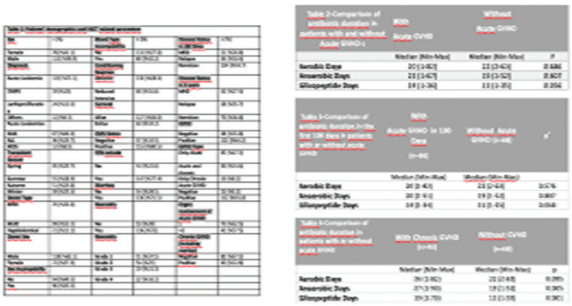
M. Kurt Yüksel [1,*], F. Doğan [2], G. Çınar [3], M. Yüksel [2], N. Öztürk [1], T. Şen [1], A. Azap [3]

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Background: The microbiome is a hot topic in recent years. It is severely disrupted by the antimicrobials during Allogeneic Hematopoietic Stem Cell Transplantation (AHSCT), resulting in a change in outcome.
Aims: This study evaluates the relationship between the usage of antibiotics with different spectrums in the first 100 days of AHSCT and GVHD incidence.
Methods: 190 patients who underwent AHSCT between March 2015 and January 2020 were retrospectively evaluated. Patients demographics and pretransplant features are shown in table-1. The antibiotics were grouped into three according to the spectrum of action: 1 -Aerobic (Levofloxacin, ciprofloxacin, amikacin, colistin, amoxicillin moxifloxacin); 2-Anaerobic (piperacillin-tazobactam, meropenem, imipenem, metronidazole, tigecycline, fosfomycin, linezolid); 3-Gram+tives (teicoplanin, vancomycin, moxifloxacin). All the patients received the same antimicrobial prophylaxis.
Results: Among the 190 patients, n=122(64.2%) developed GVHD.

The development of AGVHD in the first 100 days and one year is median 37 days (9-100) and 148.5 days (103-360), respectively. The development of chronic GVHD(including overlaps) is median six months (2-16 months). There was no difference in terms of documented microorganisms in patients with or without GVHD. In figure 1, we show the documented microorganisms in the culture in 100 days. The relationship between the duration of antibiotic usage and the development of GVHD is shown in tables 2, 3, 4. There was no relationship between the involvement of different organ GVHD, underlying diseases, and antibiotic groups. However, AHSCT from a match-related donor (MRD) had shorter usage of anti-aerobic antibiotics than match unrelated (MUD) and haploidentical donor; p=0.02, and p=0.014 respectively. However, anti-anaerobic duration was shorter in MRD compared with haploidentical donors (p=0.02) but not with MUD or MUD vs. haplo. Glycopeptide duration was longer in haploidentical donors than MRD and MUD, P=0.017 and p=0.018, respectively.
In the multivariate logistic regression analysis, patients who developed chronic GVHD had more prolonged glycopeptide usage (p<0.001). The threshold for chronic GVHD development is >14.5 days, the risk increase by 6.7 times.





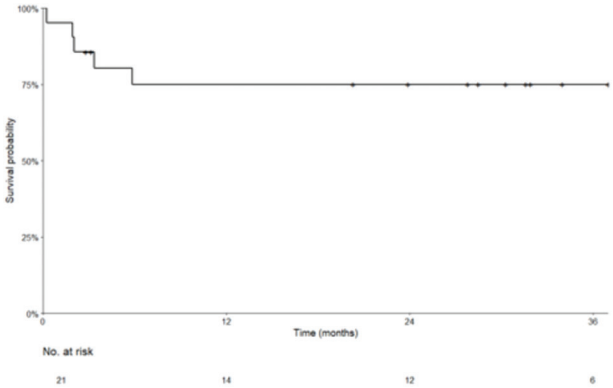
Summary/Conclusion: Many parameters can affect the outcome of HSCT. As a consequence of this study, the antibiotic's spectrum should also be considered in terms of GVHD, particularly in haploidentical transplantations.

EP1284 EXCELLENT ENGRAFTMENT AND LOW RELAPSE RATE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION FOR MYELOFIBROSIS AFTER CONDITIONING WITH FLUDARABINE, TREOSULFAN AND ATG: A RETROSPECTIVE SINGLE CENTER STUDY

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Background: Allogeneic hematopoietic stem cell transplantation is the only curative therapy for myelofibrosis but is often complicated by graft failure and high rates of relapse. The optimal conditioning regimen has not been well determined. In order to improve outcomes, our center has transplanted patients with myelofibrosis with a conditioning regimen consisting of fludarabine, treosulfan and ATG, a regiment that was previously used for second transplant after primary graft failure.
Aims: The aim of this study was to analyze the outcomes of allogeneic hematopoietic stem cell transplantation after conditioning with fludarabine, treosulfan and ATG, in terms of engraftment, relapse, non-relapse mortality, relapse-free-graft-versus-host-free survival and overall survival.
Methods: We analyzed outcomes in patients with myelofibrosis (n = 21) after allogeneic stem cell transplantation preceded by fludarabine, treosulfan and ATG (anti-thymocyte thymoglobulin) conditioning, in a retrospective single center cohort study.
Results: Patients were transplanted with stem cells from siblings (n = 4), HLA 10/10 matched unrelated donors (n=15) or HLA 9/10 mismatched unrelated donors (n = 2) between the years 2014 and 2020. The median follow-up was 2.3 years for all patients (range 0.3 - 6,1).
Median time of engraftment was 17 days and all patients were engrafted within 32 days. Mean donor chimerism at day 30-35 was 99% (T-cell and mononuclear cells). Incidence of grade III-IV acute graft versus host disease (GVHD) was 25%, of whom 60% of patients achieved complete remission with prednisolone, tacrolimus and/or ruxolitinib. Incidence of chronic GVHD was 39%, of which 71% classified as NIH stage mild. We observed high rates of EBV reactivation (86%, all responsive to rituximab) and CMV reactivation (43%), the latter often followed by development of acute GVHD. Non-relapse mortality at 1 year was 19%. The 2-year progression-free survival was 92%, the 2-year relapse-free-graft-versus-host-disease-free survival was 38%. 1 year overall survival was 76%.



Summary/Conclusion: Our results indicate that conditioning with fludarabine, treosulfan and prior to allogeneic hematopoietic stem cell transplantation for myelofibrosis results in excellent engraftment and low rates of relapse and non-relapse mortality, leading to a high overall survival.

EP1285 THE IMPACT OF PRETRANSPLANT BODY MASS INDEX ON OUTCOMES OF ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: The impact of obesity on outcomes of allogeneic stem cell transplantation (ASCT) is controversial.
Aims: The aim of this study is to evaluate the impact of pretransplant body mass index (BMI) on overall survival (OS),relapse free survival (RFS),non -relapse mortality (NRM),documented infectious complications and graft- versus host disease (GVHD).
Methods: We performed a retrospective study in patients who underwent ASCT from HLA-identical sibling donors between June 2015 and December 2018. Conditioning regimen consisted of Busulfex and Cyclophosphamide (Bu/Cy) or Fludarabine and Busulfex (F/Bu) in myeloid malignancies, TBI or thiotepa-based regimen in lymphoid malignancies and thymoglobuline and cyclophosphamide with or without fludarabine in aplastic anemia. Graft-versus host disease (GVHD) prophylaxis consisted of cyclosporine and short course of methotrexate. Patients were stratified according to pretransplantation BMI values: underweight (BMI<18 kg/m2); normal BMI (BMI 18 -25 kg/m2); overweight (BMI 25-30 kg/m2); obese(BMI 30 kg/m2).
Results: One hundred and nineteen patients were included (71 males and 48 females).The median age was 34 years (7-49y).Diseases were acute myeloid leukemia (n=37,31%),acute lymphoblastic leukemia (n=31,26%),aplastic anemia (n=27,22.7%),chronic myeloid leukemia or myeloproliferative neoplasms (n=16,13,5%),myelodysplastic syndrome (n=4,3.4%),NHL (n=4,3.4%).
According to the pretransplant BMI values,56% of patients have a normal BMI,13% were obese,23% were in overweight and 18% were in underweight.

There was no statistically significant association between pretransplant BMI and incidence of acute or chronic disease,acute infectious complications and relapse rate (p=074,p=0.15 and p=0.93 respectively).
However, obese patients have a significantly lower OS compared with other patients (78% vs 92%, p=0.004) without impact on RFS (72% vs 84%)between the two groups with p= 0.37).
The NRM was 12,5 % and it was not statistically different between the four groups(p=0.7)
Summary/Conclusion: Pretransplant obesity was associated with inferior OS after ASCT without impacting treatment related complications.

EP1286 IMPACT OF DARATUMUMAB (DARA) ADMINISTRATION DURING TRANSPLANT- ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA (TE NDMM) INDUCTION ON STEM CELL (SC) MOBILIZATION COUNT AND POST-TRANSPLANT ENGRAFTMENT.

E. Crusoe [1,2,*], A. Moura [3], M. Chaves [4], M. Salvino [3], J. Nicanor [4], J. Leal [2], H. Santos [5], A. Santos [5], V. Guimaraes [1], C. Souza [4], D. Dourado [3], L. Lucas [2], M. Santos [5], J. Santos [2], M. D. G. Arruda [2]

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Background: The combination of an anti-CD38 monoclonal antibody, Dara, to the main induction protocols (VRd, VTd, VCd) significantly improved the response rate of TE NDMM before transplantation. However, there is a concern regarding the possible interference in the SC collection and bone marrow engraftment, since SC, to some degree, express CD38 on their surface. In the MAX Dara study, Dara-CTd protocol was used sequentially close to the pre- and post-autologous stem cell transplantation-(ASCT) (D-30 and D + 30), in order to take advantage of the molecule's action as an *in vivo* purge.
Aims: In this analysis, we examine the impact of the number of Dara doses administered pre-mobilization on CD34 cell count, SC apheresis yield, and post-ASCT engraftment.
Methods: This is a phase II, open-label single-center clinical trial. The original protocol was Dara-CTd for up to four 28-day induction cycles and Dara-Td for up to four 28 days consolidation cycles. C-1500mg oral (PO) per cycle, during cycles 1 to 4, T at 100-200mg PO on days 1 to 28, during cycles 1-8, (d) at 160mg PO per cycle, during cycles 1 - 8 and Dara at 16mg/Kg/dose intravenous (IV) on days 1,8,15 and 22 during cycles 1 - 2 and every other week in cycles 3 – 8. Because of the COVID pandemic we had to adapted the protocol and moving 5-6 consolidation cycles to be used as induction, increasing the total dose of Dara from 12 to 16 and the number of cycles from 4 to 6 before ASCT. Granulocyte colony-stimulating factor (G-CSF) was administered alone for SC mobilization and plerixafor added based on day 4 pre-harvest peripheral blood CD34 counts. The target of SC collection was to enable the performance of one ASCT (≥2,5 x 10^6/kg). PMN and platelet engraftment post-ASCT was defined as the first day with sustained PMN count >1000 x 10^6/L and independence from platelet transfusion in the preceding 7 days with a count >20 x 10^9/L, respectively
Results: From a total of 21 pts that were included, 19 pts completed mobilization. 12 pts received 12 and 7 pts received 16 induction Dara doses, respectively. The median number (range) of days between the last dose of Dara infusion and SC harvest was 23 (16-63) days. A total of five (26%) pts received plerixafor during mobilization. More pts from Dara 16 doses needed plerixafor comparing with Dara 12 doses (42% vs 16%), but without difference between the groups. Pts underwent a median (range) of 1 (1-2) days of apheresis. The median number of $CD34^+$ cells collected in the total group was 3.94×10^6/kg, and no difference was found between Dara 12 vs 16 doses (3.61×10^6/kg vs 4.01x10^6/kg), p=0.27. There was no difference in the number of SC collected considering the response rate after induction ≥ or < VGPR, and the last day of Dara use ≥ or < 30 days, before SC harvesting. Hematopoietic reconstitution rates were similar for Dara 12 vs 16 doses, a median (range) of 11.0 (9-13) vs 11.0 (11-14) days was required to achieve sustained ANC > 1000 cells/mm^3, and a median (range) of 12.0 (9-14) vs 11.0 (8-16) days was required to achieve sustained platelets > 20,000 cells/mm^3 without transfusion, respectively.
Summary/Conclusion: SC mobilization was feasible with Dara-CTd induction. Despite the more doses of Dara use before mobilization increases the need of plerixafor use, the SC number difference was not significant comparing Dara 12 vs 16 doses (p = 0.3). The infusion of Dara close to harvest did not interfere with SC collection. Adding DARA to CTd allowed successful transplantation in pts with TE NDMM.

EP1287 ALLOGENEIC STEM CELL TRANSPLANTATION OF PATIENTS WITH MYELOFIBROSIS AT UNIVERSITY HOSPITAL CENTRE ZAGREB FROM 2010 TO 2020

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Background: Allogeneic stem cell transplantation (HSCT) remains the only curative option for patients with myelofibrosis (MF).
Aims: Investigate the influence of peritransplant variables on transplantation outcomes in patients with MF.
Methods: Retrospective analysis of patients treated with HSCT from 2010 to 2020 in the Department of Haematology at University Hospital Centre Zagreb.
Results: A total of 41 patients (14 women and 27 men) were transplanted, ranging in age from 32 to 65 years (median 54). Thirty (73.2%) had primary and 11 (26.8%) secondary MF. Most of the patients had intermediate or high-risk disease. Eleven patients (26.8%) received stem cells from a related, 28 (68.3%) from an unrelated, and 2 (4.9%) from a haploidentical donor. Except for 5 patients who received myeloablative conditioning (MAC), all others (36 patients, 87.8%) received reduced-intensity conditioning (RIC), in most cases FluBu3ATG. Only 2 patients received bone marrow stem cells, while others received peripheral blood stem cells. The median number of infused CD34+ cells was 6.02x10^6/kg BW (range 1.93–28.65). A total of 23 patients (56.1%) received ruxolitinib prior to transplantation, and 8 (19.5%) patients received the drug sometime during the post-transplantation period. The cumulative overall survival (OS) after a median follow-up of 574 days (range 18–3834) was 58.9% for the whole group. One patient transplanted from a haploidentical donor died of sepsis in the first weeks after transplantation and another one a year after transplantation after a series of infectious complications. Although not reaching statistical significance, patients transplanted from related donors had a better outcome than those who received a transplant from unrelated donors (OS 81.8% vs 60.7%, p=0.2), patients without splenomegaly pre-transplant compared to those with palpable spleens (OS 81.8% vs 59.3%, p=0.17), and patients who were fit enough to receive MAC compared to the large majority who received RIC (OS 100% vs 58.3%, p=0.07). Neither the diagnosis (primary or secondary MF) nor the number of CD34+ cells infused - over or below the median of 6.36x10^6/kg BW, had significant effects on outcomes (OS 58.7% vs 56%, p=0.85 and 61.2% vs 54.5%, p=0.9, respectively). Patients with chronic graft-versus-host disease had superior OS compared to patients not experiencing this transplant complication (OS 81.3% vs 54.2%, p=0.04).
Summary/Conclusion: Although wider donor availability and JAK inhibitors are making HSCT, the only available curative option for MF accesible to a larger number of patients, efforts should be made to further improve transplantation outcomes. Transplant candidates should be carefully selected with therapeutic interventions before and after transplantation tailored according to specific clinical situations. Trials addressing specific clinical scenarios are warranted.

EP1288 ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION WITH TBI-BASED REDUCED INTENSITY CONDITIONING FOLLOWED BY POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR RELAPSED/REFRACTORY LYMPHOMA PATIENTS.

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Background: Allogeneic hematopoietic cell transplantation (Allo-HCT) is a potentially curative treatment for patients with relapsed/refractory (R/R) lymphomas. Patients with R/R lymphomas usually reach allo-HCT after several lines of treatment and are often affected by comorbidities. Therefore, these patients are often unsuitable for high intensity

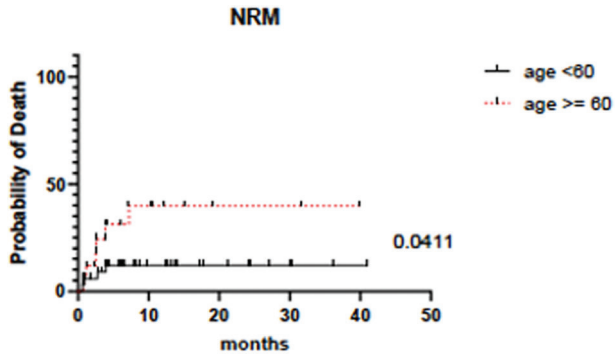
myeloablative conditioning regimen. Historically, reduced intensity conditioning (RIC) regimens are feasible in this subset of patients, but they are complicated by high rate of graft versus host disease (GvHD) and disease relapse. The more recent introduction of post-transplant cyclophosphamide (PT-Cy) for GvHD prophylaxis reduced acute and chronic GvHD rates and transplant-related mortality (TRM) in comparison to allo-HCT with conventional immune suppressive (IS) regimens. In particular, haploidentical (haplo) allo-HCT with PT-Cy showed acceptable rate of TRM and good progression free survival (PFS) in Hodgkin lymphoma patients (Castagna et al 2017). We have recently introduced total body irradiation (TBI)-based RIC followed by PT-Cy for R/R lymphoma patients. We adopted such strategy across all the different donor/recipient HLA-matching combinations.
Aims: To evaluate safety and feasibility of TBI-based RIC allo-HCT followed by PT-Cy prophylaxis for R/R lymphoma patients at our center.
Methods: We adopted TBI-based RIC allo-HCT followed by PT-Cy for R/R lymphoma patients starting in April 2016. We collected data until December 2020. Conditioning regimen to transplant was based on fludarabine (150mg/m2 in 5 days) and cyclophosphamide (14.5 mg/kg for 2 days) followed by TBI (2-4 Gy). PT-Cy dose was 50mg/kg for 2 days at day 3 and 4 after allo-HCT. GvHD prophylaxis consisted also of Tacrolimus and Mycophenolate Mofetil in patients with matched unrelated donors (MUD) or haplo donors (haplo) and Cyclosporine alone in patients with matched related donors (MRD).
Results: Since April 2016 we transplanted 27 patients with R/R lymphoma using TBI-based reduced-intensity conditioning and PT-Cy based GvHD prophylaxis. Median age at transplant was 48 years (range 25-62). Median number of previous lines of therapy was 5. Thirteen patients were affected by Hodgkin Lymphoma and 14 by Non-Hodgkin Lymphoma (7 B lymphomas, 7 T lymphomas). Twelve patients were transplanted in hematological complete remission, while 15 had active disease at transplant. All but one patient received unmanipulated G-CSF primed peripheral blood hematopoietic stem cells. Six patients received MRD allo-HCT, 1 MUD, and 20 haplo. All patients achieved primary engraftment. Acute GvHD grade ≥ II developed in 4/27 patients reaching a cumulative incidence (CI) of 15%. Two patients developed chronic GvHD. TRM occurred in 3/27 patients (CI: 11%). Causes of death were aGvHD in 1, and infective pneumonia in 2. Eight patients relapsed (CI: 30%) so far. Seven of them had active disease at transplant. The 2-year PFS is 63% and the probability of GvHD-free/relapse-free survival (GRFS) is 52% at a median follow up of 32 months (range 1.5m-5y) with 17/27 patients alive and lymphoma-free to date.
Summary/Conclusion: Here, we show that RIC allo-HCT with PT-Cy is a safe procedure with low rates of GvHD and TRM in a small series of patients. Despite the majority of patients had active disease at transplant, relapse rate appears not to be superior to the one reported after allo-HCT with myeloablative conditioning and/or with conventional IS regimens (e.g. Sureda et al. 2008). In conclusion, TBI-based RIC allo-HCT with PT-Cy ensured good PFS and GRFS in R/R lymphoma patients.

EP1289 T-REPLETE HAPLOIDENTICAL STEM CELL TRANSPLANTION UTILISING POST-TRANSPLANT CYCLOPHOSPHAMIDE IS ASSOCIATED WITH INCREASED NON-RELAPSE MORTALITY IN PATIENTS OVER THE AGE OF 60

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Background: Haploidentical stem cell transplants (Haplo-SCT) with post-transplant cyclophosphamide (PTCy) are increasing in application due to donor availability and simplicity. However, factors predictive of non-relapse mortality (NRM) in PTCy remain relatively poorly defined.
Aims: To evaluate factors predictive of NRM in patients undergoing T-replete PTCy Haplo-SCT at our centre.
Methods: Consecutive patients undertaking PTCy Haplo-SCT between January 2017 and October 2020 were identified from an institutional database and outcomes retrospectively determined from review of individual medical records. Conditioning regimens included myeloablative (MAB; Fludarabine / 12Gy TBI), reduced intensity (RIC; Melphalan/ Fludarabine/ 2Gy TBI) and non-myeloablative (NMA; Fludarabine / Cyclophosphamide / 2Gy TBI +/- rabbit ATG) regimens. All grafts were T-replete PBPC with patients commencing immunosuppression with MMF and tacrolimus post completion of PTCy.
Results: 51 patients underwent PTCy Haplo-SCT with PTCy during the time period under review. Median age at transplant was 50yrs (range 19-74yrs), with 18 patients (35%) aged ≥60yrs. Indication for SCT included AML in 26 patients (51%), MDS/ MPN in 10 (20%), B-ALL in 7 (14%), LPD in 6 (12%) and SAA in 2 (4%). Conditioning regimens were MAB in 16 (31%), RIC in 25 (49%) and NMA in 10 (20%). Haplo donors utilized included parents in 7 (14%), siblings in 15 (29%) and children in 29 (57%). Overall incidence of grade II-IV and III-IV acute GVHD was 27% and 14% respectively, with 12% of patients surviving post D100 developing extensive stage chronic GVHD. At median follow-up for survivors of 12mths 1yr OS, PFS, and NRM was 76%, 67%, and 21% respectively. In univariate analyses, factors associated with NRM included recipient age (≥60yrs) and occurrence of ICANS post PBPC infusion, which occurred in 8 (16%) of patients (n=4 ≥ grade 3). Recipient age (≥60yrs) remained predictive of NRM, with NRM of 12% in patients <60yrs vs 40% in those ≥60yrs respectively (p=0.041; see Figure). Conditioning regimen and HCT-CI score did not predict for NRM.



Summary/Conclusion: PTCy Haplo-SCT is associated with significant NRM in patients ≥60yrs. Further studies evaluating less toxic regimens is needed for this group of patients.

EP1290 IMPACT OF FLT3 INTERNAL TANDEM DUPLICATION ON THE OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

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Background: FMS-like tyrosine kinase 3 (FLT3) gene internal tandem duplication (ITD) occur in 20%-30% of adult acute myeloid leukemia (AML) patients. FLT3-ITD is widely accepted as an independent adverse prognostic factor associated with high relapse and poor survival rates. Therefore, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is generally accepted as the standard of care for AML patients with FLT3-ITD. Whether this mutation also affects outcome after allo-HSCT is controversial.
Aims: To determine the impact of FLT3-ITD on the outcome of allo-HSCT for adult AML.
Methods: Retrospective analysis of 95 adult AML patients (pts) who underwent allo-HSCT between January 2015 and December 2019 in a transplant center from north of Portugal. Clinical characteristics and outcomes were evaluated. The Kaplan-Meier method was used to describe time-to-event end points. The log rank test was used to compare the survival distribution of different groups.
Results: FLT3-ITD was detected in 17 pts (29%). Among these, 53% were female; median age at diagnosis was 43 years (22-60). Fifteen pts (88%) were transplanted in first remission, 1 in second remission and 1 in a more advanced stage of the disease. Donors were a matched sibling in eight pts (47%), a fully matched unrelated donor in six pts (35%), and a partial

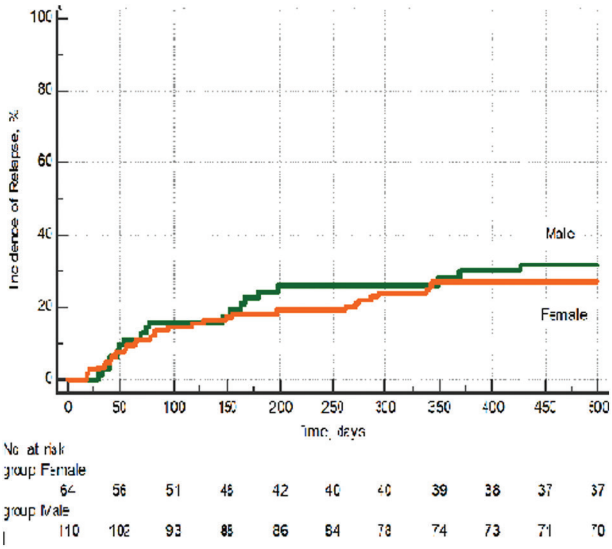
matched unrelated donor in 3 pts (18%). The stem cell source was peripheral blood in the majority of pts (n=16; 94%). Eight pts (47%) were treated with myeloablative conditioning (MAC) regimens while the remaining pts received reduced intensity conditioning (RIC). MAC regimens consisted of busulphan plus cyclophosphamide (BuCy), whereas RIC consisted of fludarabine with reduced doses of busulfan (FluBu); antithymocyte globulin (ATG) was added to the conditioning regimen for unrelated transplantations. Grade ≥ 2 acute graft versus host disease (GvHD) occurred in 5 pts (31%), at a median time of 32 days (12-81) after allo-HSCT. Five pts experienced chronic GVHD; in 3 pts chronic GVHD evolved from acute GVHD. There were no statistically significant differences between FLT3-ITD-positive and -negative patients with respect to clinical characteristics (age, gender, disease status, donor type, stem cell source and conditioning), and GvHD (incidence and overall grade). The 1-year relapse-free survival (RFS) rates for FLT3-ITD-positive and -negative patients were 58% vs 79%, respectively (HR 1.19; p=0.276); the 1-year overall survival (OS) rates were 71% vs 69%, respectively (HR 0.64; p=0.423).
Summary/Conclusion: In our cohort, there was no difference in the outcomes of allo-HSCT between AML patients with FLT3-ITD and those without the mutation. Although in the absence of allo-HSCT the FLT3-ITD mutation is predictive of a short OS, our results suggest that in patients who undergo allo-HSCT, the FLT3-ITD mutation status loses its predictive value.

EP1291 PEDIATRIC MALES RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANT SHOW AN EXTRA BENEFIT FROM THE PROCEDURE'S HORMONE IMPAIRMENT: A RETROSPECTIVE COHORT OBSERVATIONAL STUDY

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Background: Sex differences play a relevant role in cancer susceptibility, incidence and survival, with male patients being at higher risk. Genetic, epigenetic and hormonal factors are involved in such differences, and a better understanding of their close interplay in the mechanisms of cancer could improve its prevention and therapy. However, assessing the actual weight of each one of these factors is challenging.
Aims: This study aims to explore sex differences in first and advanced-line therapy outcomes in pediatric oncology. In particular, we investigated whether the known sex differences occurring after first-line therapy, and leading to a higher number of male patients requiring Hematopoietic Stem Cells Trasplantation (HSCT), persist after transplant.This study setting may represent an experimental human model that reveals the possible effects of the impairment of gonadal hormones on cancer progression, which is poorly explored in the literature.
Methods: The study is a Single-center retrospective cohort observational study. Population of the study are pediatric patients between 0 and 18 years of age admitted for hematological malignances between 2000 and 2018 who underwent allogeneic or autologous HSCT at the pediatric Department of Oncology of the Institute for Maternal and Child Health of Trieste. As part of the HSCT course, participants underwent a conditioning regimen either with high-dose (myeloablative) chemotherapy or with total body irradiation (TBI), both of which exert a substantial impairment on gonadal function.
Results: Out of a total of 485 patients (280 males, 205 females) admitted for malignant diseases between 2000 and 2018, 174 patients (111 males and 63 females) had a high-risk form of acute lymphatic leukemia, acute myeloid leukemia, myelodysplasia or solid tumors requiring HSCT. Among these patients 15 males (9%) and 6 females (3%) died from primary disease relapse, providing a DRM of 12%. Fourteen males (8%) and 13 females (7%) died from transplant-related causes, providing a TRM of 15%. No statistically significant differences between males and females were found in terms of DRM and TRM ($P > .05$). The OS was 72%, including 82 male and 44 females. One hundred eleven patients (64%) showed a disease-free survival (DFS), including 72 males and 39 females. The Cumulative Relapse Incidence (CRI) was 21%, with 25 males and 11 females having a primary disease relapse. In addition, we analyzed differences in OS, EFS, early death, TRM, DRM, and the need for a further HSCT by comparing donor-recipient pairs matched and mismatched for sex and by comparing two age groups (<12 years, >12 years). No statistically significant differences for HSCT-related complications (mucositis, gastrointestinal, hepatic, lung and kidney toxicity, and GvHD) were found between donor-recipient pairs matched and mismatched for sex. ($P > .05$) Similarly, no statistically significant differences in HSCT complications were found between males and females when comparing two age groups (<12 years, >12 years)



Summary/Conclusion: While the number of males needing HSCT was almost double that of females, confirming the well-known "male disadvantage" with respect to cancer reported in the literature, no sex-related differences in terms of overall survival, cancer relapse, or complications were reported after HSCT exposure. These findings suggest that the existing sex differences in cancer risk ab initio can be modified by HSCT and its preliminary conditioning regimen, implicating a role of hormonal factors in cancer mechanisms and management.

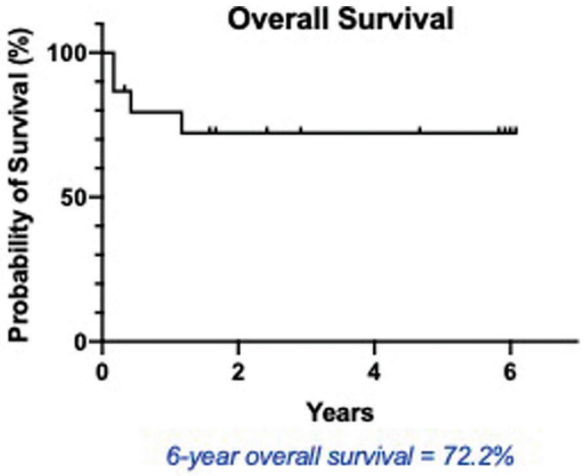
EP1292 ALLOGENEIC STEM CELL TRANSPLANTATION FOR CUTANEOUS T-CELL LYMPHOMA

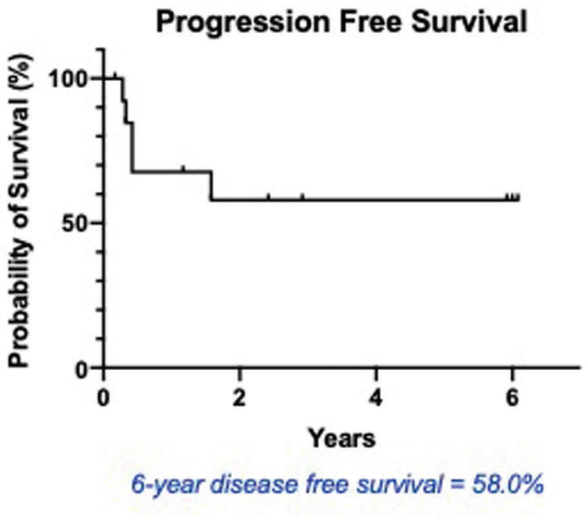
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Background: Cutaneous T-cell lymphomas (CTCL) are a heterogenous group of T-cell non-Hodgkin lymphomas with a variable prognosis. Patients with mycosis fungoides (MF) can have indolent disease, however transformed MF and Sezary Syndrome (SS) have an aggressive clinical course. CTCL are incurable with systemic chemotherapy but can achieve durable remissions with allogeneic stem cell transplantation (allo-SCT) and an SCT program was initiated for this group of poor prognosis patients in 2004 at a National allo-SCT Centre.
Aims: To review outcomes of consecutive patients with CTCL undergoing allo-SCT.
Methods: Patient demographics, disease characteristics, and outcome data were collected on consecutive CTCL patients transplanted from 2010 - 2020 at the Republic of Ireland (ROI) National allo-SCT Unit using 3 conditioning regimens; transformed MF <45 years received Cy-TBI, patients willing to travel outside ROI for Total Skin Electron Beam therapy (TSEBT) received TSEBT, total nodal irradiation, Anti-Thymocyte Globulin (ATG) and mycophenolate mofetil (Stanford) conditioning and the remaining patients received standard reduced intensity conditioning

(RIC) with Flu-Mel-ATG. Graft versus host disease (GVHD) prophylaxis with ciclosporin (+/- methotrexate) was used.
Results: Fifteen patients (10 male, 5 female) underwent allo-SCT with a median age at transplant of 49 years (range 21-64). Eight patients had SS, while 4 of 7 patients with MF had transformed disease. All four transformed MF patients [one of whom received pre-transplant brentuximab vedotin (BV)] expressed CD30. Ten patients had Stage IV disease (revised ISCL/EORTC criteria) and 7 patients had a raised LDH at referral for allo-SCT. Eleven patients (7 MF, 4 SS) received systemic chemotherapy (range 1-3 lines) pre allo-SCT; remission status pre-transplant consisted of 2 complete remissions, 10 partial remissions and 3 stable disease. Five MF patients recieved Cy/TBI conditioning, 4 SS patients received Stanford, and 6 patients (4 SS, 2 MF) received Flu-Mel-ATG conditioning. Neutrophil and platelet engraftment occurred at a median of 15 and 14.5 days respectively. Acute GVHD occurred in 13 patients, all of whom had grade 3 skin GVHD, while 5 patients had concomitant gut GVHD (grade 1-3). Early treatment-related mortality (TRM) occurred in 2 patients; one from CMV pneumonitis following Stanford conditioning and one from pneumonia following Cy-TBI. One patient progressed following Cy-TBI at 102 days and died 5 months post allo-SCT, one patient died 14 months post allo-SCT from viral pneumonitis. There were 4 overt relapses at a range of 4-19 months; 3 received donor lymphocyte infusion (DLI) and 1 had immunosuppression weaned; all 4 are in CR with a median follow up of 42 months. OS and PFS at 6 years were 72.2% and 58.0% respectively.
Summary/Conclusion: OS and PFS in this allo-SCT cohort of 15 CTCL patients was 72.2% and 58% with 4 patients achieving meaningful remissions with DLI despite post allo-SCT relapses. SS patients referred early in the disease course, had a good outcome with one post allo-SCT relapse. There were no relapses in SS patients receiving Stanford conditioning. MF patients did less well, but were referred for allo-SCT with advanced/transformed disease and may benefit (1) from earlier transplant referral and (2) from BV treatment if CD30 positive pre allo-SCT. Allo-SCT is an appropriate treatment for advanced CTCL, however improving referral timelines and conditioning in MF and reducing the incidence of skin GVHD remain challenges.





EP1293 HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR PEDIATRIC PATIENTS WITH HIGH DONOR-SPECIFIC ANTIBODY (DSA) TITERS USING A DESENSITIZING CONDITIONING REGIMEN

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Background: The application of haploidentical stem cell transplantation (haplo-SCT) greatly broadens the choice of donor pools for recipients of hematopoietic stem cell transplantation (HSCT). Recent evidence suggests that high donor-specific antibody (DSA) titer is one of the leading causes of graft failure that may contribute to higher transplant-related mortality and modality. Several approaches have been developed to reduce DSA. However, there is no available consensus or standard guidelines for the reduction of DSA for HSCT recipients due to limited evidence in published data.
Aims: Our aims are to investigate the outcomes of pediatric haplo-SCT recipients with high DSA titers using a desensitizing conditioning chemotherapy regimen.
Methods: Fourteen candidates of haplo-SCT aged 2 to 17 (median 8 years of age) were tested to have high DSA titers (HLA type I and/or HLA type II, MFI≥4000) between January 2020 and September 2020. Primary diseases included thalassemia major (13 in 14 patients) and severe aplastic anemia (1 in 14 patients). The conditioning protocol consisted of a cyclophosphamide-busulfan-based myeloablative regimen and was selectively given one or more approaches to reduce DSA titer, including high-dose intravenous immunoglobulin, rituximab, bortezomib, and plasma exchange. The GVHD prophylaxis consisted of post-transplant cyclophosphamide, mycophenolate mofetil, and tacrolimus.
Results: Clinical data of 2 girls and 12 boys were analyzed. Haplo grafts were collected from the siblings (5/14), fathers (8/14), and mothers (1/14). The mean $CD34^+$ cell dose was 12.52×10^6/kg. Neutrophil and platelet engraftment was achieved at a median of 20 days (range, 8-33 days) and 20 days (range, 8-40 days), respectively. No patients had graft failure nor had developed poor graft function. Only two patients developed grade I-II acute graft-versus-host disease (GVHD), and no chronic GVHD was observed. Viremia of cytomegalovirus (CMV) and Epstein-Barr virus was observed in three and two patients, respectively. However, none of these patients had CMV diseases or post-transplantation lymphoproliferative disorder. No other transplant-related complications were observed. All patients were alive without chronic complications at the time of last follow-up (median follow-up period 243 days, range 164 to 334 days).
Summary/Conclusion: This preliminary data suggest that our approach to use a desensitizing conditioning regimen for pediatric recipients of haplo-SCT is safe and practical to limit graft failure and transplant-related complications and may contribute to a larger cohort study in the future.

EP1294 PD-1 INHIBITOR SIGNIFICANTLY INCREASES ACUTE GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRIC REFRACTORY/RELAPSED B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: More than 90% complete remission (CR) can be achieved in relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL) with chimeric antigen receptor T cell (CART) therapy. However, a small portion of patients still cannot obtain CR or minimal residual disease (MRD) negative by CART therapy. Programmed cell death protein 1 (PD-1) inhibitor can enhance anti-leukemia effect of CART cells, but increased early

immune toxicity has been reported in allogeneic hematopoietic stem cell transplantation (allo-HSCT) after PD-1blockade in lymphoma patients.
Aims: In present study, the influence of prior application of PD-1inhibitor on acute graft-versus-host disease (aGVHD) after allo-HSCT for r/r B-ALL patients who achieved CR with CART was investigated.
Methods: Five pediatric r/r B-ALL patients who achieved CR by CART combined with PD-1 inhibitor and then underwent allo-HSCT were analyzed retrospectively. The median age was 4 (3-9) years old. Three cases were with normal cytogenetics and molecular genetics, and 2 cases were with both complex karyotypes and E2A/PBX1 (one of them also with TP53 mutation). Before allo-HSCT, all patients achieved CR (MRD^- in 3, MRD^+ in 2) by CART combined with PD-1 inhibitor. CD19-CART and/CD22-CART were used. Toripalimab at 3mg/kg was applied for one (n=4) or two (n=1) doses if CR or MRD^- was not achieved two weeks after CART therapy. All patients underwent allo-HSCT from haploidentical donors with myeloablative conditioning regimens (TBI/fludarabine/ATG in 2, busulfan/fludarabine/ATG in 3). Cyclosporine, MMF and short-term MTX were employed for GVHD prophylaxis. Interval between last PD-1 treatment and HSCT was 45 (14-60) days.
Results: All patients achieved durable engraftment. Two patients developed hyper-acute GVHD with a noninfectious febrile syndrome and severe liver dysfunction and resolved with multiple immunosuppressants including methylprednisolone (up to 4mg/kg), cyclosporine, MMF, basiliximab, ruxolitinib, and MTX. Much higher incidences of overall aGVHD and severe aGVHD were noted in this cohort compared with our previous study that r/r B-ALL patients achieved CR with CART then bridge to allo-HSCT without prior PD-1 treatment (Zhang Y, et al. Br J of Haematol. 2020;189:146-52). Two cases had chronic GVHD. No severe hemorrhagic cystitis and other infections were found. Three patients relapsed at 3, 5, 6 months and died from relapse at 10, 12, 12 months after HSCT. One patient died from severe aGVHD and transplant-associated thrombotic microangiopathy (TA-TMA) at 4 months post-transplant. One patient has been surviving free of disease.
Summary/Conclusion: Our preliminary clinical results has shown that PD-1 inhibitor significantly increases the incidence and severity of aGVHD after allo-HSCT in pediatric r/r B-ALL patients who obtained CR with CART. Severe hyper-acute GVHD has been seen that needs to use multiply immunosuppressants timely to prevent from multi-organ failure via cytokine storm. It suggests that PD-1 inhibitor should be avoided as possible if allo-HSCT is scheduled later.

Stem cell transplantation - Experimental

EP1295 HUC-MSC-EVS-ATO REDUCES ACUTE GVHD VIA RESETTING INFLAMMATORY MACROPHAGES TOWARD M2 PHENOTYPE THAT IS MEDIATED BY AUTOPHAGY

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Background: Acute graft-versus-host disease (aGVHD), a serious complication, frequently occurs following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) are considered promising candidates for treating GVHD, primarily due to their immunomodulation ability and safety. Recently, EVs have been exploited for delivery of exogenous therapeutic agents and internalized by macrophages, leading to a switch from the M1 to M2 phenotype (Mol Ther. 2010; Stem Cells Transl Med. 2017). Arsenic trioxide (As_2O_3), a promising regent for dysregulated immune diseases. In our previous study, we found that As_2O_3 prolonged the survival of aGVHD mice by polarizing macrophages toward the M2 status (Sci China Life Sci. 2020). Autophagy is a conserved cellular degradation pathway that maintains intracellular homeostasis. It has been elucidated that downregulation of autophagy levels limits repolarization of M2 to M1 (Nat Rev Immunol.2019). Based on this knowledge, herein, we hypothesized that EVs loaded with As_2O_3 could reset the M1 to M2 phenotype through autophagy for a greater therapeutic response against aGVHD.
Aims: To investigate the therapeutic effect of hUC-MSC-EVs-ATO in aGVHD mouse model and explore the immune mechanism of hUC-MSC-EVs-ATO in vivo and vitro.
Methods: hUC-MSC-EVs-ATO was injected intravenouslly at the onset of the murine aGVHD model. Moreover, we administered clodronate liposomes by intraperitoneal injection to deplete mouse macrophages before using hUC-MSC-EVs-ATO. We also established a murine GVL model with supplementation of A20 leukemia cells. At the experimental endpoint, mice were sacrificed, and target organs were extracted to analyses the phenotypic alterations in macrophages by enzyme-linked immunosorbent assay, flow cytometry, and immunohistochemistry. Finally, mTOR, p-mTOR, p62, LC3-I and LC3-II in BMDM-M1 and RAW264.7-M1 cells with or without hUC-MSC-EVs-ATO treatment were analyzed by western blot, and autophagic vacuoles were observed by electron microscopy.
Results: The severity and histological score of aGVHD were significantly reduced in response to hUC-MSC-EVs-ATO treatment. Mice receiving hUC-MSC-EVs-ATO exhibited longer lives compared to control mice. hUC-MSC-EVs-ATO reduced the number of Th1 and Th17 cells, while anti-inflammatory M2 and Treg cells were increased in aGVHD target organs liver and spleen. Notably, depletion of macrophages blocked these therapeutic effects and the effects on T-cells by hUC-MSC-EVs-ATO. In vitro, hUC-MSC-EVs-ATO repolarized inflammatory M1 macrophages to the anti-inflammatory M2 phenotype in both LPS/IFN-γ-conditioned bone marrow-derived and RAW264.7 macrophages. Furthermore, we demonstrated that hUC-MSC-EVs-ATO repolarized M2 to M1 macrophages partly through induction of autophagic flux by suppressing mammalian target of rapamycin (mTOR) activity. The mTOR signaling pathway activator MHY1485 reduced autophagy and repolarized M1 to M2 macrophages. Specifically, using murine model graft-versus-leukemia effects (GVL), we show here that treatment not only reduces aGVHD but also preserves GVL.
Summary/Conclusion: hUC-MSC-EVs-ATO alleviated aGVHD by switching the M1 phenotype to the M2 phenotype through inducing autophagy. Our findings demonstrate that hUC-MSC-EVs-ATO represents a potential therapeutic agent against GVHD, while preserving GVL activity.

EP1296 MICRORNA SERUM PROFILES AND CHRONIC GRAFT VERSUS HOST DISEASE FOR PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Chronic graft versus host disease (cGVHD) is the most common long-term complication of allogenic hematopoietic stem cell transplantation (allo-HSCT), associated with increased mortality, high disease burden and significant reduced quality of life for patients. The pathophysiology behind the disease is complex and insufficiently understood. The last decade has brought interest to single stranded noncoding RNA molecules; microRNAs (miRNAs), as important components in the pathophysiological process of cGVHD. However, their role in development of cGVHD and the possibilities of utilizing them as biomarkers are mainly unknown.
Aims: The objectives of this study were to investigate a broad specter of serum miRNAs from allografted patients and investigate associations between individual miRNAs and miRNA profiles, and cGVHD and their use as potential biomarkers for patients with cGVHD.
Methods: The study included 79 consecutively allotransplanted adults, 46 men and 33 women with median age of 49 years (range 15-71 years). Patients were transplanted with peripheral blood stem cells (PBSCs) derived from human leukocyte antigen (HLA)-matched family donors. Serum samples were obtained one year after the allo-HSCT, and stored under standard procedures before serum miRNA-seq analysis was performed using QIAGEN CLC Genomics Server v20.0.4 for all 79 patients.
Results: 50 of the 79 patients (63%) had signs of cGVHD at the one-year post-allo-HSCT control. The affected organ systems were; liver/bile duct (n=26), skin (n=22), gastrointestinal tract (n=21), eyes (n=21), mouth (n=17), lungs (n=3), urogenital tract (n=3), and musculoskeletal (n=1). miRNA-seq analysis revealed 1380 different miRNAs detected for at least one patient, while 233 miRNAs (17%) were detected in more than 70 patients. After corrections for age and by searching for discriminative miRNAs, we identified 29 microRNAs that differed significantly between patients with and without cGVHD (p-values <0.02), and 21 of these 29 miRNAs were detected for ≥ 70 of the patients. Among these 21 miRNAs, 12 were in particular differentially expressed (p-values <0.007). The results indicate that the difference in serum miRNA profiles between the two groups was considerable, and cGVHD appeared to have a profound impact on circulating miRNAs. Furthermore, five distinct miRNAs;

miR-365-3p, miR-148-3p, miR-122-3p, miR-378-3p, and miR-192-5p, were found to be highly associated with cGVHD in our analysis, and validated by receiver operating characteristics (ROC) analysis. Based on these five miRNAs, we developed a miRNA signature which by bioinformatic approaches and linear regression model utterly improved our prediction model for cGVHD. Finally, literature reviews support the association between individual microRNAs and cGVHD and inflammation.
Summary/Conclusion: To conclude, the present miRNA profiling study was conducted to identify serum miRNA signatures associated with cGVHD, and our observations suggest that cGVHD is associated with significant and profound alterations in miRNA serum profiles. We conclude that miRNAs are differently expressed among patients with and without cGVHD, although further and larger studies are needed to validate our present findings and investigate the potential diagnostic and prognostic impact of circulating miRNAs among allo-HSCT recipients.

EP1297 TRANSCRIPTOME ANALYSIS OF HAEMATOPOIETIC STEM CELLS AFTER MOBILIZATION WITH CYTARABINE AND CYCLOPHOSPHAMIDE

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Background: High dose chemotherapy with melphalan 200mg/m2 followed by autologous haematopoietic stem cell transplantation (ASCT) represents a standard of care for patients with multiple myeloma. Most transplant centers use for mobilization combination of cyclophosphamide (Cy) and granulocyte-colony stimulating factor (G-CSF). Recently our group and others demonstrated that alternative mobilization regimen with cytarabine (AraC), is safe and more effective (more than 2 times higher median of CD34+ yield) (Jelinek et al., 2018). The exact mechanism why is AraC more effective than Cy is largely unknown. To shed light into these processes we have performed transcriptome analysis of sorted haematopoietic stem cells after mobilization with AraC and Cy from apheresis product.
Aims: To find differences in transcriptome of haematiopoietic stem cells after mobilization with Cy or AraC in patients with newly diagnosed multiple myeloma.
Methods: Sorted CD34+ haematopoietic stem cells (HSCs) from 14 MM patients were used for the analysis. Nine patients were mobilized with cytarabine (AraC 400 mg/m2/12h day 1-2 followed by G-CSF) and 5 patients with cyclophosphamide (Cy 2,5 g/m2 day 1 followed by G-CSF). CD34+ HSCs were sorted from 1ml of apheresis product using FACS Arria III. RNA libraries were prepared using SMARTer Stranded Total RNA-Seq Kit v2 and sequenced aiming at 30 Mbp per sample. Raw reads were trimmed with TrimGalore. rRNA reads were filtered by sortmerna and the rest mapped and quantified by Salmon. Differential gene expression was evaluated using Deseq2.
Results: We have identified 190 significantly deregulated genes with more than 2 fold-change between groups of haematopoietic stem cell (HSC) samples mobilized by AraC or Cy. Unsupervised clustering showed distinct cluster including 3 Cy samples and second cluster with all AraC and 2 Cy samples. Pathway analysis of 171 down-regulated genes in AraC samples revealed immune system Gene Ontology term or chemokine signaling and osteoclast differentiation among the most deregulated KEGG categories. Besides, down-regulation of integrins (ITGB3, ITGAM, ITGA7) and chemokine receptors and ligands (CXCR2, CXCL16, CCR2, CCR1) suggest decreased cell homing in AraC group, however, the expression of some of the main homing molecules was not altered. E.g. CXCR4 was not markedly downregulated (FDR 0,09), chemokine ligand CXCL12 was not expressed at all. Among the top downregulated genes in AraC group was PAX5 transcription factor, which is responsible for the differentiation of B-cell lineage, though the level of expression of this gene was relatively low in both groups. We detected several histone genes to be upregulated in AraC group as well as multiple long non-coding RNAs including lncRNA for PSMF1 coding antisense RNA for the immunoproteasome inhibitor hP131 subunit suggesting potential upregulation of immunoproteasome in AraC group.
Summary/Conclusion: Our analysis focuses, for the first time, on the alteration of transcriptome after application of different mobilization agents (AraC and Cy) on HSC. Down-regulation of a number of genes involved in homing could explain increased mobilization efficacy after AraC regimen. On the other hand, pathways important for the haematopoietic stem cell function and metabolism were not deregulated and also their potential to differentiate into mature cell types was not significantly altered. The role of several long non-coding RNAs elevated in AraC group needs to be elucidated.

EP1298 EXPLOITING THE HEMATOPOIETIC SUPPORTIVE ACTIVITY OF MESENCHYMAL STROMAL CELLS TO IMPROVE THE TRANSPLANTATION OUTCOME OF GENE-EDITED HSPCS.

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Background: Hematopoietic Stem and Progenitor Cells (HSPCs) reside in a specialized microenvironment in the bone marrow (BM), named the hematopoietic niche. Mesenchymal Stromal Cells (MSCs) are key elements of the BM niche, regulating HSPC function by direct contact and through the release of paracrine factors. Due to these properties, MSCs have been employed *in vitro* to support HSPC expansion, and *in-vivo* to promote HSPC engraftment and hematopoietic reconstitution in preclinical models and clinical trials of HSPC transplantation (HSCT).
Aims: Based on these studies, in our work we aimed to improve the outcome of HSCT with CRISPR-Cas9 gene-edited (GE)-HSPCs, whose efficiency equires further advancement to fully exploit its therapeutic potential. Indeed, GE-HSPCs activate a DNA damage cascade in response to nuclease-induced double strand break and delivery of DNA repair template, which constrains HSPC proliferation and long-term repopulating capacity.
Methods: To this aim, we developed a novel MSC-based *in-vitro* approach to expand and recover GE-HSPCs. We analyzed the GE-HSPC phenotype by flow cytometry and the activation of a DNA stress response in GE-HSPCs by immunohistochemistry. We further evaluated the cell-cycle state, the level of inflammation and apoptosis by flow-cytometry and gene expression analysis. The fitness of HSPCs gene-editd according to standard procedures were compared to HSPCs gene-edited in the presence of MSCs (+MSCs). Preclinical mouse models of HSCT were used to prove the superior capability of GE-HSPCs + MSCs to long-term engraft and favor hematological reconstitution.
Results: We show that MSCs produced several hematopoietic supportive and anti-inflammatory factors, capable to reduce the proliferation arrest, and mitigate the apoptotic and inflammatory programs activated in GE-HSPCs, ultimately improving GE-HSPC expansion and clonogenic potential. This resulted into a superior GE-HSPC engraftment and hematological reconstitution in transplanted mice. Moreover, we demonstrated that MSCs favored the engraftment of limited doses of GE-HSPCs when co-transplanted *in vivo*.
Summary/Conclusion: In conclusion, our work poses the basis for the clinical use of MSCs as a novel, safe and efficient strategy to preserve the long-term repopulating capacity and promote engraftment of CRISPR-Cas9 gene corrected HSPCs.

EP1299 EFFECT OF CD34+ DERIVED MICROPARTICLES ON THE CLONOGENIC POTENTIAL OF MONONUCLEAR CELLS FROM CORD BLOOD

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Background: Umbilical cord blood is a source of hematopoietic stem cell (HSC) and is used in hematopoietic cell transplantation. The HSC

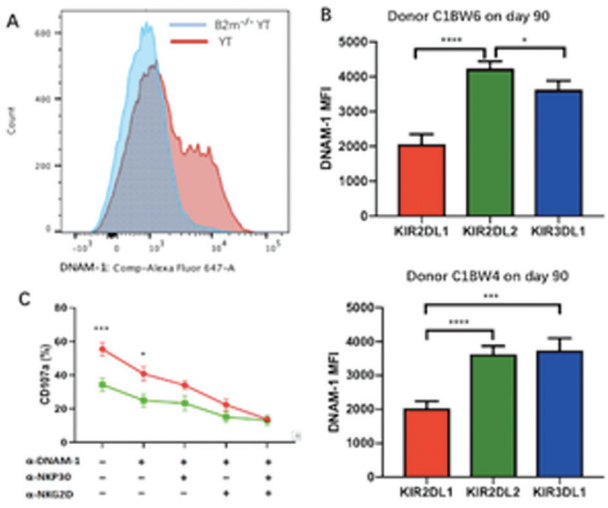
engraft in the bone marrow and differentiate to progenitor and mature blood cells. The dynamic of the HSC can be evaluated by hematopoietic colony-forming unit (CFU) assays using methylcellulose-based medium. From the plasma membrane of hematopoietic cells, like other cells, extracellular vesicles of 0.1–1μm in size germinate, called microparticles (MPs). MPs can affect normal cell functions. Our previous study showed that there are MPs derived from hematopoietic stem cells in umbilical cord blood and they carry the surface antigen CD34+ (CD34+ MPs).
Aims: The objective of this study was to analyze the role of CD34+MPs in the differentiation program of hematopoietic progenitor cells.
Methods: Umbilical cord blood units (UCB) were collected after informed consent. The low volume units were used in this study, as not appropriate for transplantation. CD34+MPs were isolated from the plasma of UCBs by centrifugation and purified using magnetic bead based technology (Miltenyi Biotec). Their number was estimated by flow cytometry using CD34-PE and Annexin V-FITC Abs. Mononuclear cells (MNCs) were isolated from UCB by ficoll density centrifugation. MNCs were cultured in liquid culture without growth factors for 24 hours with or without CD34+MPs. Furthermore, MNCs cultured in liquid culture without growth factors for 1 or 24 hours with or without CD34+MPs and then were seeded in semisolid cultures in the presence of a cocktail of growth factors for colony-forming unit-granulocyte/macrophage (CFU-GM), erythroid burst-forming units (BFU-E), colony-forming unit-granulocyte, erythrocyte, macrophage, megakaryocyte (CFU-GEMM) colony growth.
Results: The number of MNCs cultured in the presence of CD34+MPs was reduced by 15.1% compared to mononuclear cells cultured in the absence of CD34+MPs (Control) in liquid cultures of 24 hrs. In order to analyze the effect of CD34+MPs in the differentiation and proliferation of hematopoietic cells, CFU assays were performed. First MNCs were incubated for 1 hr or 24 hrs with 500, 1000 and 2000 CD34+MPs and then were seeded in semisolid culture. CFU colony numbers were decreased by 21,7% and 70,2% respectively when MNCs co-incubated for 1h with 1000 and 2000 CD34+MPs. When MNCs were incubated for 24 hrs with 500 CD34+MPs, the number of CFU colonies was increased by 26,6%, while co-incubation with 2000 CD34+MPs decreased the number by 44,2%. Furthermore, comparison between 1 and 24 hrs incubation of MNCs with CD34+MPs in liquid culture before plating in semisolid medium has shown, an increase by 77,87% and 32,8% in CFU-GEMM and CFU-GM respectively in the presence of 500 CD34+MPs while CFU-GEMM and CFU-GM colonies decreased by 11,88% and 27,3% with 1000 CD34+MPs and 73,8 and 53,1% with 2000 CD34+MPs respectively.
Summary/Conclusion: In this study we have evaluated the negative effect of CD34+MPs in the viability of MNC from cord blood. CD34+MPs were associated with CFU growth in a dose- and time- dependent manner. Low number of CD34+MPs acts beneficially for CFU viability whereas the high number of CD34+MPs decreases the number of CFU-GM and CFU-GEMM.

EP1300 COSTIMULATORY MOLECULE DNAM-1 EXPRESSION ON NK CELLS IS DETERMINED BY HLA AND CORRELATED WITH NK CELL EDUCATION POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: NK cell education is a fateful process to acquire strong responsibility through inhibitory receptors bound with MHC-I on autologous cells during NK cell development. DNAM-1 (DNAX accessory molecule-1, CD226) is a costimulatory molecule expressed by NK cells and CD8+ T cells. Interaction between DNAM-1 and its ligands on target cells triggers cell-mediated cytotoxicity and cytokine production. Previous studies illuminated the expression of DNAM-1 on NK cells was associated with inhibitory receptors KIR/NKG2A. Our previous studies have demonstrated that when both donors and recipients present all the KIR ligands for donor KIRs, reconstituted NK cells would achieve better functional education in patients post allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the mechanism that regulates DNAM-1 expression is unclear.
Aims: To explore the regulation of MHC-I on DNAM-1 expression using YT cell lines. And to investigate the influence of donor and recipient HLA on DNAM-1 expression during NK cell reconstitution and education based on the setting of allo-HSCT.
Methods: Firstly, we used crispr-cas9 to knock out HLA-I on YT cell line to study the effect of MHC-I to DNAM-1 expression. Then, we investigated the correlation of DNAM-1 expression and NK cell education during a dynamic reconstitute state in patients who had acute leukemia and underwent allo-HSCT at days 30, 90 and 180 post-HSCT. And further analyzed the relationship of donor, recipients and both HLA with DNAM-1 expression. Finally, we blocked DNAM-1 in vitro to explore whether DNAM-1 expression determined educated NK stronger function.
Results: 1. $B2m^{-/-}$ YT cells, which had lower surface HLA-I expression, showed obviously decreased DNAM-1 expression.
2. In patients post allo-HSCT, educated NK cells displayed higher DNAM-1 expression than uneducated NK cells considering no matter donors, recipients or both HLA genotypes. DNAM-1 expression on sole-recipient HLA educated NK cells was higher than sole-donor HLA educated NK cells, indicating that recipients affected more than donors for NK education. Therefore, there was a close correlation of DNAM-1 expressions and NK education post transplantation.
3. DNAM-1 expression was positively related with inhibitory KIR/NKG2A numbers when patients presented all HLA(C1C2BW4) post-HSCT.
4. Only when DNAM-1, NKp30 and NKG2D receptors were blocked simultaneously, the function of educated and uneducated NK cells would be decreased to a similar level. So, activating receptors could be synergistic with DNAM-1 to determine NK function.



Summary/Conclusion: Both the donor or/and recipient could regulate the expression of DNAM-1 through HLA-I for patients post-HSCT. DNAM-1 collaborating with NKP30 and NKG2D determined hyperresponsiveness of educated NK cells.

Thalassemias

EP1301 INTERIM RESULTS OF BETIBEGLOGENE AUTOTEMCEL GENE THERAPY IN PEDIATRIC PATIENTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA (TDT) TREATED IN THE PHASE 3 NORTHSTAR-2 AND NORTHSTAR-3 STUDIES.

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Background: Phase 3 studies evaluating betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy in patients with TDT, HGB-207 (non-β^0/β^0 genotypes; NCT02906202) and HGB-212 (β^0/β^0, $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$, $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$ genotypes; NCT03207009), demonstrated positive outcomes in adults.
Aims: Therefore, the studies were expanded to include patients <18 years of age. We report interim results in these pediatric patients.
Methods: Autologous CD34+ cells were transduced ex vivo with BB305 lentiviral vector to produce beti-cel. Patients underwent pharmacokinetic-adjusted busulfan-based myeloablation followed by beti-cel infusion. Transfusion independence (TI; weighted average hemoglobin [Hb] ≥9 g/dL without packed red blood cell transfusions for ≥12 months) was the HGB-207 and HGB-212 (as of protocol amendment dated Oct 8, 2020) primary endpoint. Data are presented as median (min–max).
Results: As of 30 November 2020, 27 pediatric patients were treated and followed for 23.1 (0.9–35.5) months, including 16 patients <12 years (HGB-207: n=8; HGB-212: n=8) and 11 patients ≥12–<18 years at assent (HGB-207: n=6; HGB-212: n=5). The youngest patients were 4 years of age (n=3). TI was achieved in 9/11 evaluable patients <12 years and 10/10 evaluable patients ≥12–<18 years. The median duration of ongoing TI was 19.5 (12.3–32.0) months. Pediatric patients achieved TI at a similar rate to adults (90.5% [19/21] vs 84.6% [11/13] in patients > 18 years).
Weighted average Hb during TI in patients <12 years and ≥12–<18 years was 10.0 (9.5–11.4) g/dL and 11.5 (9.6–13.0) g/dL, respectively. At last visit, gene therapy-derived HbA^{T87Q} levels in these patients were 8.4 (5.0–10.1) g/dL (n=9) and 9.1 (4.4–10.8) g/dL (n=10), respectively. These data are comparable to those recorded in patients ≥18 years who achieved TI; weighted average Hb was 12.6 (9.9 – 13.6) g/dL and HbA^{T87Q} at last visit was 9.9 (6.3 – 13.4) g/dL (n=11). The median nadir lymphocytes within the first month post-infusion for patients <18 years was 0.48 x10^9/L (min – max: 0.02 – 1.7 x10^9/L) (n=27).
Non-hematologic ≥ Grade 3 adverse events in ≥3 patients <18 years were stomatitis (n=14), febrile neutropenia (n=13), epistaxis (n=6), decreased appetite (n=5), increased alanine aminotransferase (n=3), hypoxia (n=3), and pyrexia (n=3). Grade 4 veno-occlusive liver disease occurred in 2 patients ≥12–<18 years and one grade 2 event occurred in a patient <12 years; all events resolved after treatment with defibrotide. Drug-product related AEs as per investigators opinion were reported in 2 patients < 12 years of age (thrombocytopenia, tachycardia) and 2 patients 12-18 years of age (abdominal pain (2)). No replication-competent lentivirus was reported. All patients had polyclonal vector integration; no integration site contributed >3% of all integration sites at last assessment (n=22).

Table 1. Patient, drug product, engraftment characteristics (median [min–max])

		<12 years (N=16)	≥12–<18 years (N=11)
Age, years		8 (4–11)	15 (12–17)
Genotype	β^0/β^+	8 (50)	3 (27)
	β^0/β^0	6 (38)	4 (36)
	β^+/β^+	1 (6)	4 (36)
	β^E/β^0	1 (6)	0
Drug product			
Vector copies/diploid genome		2.9 (1.9–7.0)	3.3 (1.2–6.0)
Transduced cells, %		71 (34–94)	82 (34–90)
Cell dose, x 10^6 cells/kg		10.2 (6.1–42.1)	7.4 (5.0–19.4)
Neutrophil engraftment		26 (17–39)	26 (16–38)
Platelet engraftment		50 (13–94)*	50.0 (25–84)

*1 patient with <3 months follow-up had not yet achieved platelet engraftment.

Summary/Conclusion: Pediatric patients with diverse TDT genotypes achieved TI rates comparable to adults after beti-cel gene therapy, suggesting that beti-cel is a viable treatment option for patients with TDT of all ages. The treatment regimen had a safety profile consistent with busulfan myeloablation.

EP1302 TFR2-HAPLOINSUFFICIENCY IMPROVES THE PHENOTYPE IN A MURINE MODEL OF TRANSFUSION-DEPENDENT B-THALASSEMIA

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Background: β-thalassemia is a genetic disorder characterized by anemia, ineffective erythropoiesis and iron overload. Patients affected by the most severe form of the disease, transfusion-dependent thalassemia (TDT), require lifelong blood transfusion and an iron chelation therapy, symptomatic treatments that affect the quality of life. The only well-established curative therapy is allogenic bone marrow (BM) transplantation, but it is applicable only to a minority of patients because of the scarcity of suitable donors. Other recently approved treatments (i.e. gene therapy and luspatercept), despite promising, are only partially effective and/or suitable for selected patients. For these reasons, the identification of novel therapeutic approaches is a clinical need. We have already proved that the selective BM deletion of transferrin receptor 2 (TFR2), a partner of Erythropoietin receptor, improves erythropoiesis and ameliorates anemia in a non-transfusion-dependent thalassemia murine model, despite the persistence of the genetic defect (Artuso et al., *Blood* 2018; Casu, Pettinato et al., *Blood* 2020).
Aims: Here, we investigate whether *Tfr2* targeting might represent a therapeutic option for TDT.
Methods: TDT mice ($Hbb^{th1/th2}$) with BM *Tfr2* heterozygous deletion ($Tfr2^{BMhetero}/Hbb^{th1/th2}$) were generated by transplantation of fetal liver cells (FLT) harvested from day 14.5 $Tfr2^{+/-}/Hbb^{th1/th2}$ (or $Hbb^{th1/th2}$ as a control) embryos. Two x 10^6 fetal liver cells were retro-orbitally injected into lethally irradiated 8-week-old C57BL/6-Ly-5.1 wild-type male mice. Complete blood count was evaluated 8 and 12 weeks after FLT, when mice were sacrificed, before the onset of blood transfusion requirement. A full phenotypic analysis was performed to analyze the hematological parameters, erythropoiesis and the iron phenotype.
Results: Twelve weeks after FLT, chimerism was superior to 90% in all mice and the mortality rate was consistently higher among $Hbb^{th1/th2}$ than $Tfr2^{BMhetero}/Hbb^{th1/th2}$ mice (50% and 20%, respectively). BM *Tfr2* haploinsufficiency was sufficient to increase RBC count, Hb levels and hematocrit, despite the attenuation of the beneficial effect over time due to the worsening of anemia. *Tfr2* heterozygous deletion decreased the total amount of $Ter119^+$ cells and of polychromatic erythroblasts in the BM, showing a partial improvement of ineffective erythropoiesis. As expected, splenomegaly was not alleviated, while hepatic iron overload was reduced. Moreover, BM *Tfr2* haploinsufficiency partially corrected cardiomegaly, a secondary TDT complication caused by chronic anemia and iron overload, and attenuated the endoplasmic reticulum stress in the BM, preventing the activation of the unfolded protein response. However, whether this effect is directly due to the deletion of *Tfr2* or it

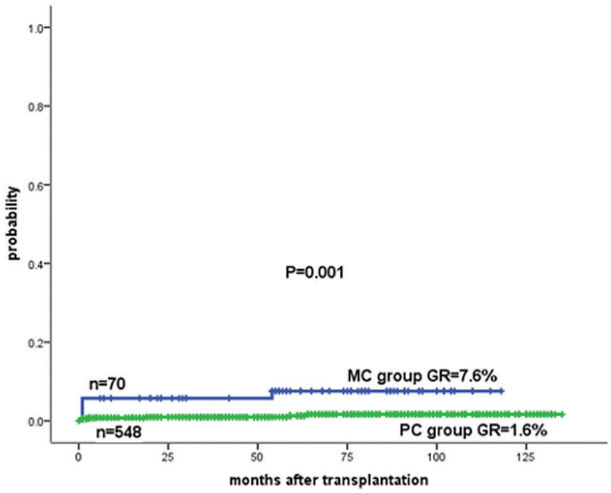
is an indirect consequence of the improved cell fitness is still unknown and worth to be assessed.
Summary/Conclusion: Overall our data show that *Tfr2* targeting might represent a valuable therapeutic option for the most severe form of β-thalassemia, ameliorating several features of the disease. However, the effect of full BM *Tfr2* inactivation, that we expect more efficient in correcting anemia and ineffective erythropoiesis, and the potential role of *Tfr2* deletion in the reduction of blood transfusion requirement, the standard treatment for TDT but correlated to several complications, remain to be evaluated.

EP1303 POSSIBLE CORRELATION OF MIXED CHIMERISM WITH POST-TRANSPLANT OUTCOME IN PATIENTS WITH B THALASSEMIA:RISK OF GRAFT FAILURE

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Background: Secondary graft failure (SGF) is a major obstacle in allogeneic hematopoietic stem cell transplantation for patients with thalassemia major (TM). However, the impact of the persisting mixed chimerism (MC) on transplant outcome remains controversial.
Aims: To assess risk factors of mixed chimerism and to evaluate possible correlations between mixed chimerism and transplantation outcomes.
Methods: A total of 618 patients with thalassemia major (TM) underwent allogeneic HSCT from December2008 until December 2019 were identified with median age of 6 years old (1-23) and median follow up time of 70 months(1-135), from HLA-identical sibling donors (SD) (n=212; 34.3%), unrelated donors (UD, n=313; 50.6%),sibling Cord blood(CB, n=49,7.9%)and parent donors (PD, n=44,7.1%). Source of graft were 538 (87.1%) from peripheral stem cells, 32(5.2%) from bone marrow and 48(7.8%)from sibling cord blood. Cy+Bu+Flu+TT+ATG conditioning regimen was used in 416 pts while a reduced conditioning regimen Cy+Bu+Flu+ATG was used for 167pts and Cy+Bu+Flu for the other 35 pts.
Results: Overall Survival (OS), Thalassemia-Free survival (TFS), Transplantation-related mortality (TRM) and graft rejection (GR) for the entire group were 94.8%, 92.7%,5.2% and 2.4% respectively. MC was presented in 70 pts, with median present time 4 months (1-59 months). The cumulative incidence MC was 12.4%.
No significant difference was observed in OS and Thalassemia-Free survival (TFS) between MC and full donor chimerism (FC) pts. The cumulative probability of OS, TFS between MC pts and FC pts was 97.1% vs. 94.4% (P=0.343) and 89.6% vs. 93.2% (P=0.272),respectively. However, the incidence of MC was significantly associated with the development of graft failure/rejection. Graft failure occurred in 5 pts in the MC group vs.7 pts in the FC group, the corresponding incidence were 7.6% vs. 1.6 % respectively. (P =0.001, Figure).
Acute GVHD incidence was much lower in MC pts than in FC pts (2.9% vs. 12.7%, P=0.022,), whereas MC pts had significantly higher chronic GVHD(16.8% vs. 4.2%, P=0.000).MC was associated with an increased risk of chronic GVHD, mostly were DLI derived
Patients receiving stem cells from cord blood of matched sibling donors had a high risk of MC.MC incidence of stem cell source from peripheral blood(PB), bone marrow(BM), cord blood (CB)were 10.6%, 10%, 34.2% respectively.(P=0.000).Unrelated donors had a lower risk of MC than sibling donors. Incidence of MC from unrelated donors was 9.5% vs. 16.1% from sibling donors (P=0.007).
Intravenous Thiotepa (TT) in combination with Busulfan (Bu), cyclophosphamide (Cy) anti-thymocyte globulin (ATG) on HSCT could reduce the risk of MC. The corresponding incidence of MC in Cy+Bu+Flu+TT+ATG, Cy+Bu+Flu+ATG, Cy+Bu+Flu conditioning regimen were 9.2%,15.9%,40.9% resepectively(P=0.000).
There was also a significant difference in chimerism based on donor-recipient gender pairing (P = 0.041): male grafts into male patients having the greatest risk of MC and female grafts into female patients having the least. Patients who under 9 years old had a higher risk of MC than that of pts>9 years old (P=0.018).



Summary/Conclusion: Our results show that patients who presented mixed chimerism showed a similar post-transplant outcome in OS and TFS but was associated with higher risk of graft failue.Patients receiving stem cells from CB had a high risk of MC than from PBSC. Reduced nonmyeloablative approach capable of achieving allogeneic mixed hematopoietic chimerism. Our data suggests that Cy+Bu+Flu+TT+ATG is a preferred conditioning regimenfor TM patients could reduce the risk of mixed chimerism.

EP1304 FEWER RED BLOOD CELL TRANSFUSION UNITS AND VISITS ACROSS BASELINE TRANSFUSION BURDEN LEVELS IN PATIENTS WITH BETA-THALASSEMIA TREATED WITH LUSPATERCEPT IN THE PHASE 3 BELIEVE TRIAL

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Background: β-thalassemia is a genetic blood disorder marked by ineffective erythropoiesis and anemia. The first-in-class erythroid maturation agent, luspatercept, enhances late-stage erythroid hematopoiesis. Luspatercept was shown to be effective in reducing red blood cell (RBC) transfusion burden (TB) in adult patients (pts) with β-thalassemia requiring regular RBC transfusions in the phase 3, double-blind, randomized, placebo-controlled BELIEVE trial (NCT02604433). The effect of luspatercept treatment on RBC TB warrants further investigation.
Aims: To assess the mean cumulative number of RBC transfusion visits and units across baseline (BL) low, medium, and high TB levels among pts with β-thalassemia in the BELIEVE trial.
Methods: Eligible pts were aged ≥18 years with β-thalassemia or hemoglobin (Hb) E/β-thalassemia (compound β-thalassemia mutation and/or multiplication of α-globin genes was allowed) and required regular RBC transfusions (defined as 6–20 RBC units in the 24 weeks (wks) prior to randomization with no transfusion-free period >35 days). Pts were randomized 2:1 to luspatercept 1.0 mg/kg (up to 1.25 mg/kg allowed) or placebo subcutaneously every 3 wks for 48 wks during the double-blind period. After study unblinding, pts randomized to placebo were eligible to cross over to receive luspatercept in an open-label phase.

Luspatercept responders (n = 47; 21%) were defined as pts who achieved the primary endpoint of RBC TB reduction of ≥33% during Wks 13–24 from BL (≥2 RBC units). BL low, medium, and high TB were defined as receipt of ≤10, >10–≤15, and >15 RBC units/24 wks, respectively. The mean cumulative number of RBC transfusion units and visits was assessed per pt in luspatercept responders and placebo-treated pts up to Wk 48, and in luspatercept responders and non-responders up to Wk 120, excluding pts who crossed over from placebo. Cumulative mean numbers of RBC transfusion units and visits were estimated using the Nelson-Aalen nonparametric estimator with robust variance estimate. The data cutoff was July 1, 2019.

Results: Luspatercept responders had fewer RBC units transfused vs placebo up to Wk 48 and vs luspatercept non-responders up to Wk 120, across BL TB levels (Table). Up to Wk 120, the mean cumulative number (95% confidence interval [CI]) of RBC units transfused per pt for luspatercept responders vs non-responders was 15.2 (9.0–25.5) vs 34.5 (30.6–38.8) for low BL TB, 37.8 (33.1–43.3) vs 53.2 (50.6–55.9) for medium BL TB, and 56.4 (50.0–63.6) vs 71.1 (67.3–75.1) for high BL TB.

Luspatercept responders also had fewer RBC transfusion visits vs placebo up to Wk 48 and vs luspatercept non-responders up to Wk 120, regardless of TB at BL (Table). Up to Wk 120, the mean cumulative number (95% CI) of RBC transfusion visits per pt for luspatercept responders vs non-responders was 13.5 (7.9–23.1) and 29.6 (26.5–33.0) for low BL TB, 28.3 (24.6–32.4) and 33.8 (32.1–35.6) for medium BL TB, and 35.1 (31.6–38.9) and 35.9 (34.0–37.9.) for high BL TB.

Table. Mean cumulative number of RBCT units and visits per pt for luspatercept responders, luspatercept non-responders, and placebo-treated pts across BL TB levels

Low BL TB[a]	Mean RBCT units per pt (95% CI)			Mean RBCT visits per pt (95% CI)		
	Responders[b]	Non-responders	Placebo	Responders[b]	Non-responders	Placebo
Up to Wk 48	n = 9	n = 22	n = 14	n = 9	n = 22	n = 14
	7 (4.3–11.5)	14.8 (13.0–16.9)	18.9 (16.4-21.7)	6.1 (3.7–10.1)	12.4 (11.2–13.6)	15.0 (13.2–17.0)
Up to Wk 120	n = 6	n = 12	n = 0	n = 6	n = 12	n = 0
	15.2 (9.0–25.5)	34.5 (30.6–38.8)		13.5 (7.9–23.1)	29.6 (26.5–33.0)	
Medium BL TB[a]	**Mean RBCT units per pt (95% CI)**			**Mean RBCT visits per pt (95% CI)**		
	Responders[b]	Non-responders	Placebo	Responders[b]	Non-responders	Placebo
Up to Wk 48	n = 21	n = 68	n = 39	n = 21	n = 68	n = 39
	17.4 (15.5–19.5)	23.6 (22.6–24.7)	27.5 (26.0–29.0)	12.9 (11.5–14.6)	14.6 (13.9–15.3)	14.3 (13.4–15.2)
Up to Wk 120	n = 12	n = 32	n = 0	n = 12	n = 32	n = 0
	37.8 (33.1–43.3)	53.2 (50.6–55.9)		28.3 (24.6–32.4)	33.8 (32.1–35.6)	
High BL TB[a]	**Mean RBCT units per pt (95% CI)**			**Mean RBCT visits per pt (95% CI)**		
	Responders[b]	Non-responders	Placebo	Responders[b]	Non-responders	Placebo
Up to Wk 48	n = 16	n = 65	n = 43	n = 16	n = 65	n = 43
	22.8 (20.2–25.8)	31.1 (29.5–32.7)	34.8 (33.3–36.4)	14.1 (12.6–15.8)	15.4 (14.6–16.3)	16.6 (15.6–17.7)
Up to Wk 120	n = 13	n = 29	n= 0	n = 13	n = 29	n = 0
	56.4 (50.0–63.6)	71.1 (67.3–75.1)		35.1 (31.6–38.9)	35.9 (34.0–37.9)	

[a]BL low, medium, and high TB were defined as receipt of ≤10, >10–≤15, and >15 RBC units/24 wks, respectively; [b]Luspatercept responders were defined as patients who achieved an RBC TB reduction of ≥33% during Wks 13–24 from BL (≥2 RBC units).
BL, baseline; CI, confidence interval; patients, pts; RBC, red blood cell; RBCT, RBC transfusion; TB, transfusion burden; wk, week.

Summary/Conclusion: These findings show that luspatercept responders in the BELIEVE trial had reduced numbers of RBC units transfused and transfusion visits over 120 wks, regardless of BL TB. The observed reduction in TB in pts with β-thalassemia treated with luspatercept may have a positive impact on clinical and economic outcomes.

EP1305 LONG-TERM EFFICACY AND SAFETY OUTCOMES IN THE PHASE 2 STUDY OF LUSPATERCEPT IN B-THALASSEMIA

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Background: β-thalassemia is a hereditary anemia characterized by ineffective erythropoiesis. Luspatercept binds to selected TGF-β superfamily ligands, reducing aberrant Smad2/3 signaling and promoting late-stage erythroid maturation. Luspatercept is approved by the EMA and FDA for the treatment of adult patients (pts) with transfusion-dependent (TD) β-thalassemia. In a phase 2 study in pts with either TD or non-transfusion dependent (NTD) β-thalassemia, luspatercept increased hemoglobin (Hb) levels in NTD pts, reduced transfusion burden in TD pts, was well tolerated (Piga et al., *Blood* 2019;133(12):1279–89), and allowed the design of a 5-yr extension study.

Aims: To evaluate long-term efficacy and safety in pts enrolled in the phase 2 open-label study of luspatercept in β-thalassemia.

Methods: Eligible pts were ≥18 yrs old and either NTD (<4 red blood cell [RBC] U/8 wks prior to first dose with baseline Hb <10 g/dL) or TD (≥4 RBC U/8 wks prior to first dose, confirmed over 6 months). Pts received luspatercept for up to 3 months in the base study (NCT01749540); pts were then eligible for treatment for up to 5 additional yrs in the extension study at a starting dose of 0.8 mg/kg (with dose titration up to 1.25 mg/kg) every 3 wks subcutaneously (NCT02268409).

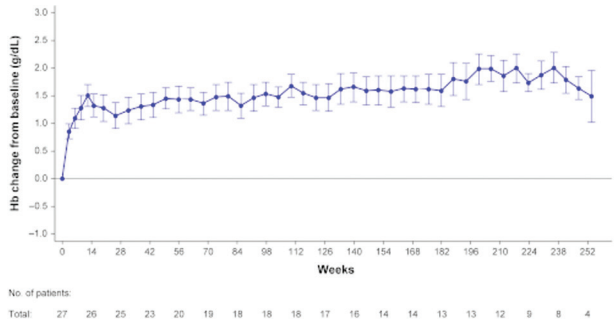
Results: As of 18 June 2020, 51 (80%) of the 64 pts from the base study continued onto the extension study. Of the 51 pts, 27 were NTD and 24 TD; median (range) age was 37 (22–62) yrs; 62.7% had prior splenectomy. For NTD pts, at baseline, median (range) Hb was 8.65 (7.6–9.8) g/dL; mean (SD) serum ferritin was 635.1 (387.3) µg/L. For TD pts, at baseline, median (range) transfusion burden was 8 (4–15) U/12 wks; mean (SD) serum ferritin was 1011.6 (795.5) µg/L.

Of the 27 NTD pts, 21 (78%) achieved a mean Hb increase ≥1.0 g/dL, and 17 (63%) achieved a mean Hb increase ≥1.5 g/dL over any 12 wks vs baseline. Mean Hb increase in NTD pts exceeded 1.0 g/dL by Wk 6 and was sustained throughout the extension study (Figure); mean (SD) duration of consecutive 12-wk periods of response was 1147.0 (637.5) days. Improvement in FACIT-Fatigue score in NTD pts correlated with change in Hb level at Wk 24 (r=0.71, *P*=0.0015). Improvement in 6-minute walk distance in NTD pts trended with change in Hb level at Wk 48 (r=0.64, *P*=0.0658).

Of the 24 TD pts, 20 (83%) achieved a ≥33% reduction in transfusion burden over any 12-wk interval vs baseline; mean (SD) duration of consecutive 12-wk periods of response was 462.5 (579.9) days. 12/24 (50%) TD pts achieved ≥33% reduction in transfusion burden over a fixed 12-wk interval (Wks 13–24) compared to baseline, and 8/24 (33%) responded during Wks 37–48. There was a trend for decreased mean serum ferritin levels from baseline for NTD and TD pts treated in the extension study which was maintained at Wk 252 (4.8 yrs after start).

Luspatercept had a tolerable safety profile across all pts in the extension study; 1 (2%) pt experienced a serious adverse event (AE) related to study drug (grade 3 biliary colic) and 5 (10%) pts experienced treatment-emergent AEs leading to study discontinuation (1 pt each: hemolytic anemia, musculoskeletal cerebrovascular accident, paresthesia, priapism, and pulmonary embolism).

Figure 1. Mean change in Hb level from baseline for NTD pts treated in the extension study (N=27). Error bars represent standard deviation.



Summary/Conclusion: In this assessment of longer-term outcomes in pts with β-thalassemia, luspatercept treatment was associated with sustained increases in Hb levels in NTD pts, and sustained decreases in transfusion burden in TD pts. There was a trend for a decrease in mean serum ferritin levels in NTD and TD pts. Luspatercept was associated with a tolerable safety profile over the extended observation period.

EP1306 BENEFIT OF CONTINUING THERAPY WITH LUSPATERCEPT IN PATIENTS WITH BETA-THALASSEMIA WHO DO NOT ACHIEVE ≥33% REDUCTION IN RED BLOOD CELL (RBC) TRANSFUSION BURDEN (TB) IN WEEKS 13–24 IN THE BELIEVE TRIAL

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Background: β-thalassemia is characterized by anemia and ineffective erythropoiesis. Appropriate schemes of RBC transfusions (RBCT) are the backbone of effective anemia treatment, but at the cost of progressive iron overload and iron-related complications. In the BELIEVE trial (NCT02604433), a phase 3, double-blind, multicenter, placebo-controlled study, the safety and efficacy of luspatercept, a first-in-class erythroid maturation agent, was evaluated in adult patients (pts) with β-thalassemia receiving RBCT. Luspatercept significantly reduced TB vs placebo (primary endpoint ≥33% reduction in RBCT in Weeks (Wks) 13–24 from baseline [≥2 RBC units]). As per protocol, pts that did not fully achieve the primary endpoint were defined as non-responders. In this group, the potential clinical benefit of treatment continuation with luspatercept has not yet been explored.
Aims: To evaluate the treatment benefit of continuing luspatercept therapy in pts who did not achieve the primary endpoint.
Methods: The BELIEVE trial enrolled pts aged ≥18 years with β-thalassemia or hemoglobin (Hb) E/β-thalassemia (including compound β-thalassemia mutation and/or multiplication of α-globin genes was allowed) and required regular RBCT (6–20 RBC units in the 24 wks prior to randomization, no RBCT-free period >35 days). Pts were randomized 2:1 to luspatercept 1.0 mg/kg (up to 1.25 mg/kg allowed) or placebo subcutaneously every 3 wks for 48 wks during the double-blind period. Pts in both treatment arms continued to receive best supportive care, including RBCT to maintain target Hb levels and iron chelation therapy adjusted to iron overload level. In this analysis, pts who did not achieve the primary endpoint during Wks 13–24 were followed until Wk 48. The data cutoff for this analysis was July 1, 2019.
Results: Of 224 pts who received luspatercept, 177 (79%) did not fully achieve the primary endpoint and were defined as non-responders. Of 163 luspatercept non-responders who continued treatment in Wks 25–48, 112 (68.7%) achieved a subsequent reduction in RBCT units from baseline vs 26/97 (26.8%) pts in the placebo arm (Table). For RBC units transfused, luspatercept non-responders had a mean change from baseline of –1.85 RBC units/24 wks vs +0.21 RBC units/24 wks in placebo-treated pts during Wks 25–48. For RBCT visits, luspatercept non-responders experienced a mean change of –0.38 RBCT visits/24 wks vs +0.14 RBCT visits/24 wks in placebo-treated pts during Wks 25–48.
In any 12-wk period during Wks 1–48, a reduction of ≥33% RBCT units from baseline was achieved by 119/163 (73.0%) luspatercept non-responders vs 33/97 (34.0%) pts in the placebo arm. A reduction of ≥50% RBCT units from baseline was achieved by 62/163 (38.0%) luspatercept non-responders vs 6/97 (6.2%) pts in the placebo arm.
In Wks 25–48, 97/163 (59.5%) luspatercept non-responders achieved a reduction in serum ferritin (SF) from baseline vs 36/97 (37.1%) pts in the placebo arm. For non-responders, the mean change in SF from baseline was –203.34 mg/L (–8.07%). Of 103 non-responders with baseline mean SF ≥1,000 µg/L, 20 (19.4%) achieved post-baseline mean SF <1,000 µg/L in Wks 25–48.

Table. RBCT burden in Wks 25–48 in pts treated with luspatercept who did not achieve the primary endpoint and pts who received placebo

Wks 25–48	Luspatercept non-responders[a]	Placebo-treated pts
Reduction in RBCT units from baseline, n (%)	n = 163	n = 97
	112 (68.7)	26 (26.8)
Mean change from baseline in RBC units transfused, RBC units/24 wks	n = 155	n = 96
	–1.85	+0.21
LS mean difference[b] (95% CI)	–2.07 (–2.71, –1.42); $P < 0.0001$	
Mean change from baseline in RBCT visits, RBCT visits/24 wks	n = 155	n = 96
	–0.38	+0.14
LS mean difference[b] (95% CI)	–0.43 (–0.76, –0.11); $P < 0.01$	

[a]Non-responders were defined as pts who did not fully achieve the primary endpoint of ≥33% reduction in RBCT in Wks 13–24 from baseline [≥2 RBC units]); [b]Calculated as placebo minus luspatercept. Estimates are based on an ANCOVA model with geographical regions defined at randomization and baseline transfusion burden as covariates.
ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; pt, patient; RBC, red blood cell; RBCT, RBC transfusion; wk, week.

Summary/Conclusion: Most pts with β-thalassemia who did not meet the primary endpoint during the BELIEVE trial and were defined as non-responders to luspatercept had clinical benefit from continuing therapy. Pts received fewer RBC units, had fewer hospital visits due to RBCT administration, and had lower SF levels.

EP1307 COVID-19 PREVALENCE AND MORTALITY IN A LARGE ITALIAN HEMOGLOBINOPATHIES COHORT

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Background: Data on SARS-CoV-2 infection in Hemoglobinopathies are still scarce and controversial. Since March 2020, we, as Italian Society for Thalassemia and Hemoglobinopathies (SITE), recommended close monitoring and set up an Italian survey to verify the impact of SARS-CoV-2 infection on patients with Hemoglobinopathies (EMO AER COVID-19 NCT04746066) among Italian Centers.
Aims: To explore the hypothesis of an increased vulnerability of Hemoglobinopathies to SARS-COV2 infection.
Methods: After SITE proposal and Ethics Committee approval, each participating Center entered data on a specific electronic Case Report Form (eCRF) (https://covid19.site-italia.org). Inclusion criteria included positive swab or serology and at least 15 days of follow-up from either the onset of symptoms or SARS-CoV2 positivity. This cut-off is updated to February 15, 2021.

Results: Twenty-seven Centers that provide care to 6121 patients with Hemoglobinopathy (65% of the Italian population) recorded a total of 275 SARS-CoV2 infections (overall, prevalence 4.5%), in 191 transfusion-dependent thalassemia cases (TDT, prevalence 5.8%), 36 non-transfusion-dependent thalassemia (NTDT, prevalence 2.3%) and 48 sickle cell disease patients (SCD, prevalence 3.7%). Median age was 41 years (IQR: 30-48, range: 9 months-85 year). Twenty-eight patients (10 %) were pediatrics (median age: 6.5 years, IQR: 4-11). Most patients (72%) had comorbidities; 134 (49%) had splenectomy or functional asplenia. We observed a broad spectrum of disease severity, ranging from no symptoms in 65 patients (24%) to multisystem organ failure and death in 5 patients: 2 TDT (age: 49 and 56 years), 1 NTDT (age: 45 years), 2 SCD (age: 57 years both). Overall, 56 (20%) patients required hospitalization, 12 in high-intensity care unit; 10 required support by oxygen, 11 needed more intensive ventilation support with continuous positive airway pressure (CPAP), and 7 required intubation. Nine patients required ad hoc transfusion or more than scheduled. Two SCD patients of 9 and 20 months of age, respectively, recovered after a long and life-treating disease. One TDT patient experienced reinfection after 3 months from the first; one 30w-pregnant SCD woman developed COVID-19 without consequences for herself and the fetus. Overall clinical severity has been higher in SCD than in thalassemia patients.
Summary/Conclusion: The prevalence of COVID-19 in Hemoglobinopathies apparently overlaps the general population (4.5% vs 4.6%), however, these patients are more strictly observed and we could postulate that the precautions suggested or self-applied by the patients were effective. The overall mortality is 1.8% vs 3.4% and the difference may be due to the younger age of patients with Hemoglobinopathies. Our data confirm the higher risk of severe disease and death in SCD.

EP1308 HIGHLY EFFICIENT THERAPEUTIC GENOME EDITING OF HEMATOPOIETIC STEM AND PROGENITOR CELLS TO CURE SICKLE CELL DISEASE AND THALASSEMIA

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Background: Sickle cell disease and β-thalassemia are globally the most common monogenic diseases. The common feature is mutations within the beta-globin gene leading to aberrant expression or protein function. Allogeneic stem cell transplantation is currently the only potential curative option, however, donor matching as well as post transplantation complications significantly hamper the success rate of this therapy. With the most recent developments in the CRISPR/Cas9 field we aim to develop a genome editing strategy on HSPCs that allow for autologous stem cell transplantations for both hemoglobinopathies. Our objective is to re-express gamma-globin(g) at the expense of the mutated beta-globin. Gamma-globin is normally only expressed during fetal development and the first 1-3 years after birth. It is widely accepted that 25% fetal hemoglobin (g2a2) expression in erythrocytes is sufficient for patients to remain symptom free as indicated by asymptomatic individuals with beta globin mutations but with concomitant high levels of fetal hemoglobin. Gamma-globin expression is controlled by the master regulator BCL11A. However, downregulation of this gene should be performed with great precision since it also exerts a critical role in B-cell development and hematopoietic stem cells homeostasis.
Aims: Developing a gene therapy to cure sickle cell disease and thalassemia
Methods: We and others have identified intronic erythroid specific enhancer elements in *BCL11A* using ATAC sequencing to which multiple guides where developed disrupting specific element regions. We have setup a viral free highly optimized CRISPR/Cas9 ribonucleoprotein (RNP) nucleofection that allows for knockout efficiencies up to 80% in human HSPCs. Furthermore, we have developed a novel transfection buffer that results in reduced toxicity for HSPCs.
Results: We demonstrate a fast and efficient method for gRNA selection and to genome edit HSPCs. We report knockout efficiencies up to 80% in human CD34+ HSPCs. Editing efficiency was similar between the different CD34+ progenitor and stem cell subpopulation including the immature CD34+CD38- subpopulation, which is enriched for hematopoietic stem cells. Ribonucleoprotein (RNP)-induced genome editing in human CD34+ HSPCs does not affect cell proliferation, differentiation or in vitro hematopoietic lineage commitment nor upregulated P21 expression. Deletion of various regions within the BCL11A erythroid specific enhancer element led to variable induction of fetal hemoglobin expression, up to 60%, that could be correlated to the specific transcription factors bound to the respective edited regions.
Summary/Conclusion: Making modifications in the BCL11A enhancer results in fetal hemoglobin levels that exceed the minimum clinical limit to cure SCD and thalassemia. In general, we show that mutations created in HSPCs are stable and we do not observe major toxic effects. Targeting specific sites that are occupied by erythroid restrictive transcriptional regulators may prevent collateral BCL11A knockout in other lineages. These data pave the road towards transplanting genome edited HSPCs to allow for autologous stem cell transplantations and thereby bypass current limitations.

EP1309 A RETROSPECTIVE DATABASE STUDY OF DISEASE COURSE AND CLINICAL OUTCOMES IN PATIENTS WITH TRANSFUSION-DEPENDENT THALASSEMIA (TDT) IN ITALY

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Background: β-thalassemia confers a substantial burden on both patients and the healthcare system.
Aims: We systematically quantified the outcomes and disease burden in 2,520 patients with transfusion-dependent thalassemia (TDT) or thalassemia major (TM) receiving regular treatment with red blood cell (RBC) transfusions and iron chelation therapy (ICT).
Methods: The data for this study came from the International Health Repository (IHR) protocol (EudraCT and Sponsor Protocol Code Numbers: 2017-004457-17 and 143AOR2017). This cross-sectional study focused on 3,106 patients with thalassemia presenting at 5 centers in Italy between July 2000 and July 2018, and employed retrospective, cross-sectional analyses of individual patient data at a given date during this timeframe. Here, we present a subgroup analysis of the 2,520 patients in the cohort with TDT.
Results: Of the 2,520 TDT patients included in the analysis 1,107 had a known genotype; in particular, 401 (36.2%) had a β^0/β^0 genotype, 237 (21.4%) had a IVS-1-110/β^0 genotype, 93 (8.4%) had a IVS-1-110/β^+ genotype, 133 (12.0%) had a IVS-1-110/IVS-1-110 genotype, 201 (18.2%) were β^0/β^+, and 42 (3.8%) were β^+/β^+. The percentage of patients with IVS-1-110 genotype was 41.8%, corresponding to 12.0% homozygous and 29.8% heterozygous patients. The mean age of patients was 36.8 (±10.7) years (range, 2.6-74.0), and 52.6% were females. The mean (range) age at diagnosis, initiation of RBC transfusions, and initiation of ICT was 1.1 (±1.2) years (0.08-13), 2.1 (±2.9) (0.08-43), and 5.1 (±5.1) (0.6-65), respectively.
The median (range) transfusion requirement for TDT patients was 175.0 mg/dL/year (100.7-417), the median of the mean hemoglobin (Hb) level was 9.5 g/L (6-20), and the median serum ferritin was 1003 ng/ml (37.6-12484). More patients (31.7%) underwent chelation with desferrioxamine (DFO), whereas deferiprone (DFP) and deferasirox (DFX) were used in 18.5% and 23.1% of patients, respectively. Furthermore, 19.3% of patients underwent sequential or combined DFO-DFP, 0.6% sequential or combined DFO-DFX, and 0.4% sequential or combined DFP-DFX. Chelation data were not available for 164 patients (6.5%).
Median (range) alanine transaminase (ALT) and aspartate transaminase (AST) levels in TDT patients were 29 IU/L (6-381) and 29 IU/L (7-320), respectively. The median (range) of the cardiac ejection fraction, liver T2*, and cardiac T2* was 64% (24-97), 7.5 ms (0.2-49.6), and 38 ms (0-64), respectively.
Eighty-two percent of TDT patients experienced one or more thalassemia-related complication, with 533 (21.1%) experiencing one complication, 486 (19.3%) experiencing two complications, 424 (16.8%) experiencing three complications, and nearly a quarter (625 patients (24.4%)) experiencing four or more complications. Eighteen percent of patients experienced no complications. The most frequently observed complications were liver complications, followed by splenectomy, osteoporosis, hypogonadism, cardiac complications, hypothyroidism,

diabetes, hypoparathyroidism, lung complications, infections, and cancer (Table 1).

Table 1: Number of complications in TM patients by diagnosis

Complications	Number of patients
Liver complications	1397
Splenectomy	1264
Osteoporosis	829
Hypogonadism	780
Cardiac complications	464
Hypothyroidism	429
Diabetes	221
Hypoparathyroidism	120
Lung complications	100
Infections	76
Cancer	35

Summary/Conclusion: In this study, more than 80% of TDT patients experienced one or more disease-related complication, with nearly a quarter of patients experiencing four or more complications. This high rate of complications occurred despite well-managed serum transferrin levels in this patient group. This demonstrates that patients with TDT experience a significant burden of disease, even with appropriate iron chelation.

EP1310 AUDITORY CORTEX HYPOPERFUSION: A METABOLIC HALLMARK IN BETA THALASSEMIA

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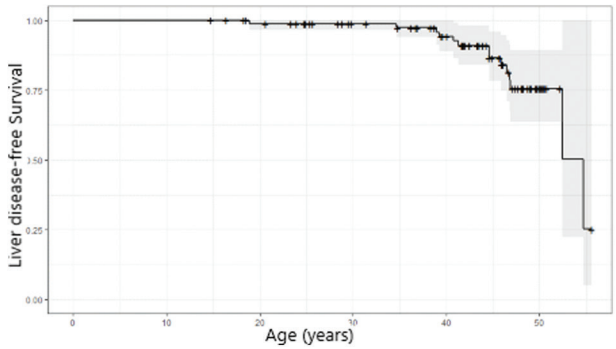
Background: Sensorineural hearing loss in beta-thalassemia is common and it is generally associated with iron chelation therapy. However, data are scarce, especially on adult populations, and a possible involvement of the central auditory areas has not been investigated yet.
Aims: We aimed at investigating the metabolism of the cerebral auditory areas in thalassemia, trying also exploratively to assess if this may correlate with the cognitive impairment previously shown in this disease.
Methods: We performed a multicenter cross-sectional audiological and single-center 3Tesla brain perfusion MRI study enrolling 77 transfusion-dependent/non transfusion-dependent adult patients and 56 healthy controls. Pure tone audiometry, demographics, clinical/laboratory and cognitive functioning data were recorded.
Results: Half of patients (52%) presented with high-frequency hearing deficit, with overt hypoacusia (Pure Tone Average (PTA)>25dB) in 35%, irrespective of iron chelation or clinical phenotype. Bilateral voxel clusters of significant relative hypoperfusion were found in the auditory cortex of beta-thalassemia patients, regardless of clinical phenotype. In controls and transfusion-dependent (but not in non-transfusion-dependent) patients, the relative auditory cortex perfusion values increased linearly with age ($p<0.04$). Relative auditory cortex perfusion values showed a significant U-shaped correlation with PTA values among hearing loss patients, and a linear correlation with the full scale intelligence quotient (right side p=0.01, left side p=0.02) with its domain related to communication skills (right side p=0.04, left side p=0.07) in controls but not in beta-thalassemia patients. Audiometric test results did not correlate to cognitive test scores in any subgroup.
Summary/Conclusion: In conclusion, primary auditory cortex perfusion changes are a metabolic hallmark of adult beta-thalassemia, thus suggesting complex remodeling of the hearing function, that occurs regardless of chelation therapy and before clinically manifest hearing loss. The cognitive impact of perfusion changes is intriguing but requires further investigations.

EP1311 THE VALUE OF EARLY HISTOLOGICAL FINDINGS IN PREDICTING SEVERE HEPATIC EVENTS IN B-THALASSEMIA

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Background: Current therapeutic modalities has rendered thalassemia a chronic disease. With patients' advanced age, previously unknown complications are observed with increasing frequency. Among them, liver disease and hepatocellular carcinoma(HCC) are on the rise. Viral hepatitis, mainly hepatitis C, and chronic iron overload are the main causes of liver disease, presenting as significant fibrosis, cirrhosis and/or HCC. Direct histological examination of hepatic tissue obtained by biopsy, remains highly sensitive and specific for the diagnosis of liver disease, but its predictive value is not established.
Aims: To evaluate the predictive value of histological findings of liver biopsy in the long-term liver-related morbidity and mortality in patients with β-thalassemia.
Methods: A retrospective analysis was performed in a group of Transfusion-Dependent (TDT) or Non-Transfusion-Dependent (NTDT) β-Thalassemia patients, who had undergone liver biopsy from 1992 to 2005, and were followed till 31/12/2020 in a single institution. Severe hepatic events were defined as either liver cirrhosis, HCC or death due to liver disease.Kaplan-Meier estimator was used to estimate disease-free survival (DFS). Cox proportional hazards model or Peto&Peto modification of the Gehan-Wilcoxon test were used to investigate risk factors. Time-To-Event (TTE) was performed from the date of: (1) birth or (2) biopsy, to the date of the liver event or of last follow up for censored records. The association of siderosis burden with ferritin was assessed through the Mann-Whitney U test. Statistical analysis was conducted using RStudio v. 3.6.3.
Results: In total, 87 patients (54 males, 79 TDT) had undergone liver biopsy at the age of 21.8±6.1 years and were monitored for 19.4 (IQR; 14.3-27.9) years. Forty-eight patients (55.2%) had viral hepatitis C. Histology evaluation showed low siderosis (grade:0-2 in a scale of 0-4) in 34 (39.1%) and high siderosis (grade: 3-4) in 50 (57.5%) patients, while it was not reported in 3 (3.4%). Mild fibrosis (grade: 0-2 in a scale of 0-6, as per Ishak classification) was observed in 22 (25.3%) patients, advanced fibrosis (grade 3-6) in 62 (71.3%), while in 3 patients was not recorded. We identified 14 (16.1%) events (all in TDT patients);7 developed HCC, 4 liver cirrhosis and 3 died from other liver-related causes. At 50 years of age DFS was 75% (figure 1), while 25% of patients developed liver disease in 24.4 years after the date of biopsy.High siderosis carries a greater risk for developing liver disease compared to group with low siderosis, Hazard Ratio (HR) 3.00 (95% CI:1.01-8.95, p=0.05), adjusted for age (aHR) 2.9 (95% CI: 0.90 – 9.01, p=0.07). An increase of 50 μg/L in ferritin level at time of biopsy is associated with an increased risk of developing liver disease (aHR 1.02, 95% CI:1.00-1.03, p=0.03). A statistically significant correlation was observed between high serum ferritin levels and high siderosis at the date of biopsy (1712(IQR;1000-2985) vs 3715(IQR;1721-5197.5),p=0.0003). No statistically significant correlation in the development of liver disease was observed between gender, HCV and degree of fibrosis at time of biopsy, p=0.2, p=0.3 and p=0.2, respectively.



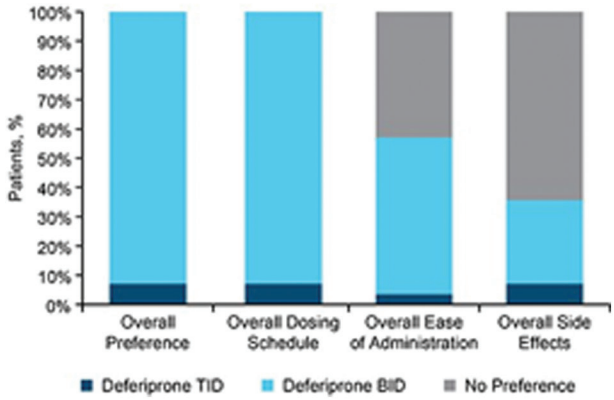
Summary/Conclusion: The occurrence of liver-disease is increasing after the 4th decade of life. Serum ferritin and liver siderosis at the time of biopsy was found to be statistically significant risk factors for the progression of the disease. Degree of liver fibrosis does not seem to be related to progression, which may be due to stabilization and/or reversal of fibrosis achieved with current chelation therapy.

EP1312 A MULTICENTER OPEN-LABEL STUDY ON THE SAFETY AND ACCEPTABILITY OF TWICE-DAILY DEFERIPRONE TABLETS AMONG PATIENTS WITH TRANSFUSION-DEPENDENT THALASSEMIA AND SYSTEMIC IRON OVERLOAD

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Background: Adherence with life-long iron chelation therapy is critical for the survival of transfusion-dependent patients. Deferiprone is an orally absorbed bidentate hydroxypyridinone iron chelator with high efficacy in binding excess intracellular iron to reduce iron toxicity and is approved for the treatment of iron overload. The current formulation of deferiprone is immediate release (IR) and requires three-times-daily (TID) administration, which may result in decreased adherence in some patients.
Aims: A twice-daily (BID) deferiprone formulation was developed as a more convenient dosing regimen to improve patient adherence. In the current study, we evaluated the safety, tolerability, and acceptability of deferiprone BID tablets in a cohort of patients with transfusion-dependent thalassemia (TDT).
Methods: TWICE (NCT03802916) was a multicenter, open-label, switch-over study of 30 adult patients with TDT who were taking deferiprone IR TID, and the first study where patients with iron overload were administered deferiprone BID. The currently approved dosage of deferiprone IR TID is 75-99 mg/kg/d. To assess the impact of the BID formulation within the approved dosage range on adverse events (AEs), an equal number of patients were enrolled into either a "low-end standard dose" (LSD; ~75 mg/kg/d) or "high-end standard dose" (HSD; ~100 mg/kg/d) group based on their deferiprone IR TID dosage. At the end-of-study visit (day 28 of treatment), patients completed a preference questionnaire on the acceptability of the BID versus the IR TID formulation.
Results: The study enrolled 30 patients with TDT; 1 patient in the HSD group withdrew before receiving deferiprone BID. The study population consisted of 29 participants (44.8% female) with a mean age of 41.1 (SD: 8.4) years. Nineteen patients (10 in the LSD and 9 in the HSD group), experienced a total of 49 AEs; 41% were classified as mild, 57% moderate, and 2% severe. The most common AEs, irrespective of a causal relationship with therapy, were headache (21%), arthralgia (14%), and diarrhea (10%). 13 AEs (27%) were considered "at least possibly related" to therapy; those which were reported in 2 or more patients included diarrhea (n=3, HSD) and arthralgia (n=1, LSD; n=1, HSD). One patient in the LSD group experienced a severe AE of arthralgia (elbow pain) that resolved without interruption of therapy. All episodes of diarrhea were transient and resolved without interruption of therapy. One patient in the HSD group withdrew after experiencing a mild AE of renal colic, which was considered "possibly related" to therapy. Serious AEs previously ascribed to deferiprone IR TID (ie, agranulocytosis, neutropenia, or clinically concerning increases in liver enzymes) were not observed with deferiprone BID. The mean adherence to the deferiprone BID dosing regimen was 99.3% in the LSD and 98.5% in the HSD group. At the end-of-study visit, most patients (92.9%) indicated their strong preference for the deferiprone BID formulation over the IR TID formulation (Figure).



Summary/Conclusion: The new formulation of deferiprone BID tablets was safe and well-tolerated among patients with TDT. Most AEs were mild or moderate, and none of the serious AEs previously observed with deferiprone IR TID were reported. Patients reported high adherence to the deferiprone BID formulation and most (92.9%) preferred the deferiprone BID formulation over the IR TID, suggesting the BID formulation has the potential to improve patient adherence.

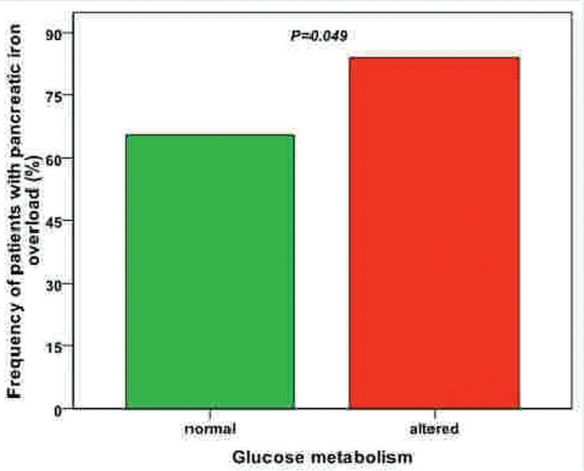
EP1313 PANCREATIC IRON CORRELATES WITH ALTERATIONS OF GLUCOSE METABOLISM AND CARDIAC IRON IN REGULARLY TRANSFUSED THALASSEMIA INTERMEDIA PATIENTS

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Background: In thalassemia major pancreatic iron was shown to be correlated to splenectomy, hepatitis C virus (HCV) infection, altered glucose metabolism, hepatic and cardiac iron, biventricular function, and myocardial fibrosis.
Aims: In the present multicenter study we explored the clinical correlates of pancreatic T2* in a cohort of patients with thalassemia intermedia (TI) under regular transfusion therapy.
Methods: We considered 150 patients (85 F, mean age 42.3±13.7 years) consecutively enrolled in the E-MIOT (Extension-Myocardial Iron Overload in Thalassemia) project. Magnetic Resonance Imaging (MRI) was performed to quantify hepatic, cardiac, and pancreatic iron overload by the T2* technique, to evaluate biventricular function parameters by cine images and to detect replacement myocardial fibrosis by late gadolinium enhancement (LGE) technique. To assess the disturbances of glucose metabolism, patients non already diagnosed with diabetes performed an oral glucose tolerance test (OGTT).
Results: Global pancreas T2* values were not correlated to age or gender. One-hundred and three patients (68.7%) showed a pathologic pancreas T2* value (<26 ms).
Splenectomised patients (76%) showed significantly lower global pancreas T2* than patients with the spleen (18.4±11.2 ms vs 23.8±13.4; P=0.017). Patients with an active or eradicated HCV infection (34.9%) had significantly lower global pancreas T2* values than negative patients (17.1±10.6 ms vs 22.6±12.6; P=0.021).
Patients with an altered OGTT (23%) showed a significant higher frequency of pancreatic iron overload than patients with a normal OGTT (83.9% vs 65.4%; P=0.049) (Figure 1). In non-diabetic patients global pancreatic T2* values were inversely correlated with glucose levels fasting (R=-0.366; P<0.0001) and 1-hr after OGTT (R=-0.308; P=0.016) and positively associated with the HOMA of β-cell function index (R=0.391; P=0.001).
Pancreas T2* values showed a negative correlation with MRI liver iron concentration values (R=-0.255; P=0.002) and a positive correlation

with cardiac T2* values (R=0.184; P=0.024) and all the 6 patients with global heart T2*<20 ms had also pancreatic iron load.
Global pancreas T2* values were not correlated to biventricular volumes and ejection fraction and were comparable between patients without and with replacement myocardial fibrosis.



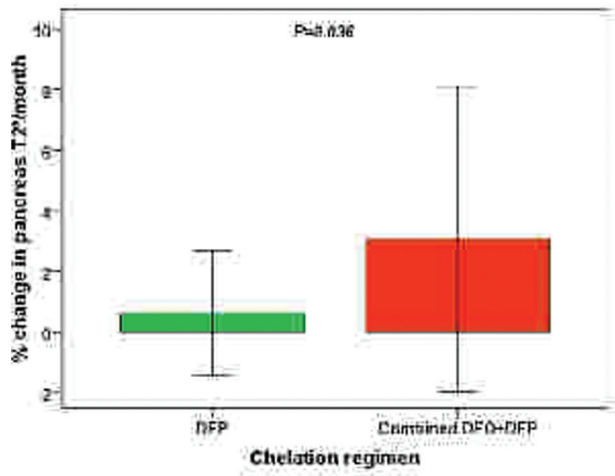
Summary/Conclusion: In regularly transfused TI patients higher pancreatic siderosis was found in splenectomised patients, in patients with an history of HCV infection, and in patients with altered glucose metabolism. Moreover, a normal pancreas T2* showed a negative predictive value of 100% for cardiac iron. These data support for starting or intensifying iron chelation therapy in TI patients with pancreatic iron overload. By this way it may be prospectively possible to prevent both alterations of glucose metabolism and cardiac iron accumulation rather than wait for the manifestation of overt diabetes and cardiac complications.

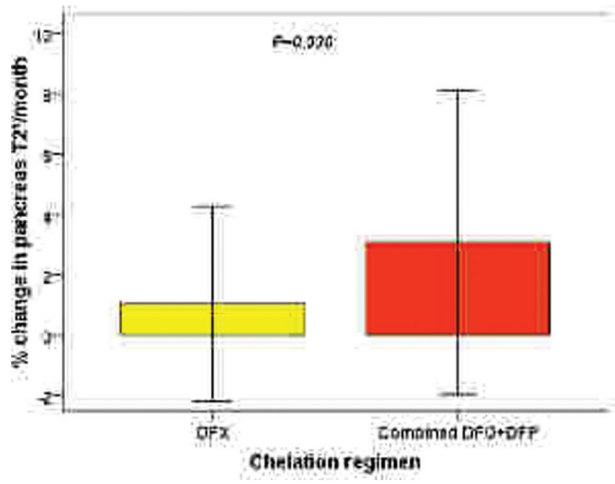
EP1314 PROSPECTIVE COMPARISON ON PANCREATIC IRON BY MAGNETIC RESONANCE IN THALASSEMIA MAJOR PATIENTS TREATED WITH COMBINATION DEFERIPRONE–DESFERRIOXAMINE VERSUS DEFERIPRONE AND DEFERASIROX IN MONOTHERAPY

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Background: The combination therapy with deferiprone (DFP) and desferrioxamine (DFO) was associated with an overall improvement in glucose metabolism disorders in β-thalassaemia, but no data are available about its efficacy in removing pancreatic iron.
Aims: The aim of this multi-center study, conducted in a large clinical observational setting of thalassemia major (TM) patients, was to prospectively evaluate the effects of combined DFO+DFP therapy versus both oral iron-chelators in monotherapy on pancreatic iron over a follow-up of 18 months.
Methods: Among the first 1176 TM patients consecutively enrolled in the E-MIOT (Extension-Myocardial Iron Overload in Thalassemia) network, 416 patients had a FU at 18±3 months. We selected those who had been received combined regimen (N=28) or DFP (N=61) and deferasirox-DFX (N=159) monotherapies between the two MRI scans. Pancreatic iron overload was quantified by multi-slice multiecho T2* technique; measurements were performed over pancreatic head, body and tail and global value was the mean.
Results: The comparison was restricted to patients with a normal baseline global pancreatic cut off value (T2*<26 ms): 28 in the combined DFO+DFP group, 54 in the DFP group and 129 in the DFX group.
The dosages were: 1) DFP in combined regimen 84.8±14.9 mg/kg body weight per day with a frequency of 6.9±0.6 days/week and DFO in combined regimen 37.9±7.8 mg/kg body weight per day with a frequency of 3.9±1.7 days/week; 2) DFP in monotherapy 84.5±14.3 mg/kg body per day; 3) DFX in monotherapy 24.9±7.1 mg/kg body per day if in dispersible tablets (N=98) and 18.3±4.4 mg/kg body per day if in film-coated tablets (N=31). The percentage of patients with excellent/good levels of compliance to the active chelation treatment was significantly lower in the combined DFP+DFO group versus both the DFP group (82.1% vs 98.1%; P=0.016) and the DFX group (82.1% vs 99.2%; P=0.001).
Global pancreatic T2* values were significantly lower in the combined DFO+DFP group compared to both DFP and DFX groups. A significant negative association was detected between changes in global pancreas T2* values and baseline global pancreas T2* values (R=-0.192; P=0.005). So, the % changes in global pancreas T2* values, normalized for the baseline values, were considered.
In no treatment group there was a correlation between the % changes in global pancreas T2* values and the iron chelator dosage.
The % changes in global pancreas T2* values were significantly higher in the combined DFO+DFP group versus both DFP (P=0.036) and DFX groups (P=0.030) (Figure 1).





Summary/Conclusion: Prospectively in TM patients at the dosages used in the real world, combined DFP+DFO was significantly more effective in reducing pancreatic iron versus both DFP and DFX in monotherapy.

EP1315 QUANTIFYING THE HEALTHCARE RESOURCE USE AND CLINICAL OUTCOMES OF PATIENTS WITH BETA THALASSAEMIA IN ENGLAND

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Background: Beta-thalassaemias are a group of hereditary haemoglobin disorders characterized by anomalies in the synthesis of the beta chains

of adult haemoglobin resulting in ineffective erythropoiesis (IE) and anaemia. Beta-thalassaemia (BT) is classified clinically as transfusion-dependent (TD) or non-transfusion-dependent (NTD) based on patients red blood cell transfusion (RBCT) needs. IE, anaemia and RBCT treatment can lead to iron overload and various morbidities such as endocrine, liver and cardiac complications.
The Hospital Episodes Statistics (HES) database in England contains universal coverage of secondary care data from NHS hospitals, covering three main patient groups: 1) inpatient patient care; 2) Outpatient appointments and attendances (OP); and 3) Emergency Room (ER) visits with approximately 17 million episodes recorded each year.
Aims: To describe patients diagnosed with BT in England in terms of demographics and clinical characteristics and to quantify the associated healthcare resource use (HCRU) and tariffs for this patient cohort including inpatient, day case, outpatient, and A&E care.
Methods: All data within an observation period between 01 January 2015- 31 December 2019, to include baseline characteristics for patients with ICD10 diagnosis code of D561 or D565 (BT) were extracted from HES and presented as crude counts. Descriptive statistics including frequency and percentage were calculated as categorical variables; whereas, mean, median and interquartile range (IQR) were calculated for continuous variables. Length of follow-up was calculated as the total number of days between diagnosis date (index date) and end of study period. Tariffs were derived based on case mix; a method of classifying patient care based on expected clinical resource use for the provision of that care.
Results: Overall 1,986 patients (mean age at inclusion 28 years [youngest; <1, oldest; 95]; 49.65% female) were identified. During a mean observation period of 35 months (IQR 54), 585 (29.46%) patients experienced a disorder of iron metabolism, 222 (11.18%) suffered from sepsis and 157 (7.91%) from heart failure.
2 (0.10%) patients had no inpatient admissions. For those who had ≥1 inpatient admissions, the mean number of inpatient blood transfusion visits per-patient-per-year was 11.31 (IQR 11.22), the mean number of outpatient blood transfusion visits per-patient-per-year was 17 (IQR 0.84). 1,032 patients (55.81%) had ≥12 blood transfusion visits per year.
Overall HCRU is split by inpatient and outpatient care and ER attendance. In the inpatient setting there were a mean of 14.9 admissions per-patient-per-year, of which 97.57% were elective (resulting in a mean of 4.34 bed days per-patient-per-year). In the outpatient setting there were a mean of 8.9 appointments per-patient-per-year. There were a mean of 5.81 ER visits per-patient-per-year.
Overall tariff costs on the health service per-patient-per-year were £23,120 (inpatient tariff £10,563, outpatient tariff £1,506, transfusion £10,200, ER visits £851).
Summary/Conclusion: The results of this database analysis with a large number of patients offer insights into the real-world management of patients with BT in England and the high HCRU associated with its management. A burden on patients and the healthcare system has been identified due to the frequent hospitalisations and secondary care visits. This highlights the need for novel treatment options in the management of BT.

EP1316 THE DATA FROM NATIONAL REGISTER FOR SURVEILLANCE OF STANDARD OF CARE IN THALASSEMIA IN TURKEY

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Background: The National Hemoglobinopathy Registry of the Turkish Society of Hematology (TSH) records the data of hemoglobinopathy patients (pts) in Turkey. In the modern era, there has been a marked improvement in the standard of care in thalassemia.
Aims: We analyzed the conventional treatment indicators of disease to assess the delivery of high-quality care all over Turkey.
Methods: The registry has Ethical approval. Participating physicians recorded patients' data into the database after receiving informed consent from the patients/legal representatives. We extracted the data onto an Excel spreadsheet for analysis in January 2021.
Results: The register included 3554 pts' data entered by 56 thalassemia centers. There were 1998 pts with beta-thalassemia major (B-TM) and 415 pts with beta-thalassemia intermedia (B-TI).
The mean hemoglobin (Hb) at starting regular transfusion remained the same over the decades in B-TM pts. The mean Hb was 8.8±0.8 (median 9.0) g/dl in B-TM and 8.7±1.4 (range 6-13.5) g/dl in B-TI pts previous year. Overall, 4.6% and 7.0% of patients with B-TM and B-TI, respectively, were alloimmunized. 39% of non-immunized and 84.5% of alloimmunized pts were receiving ABO-RhEeDCc-Kell compatible pRBCs. Alloimmunization was significantly higher in patients who started regular Tx after the age of one year (3.9 vs. 10.0%) (p<0.0001). Transfusion transmitted infections affected 3% of the B-TM and 1% of the B-TI. Overall, 51 of 63 (80%) were HCV, in which 40% of those were reported as having chronic HCV infection. HCV-associated hepatocellular carcinoma was the cause of death in one.
Overall, 87% of pts with B-TM were on iron chelation therapy (ICT). Physicians prescribed ICT to 22% of pts with B-TI. Overall, 90% of pts were receiving chelator as monotherapy, and 90% of monotherapies were composed of Deferasirox (DFX). The combination was the choice in 1 of the 10th pts, and DFX & Deferiprone was the most prevalent (58.5% of the combined regimens). The data showed a gradually increasing trend towards monotherapy and the DFX use by each 10-year birth cohort. The median serum ferritin (SF) at starting ICT improved gradually by each 10-year birth cohort since 1960 from 2600 ug/L to as low as 1479 ug/L in the last cohort. Overall, median SF in B-TM pts settled down to 1200 ug/L in the previous year. Only 30% of B-TM patients had access to myocardial (T2*) MRI. The mean age of the first MRI assessment was 19±9 years. The majority (70%) had an mT2*of >20 ms, while 16.3% showed an mT2*of 10-20 ms and 6.7% an mT2* of <10 ms. Although SF was significantly correlated with the severity of cardiac siderosis, the pts' age was not.
In each 10-year birth cohort, 78% of pts with B-TM born between 1960-1990, and 54% of those born between 1990-2000 had a splenectomy. Further, half of those patients in each cohort had undergone splenectomy <10 years-old. The rate of splenectomy was lower (14%) in patients of the 2000-2010 cohort. It seems likely that the rate will less than that of the previous decades. Splenectomized patients showed less

pRBC consumption than the non-splenectomized ones (median 125 vs. 173 ml/kg/y, p<0001). Although SF has not markedly differed in splenectomized and non-splenectomized patients, myocardial siderosis was higher in patients with splenectomy (25.7±11.0 vs. 29.2±8.5, p<0.001).

Table. Transfusion and chelation indicators of patients with beta-thalassemia major (B-TM) and intermedia (B-TI)

Patients	B-TM	B-TI
n	1998	415
Age ± SD (year)	19 ± 11	24 ± 15
F/M	952/1046	226/189
Age of diagnosis (*year*)	1.2±2.1 (0.6)*	5.7±7.6 (3.2)*
Age of 1st transfusion (year)	1.1±2.0 (0.7)*	6.4 ±9.4 (3.8)*
Hb at 1st transfusion (g/dl)	6.6 ±1.1 (6.4)*	*NA*
Age of chelation start (year)	4.2±4.9 (2.8)*	11.9±9.8 (8.4)
SF at chelation start (ug/L)	1946±1402 (1594)*	1624±1127 (1318)*
Hb at previous year (g/dl)	8.8±0.8 (9.0)*	8.7±1.4 (8.5)*
SF at previous year (ug/L)	1760±1852 (1200)*	1087±729 (974)*
Splenectomy (%)	38	38

**mean±SD (median), NA; not applicable*

Summary/Conclusion: The register's data demonstrated the current status of a standard of care in thalassemia that still needs to achieve higher standards in this relatively young cohort in Turkey.

EP1317 THE PATIENTS WITH THALASSEMIA MAJOR MAY STILL DISPLAY GROWTH HORMONE DEFICIENCY DESPITE OPTIMUM TRANSFUSION AND IRON CHELATION THERAPY

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Background: Growth retardation (GR) and pubertal disorders are the earliest consequences of iron toxicity resulting from the pituitary iron deposition in children and adolescents with thalassemia major (TM). It is suggested that appropriate transfusion and iron chelation therapy (ICT) may achieve growth and development in TM.
Aims: The purpose of this study was to evaluate if the current transfusion and ICT protocols may support a normal growth progression and sexual development in patients (pts) with TM.
Methods: We recruited male (M) and female (F) TM pts born after 2000. The pts with an acute or chronic illness that may interfere with growth and development were excluded. The Ethical Committee of Clinical Investigation (19.02.2020, 20-2.1T/2) approved this study. Transfused packed red cell units (pRBC) and average pre-transfusion hemoglobin (Hb) per year were recorded. Serum ferritin (SF) was monitored monthly (m). Myocardial (T2*) and liver (R2) iron were assessed by magnetic resonance imaging (MRI) after 8-years (y) of age. Annual median SF, prescribed chelator(s), mean chelator doses were recorded. Transfusional iron intake (TII) was estimated and expressed as mg/kg b.w./days. Height (H) and weight (W) assessments were performed using the Harpenden stadiometer, and puberty was evaluated by Tanner staging at 3 m. H-standard deviation scores (h-SDS) were calculated. All pts were evaluated annually for bone mineral density (BMD) after 8 y. The mean SDS of the lumbar spine (L1-4) BMD between -1 and -2.5 was defined as osteopenia and <-2.5 as osteoporosis. Growth hormone (GH) secretion was assessed by L-dopa and insulin tests in those with standing-H below the –2 SD. Pts whose GH response to both stimulation tests were less than 5 ng/ml with the monoclonal assay was defined as GH deficient.
Results: We evaluated 30 TM (28 β/β, 1 β/δβ, and 1 non-deletional HbH) pts (13 F and 17 M) with the mean age of 12,5 ± 4,5 y. All pts have received pRBC for 11,1 ± 4,4 y and maintained pre-transfusion Hb> 9 g/dl. The patients started ICT by the SF of 1430 ± 795 ug/L and maintained ≤1500 ug/L at all times during 9 ± 4.2 y. Twenty-four pts received only Deferasirox (DFX) chelation while 6 were initiated ICT by Deferoxamine (DFO) and continued with DFX. Liver iron concentration (LIC) and myocardial T2* (mT2*) in 22 pts were between 0.9-5.4 (2.1 ± 1.3 SD) mg Fe/g d.w. and 19.4-43.5 (28 ± 6.7 SD) ms, respectively, in all assessments. The puberty initiated at 12.8 ± 1.1 y in M (n=12) & 11.2 ± 1.3 y in F (n=12) and progressed without hormone replacement in all. Overall, growth velocity reduced compared to the non-thalassemic population after 8 y with clear evidence of growth catch-up by the onset of puberty. Five pts (16.5%) developed h-SDS< -2 at 10-12 y-old when all but one had S1/2 puberty and displayed GH deficiency. All pts received GH therapy. The pt no 4 was entirely unresponsive to GH stimulation tests, developed GR at 1 y-old, and has remained unresponsive to GH therapy (Table). The 14 (%58) and 5 (21%) of 24 pts demonstrated osteopenia and osteoporosis, respectively. The BMD-SDS improved following pubertal spurt.

Table. The growth progression by GH treatment in thalassemia major patients with GR and GH deficiency

Pts no	Iron chelator		Max SF (ug/L)	Target h-SDS	Prior GH therapy			1st y of GH		Final G & D		
	I	FU			P	B-/C-age (y)	h-SDS	P	GV (cm)	P	C-age (y)	h-SDS
1	DFO	DFX	*4725	-1,41	S1	11,5/13	-2,46	S2	7,1	S5	18	-1,68
2	DFO	DFX	*2465	0,24	S1	10/13,2	-3,10	S2	8,9	S5	18	-0,19
3	DFX	DFX	1528	0,66	S2	11/12,7	-3,16	S3	9,2	S5	16	-1,64
4	DFX	DFX	1580	0,21	S1	6/10,7	-3,41	S1	3,2	S3	16	-4,30
5	DFX	DFX	1183	-0,54	S1	7,5/11,5	-2,31	S1	6,8	S1	13	-1,90

I: Initial, FU: Follow-up, B-age: Bone-age, C-age: Chronological-age, GV: Growth velocity, DFO; Deferoxamine, DFX; Deferasirox, G&D; Growth and Development
*The max. SF reached during 1st years on DFO then SF normalized around 1000 ug/L

Summary/Conclusion: The high prevalence of the diagnosis of GH deficiency in TM patients receiving an optimum transfusion and ICT throughout their life was disappointed. Either the growth pattern and bone-maturation in TM pts might differ from the non-thalassemic population, and the GH stimulation tests may lead to overdiagnosis of GH deficiency or the current chelation modalities may not prevent iron toxicity in pts with TM.

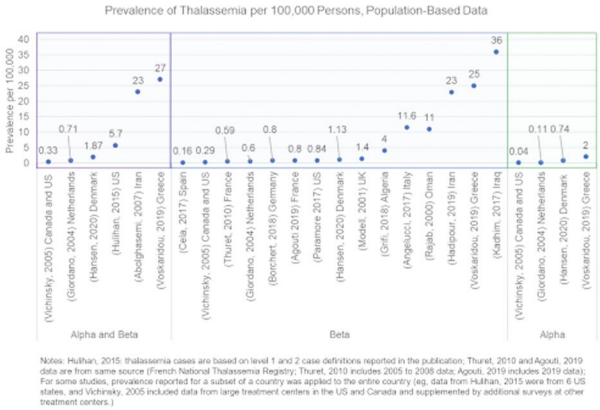
EP1318 GLOBAL THALASSEMIA EPIDEMIOLOGY: A SYSTEMATIC LITERATURE REVIEW

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Background: Alpha and beta-thalassemia are characterized by imbalanced globin chain production, resulting in ineffective erythropoiesis and hemolytic anemia. Patients with thalassemia intermedia or major may experience serious complications including iron overload, osteoporosis, thrombosis and increased mortality. While thalassemias are common in areas historically endemic to malaria, the global epidemiology is changing due to factors such as population screening, improved survival rates, and migration. Comprehensive understanding of the global prevalence particularly with region- and subtype-specific estimates is limited.
Aims: To determine the global prevalence of alpha- and beta-thalassemia (excluding minor/trait types), and to identify critical evidence gaps.
Methods: A systematic literature review (SLR) was conducted. Excerpta Medica database (Embase), PubMed (via MEDLINE), and the Cochrane Library (Database of Systematic Reviews) were searched to identify real-world observational studies published from Jan. 1, 2000 to Jun. 15, 2020 reporting on the incidence and/or prevalence of thalassemia. Dual independent screening was performed with disagreements resolved by a third researcher. Data extraction was performed by a single reviewer with full validation by a second reviewer. Prevalence per 100,000 people was estimated based on dates of data collection from respective included publications. Results were also extrapolated to estimate the number of patients with thalassemia in European countries and the United States (US).
Results: Of 1,900 records screened, 58 publications met the protocol-defined selection criteria for inclusion in the SLR.
Population-based prevalence data were reported in 17 studies (see Figure) from North America, Europe, the Middle East, and North Africa. In the US, the estimated population-based prevalence of alpha- and beta-thalassemia combined was 5.7/100,000. Among other countries with population-based studies, prevalence data were predominantly reported for beta-thalassemia only. In Europe, the estimated beta-thalassemia prevalence (9 studies) ranged from 0.16/100,000 in Spain to 25/100,000 in Greece; alpha-thalassemia prevalence (3 studies) was low, ranging from 0.11/100,000 in the Netherlands to 2/100,000 in Greece. In a single population-based analysis from North Africa, the prevalence of beta-thalassemia was 4/100,000 in Algeria, and across the Middle East (3 studies), the prevalence of beta-thalassemia ranged from 11/100,000 in Oman to 36/100,000 in Iraq.
Thalassemia prevalence data from Africa, Asia, and South America were mainly limited to specific sites or study samples that may not be generalizable to their respective countries. Further, the prevalence results ranged widely, indicating potential selection bias in these non-population-based studies.

Key evidence gaps in the published literature included incomplete reporting of thalassemia subtypes, lack of diagnosis confirmation, and a paucity of recent, population-based analyses, including from countries with thalassemia registries.



Notes: Hulihan, 2015: thalassemia cases are based on level 1 and 2 case definitions reported in the publication; Thuret, 2010 and Agouti, 2019 data are from same source (French National Thalassemia Registry; Thuret, 2010 includes 2005 to 2008 data; Agouti, 2019 includes 2019 data); For some studies, prevalence reported for a subset of a country was applied to the entire country (eg, data from Hulihan, 2015 were from 6 US states, and Vichinsky, 2005 included data from large treatment centers in the US and Canada and supplemented by additional surveys at other treatment centers.)

Summary/Conclusion: Based on available published data, the estimated prevalence of thalassemia (excluding minor/trait types) varied globally, with highest prevalence in Greece and the Middle East, and lowest prevalence in the Netherlands, Spain, France and Germany. There is limited prevalence data in non-Western countries, and in alpha-thalassemia in general. Additional studies, including global and country-specific thalassemia registries, are needed to better understand the current prevalence of this condition.

Thrombosis and vascular biology - Biology & Translational Research

EP1319 DIRECT ORAL ANTICOAGULANTS FOR THE SECONDARY PROPHYLAXIS OF VENOUS THROMBOEMBOLISM: COMPARISON BETWEEN PATIENTS WITH MAJOR CONGENITAL THROMBOPHILIA AND NON-THROMBOFILIC PATIENTS

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Background: Direct oral anticoagulants (DOACs) are widely used for the treatment and secondary prophylaxis of venous thromboembolism (VTE). Congenital thrombophilia is a condition that predisposes to a higher incidence of VTE, more frequent VTE recurrences, some also in atypical sites, and often require long-term anticoagulation for secondary prevention. It is less clear whether DOACs have the same effectiveness in patients with major thrombophilia than in non-thrombophilic patients for the prevention of VTE recurrences.
Aims: The aim of our study was to evaluate the efficacy, in terms of VTE prevention, and safety, in terms of absence of bleeding complications, in patients with major thrombophilia compared to non- thrombophilic patients candidate to long-term anticoagulation for recurrent VTE.
Methods: We evaluated consecutive patients who required long-term anticoagulation for recurrent VTE, treated with DOACs, and compared the outcomes between patients affected by major thrombophilia and non-thrombophilic patients. All patients presented at least 2 thrombotic events. Major thrombophilia was defined as the presence of physiologic inhibitors deficiency (protein C [PC], protein S [PS], and antithrombin (AT); homozygous Factor V Leiden, homozygous Factor II G20210A, combined heterozygosity of these defects. After DOACs start, patients were checked every 6 months for blood count, renal and liver function, coagulation, and for the onset of thrombotic and hemorrhagic adverse events.
Results: The examined patients were 167: 72 (43.4%) with major thrombophilia and 94 (66.6%) non-thrombophilic. Patients with major thrombophilia were younger than non-thrombophilic: median age 42 years (range 18-91 years) vs 56 years (range 18-94 years) (p <0.0001). All patients' characteristics are specified in table 1. The median time of DOACS therapy was 32 months (range 6-90) in the group with major thrombophilia; 20 months (range 6-80) in the other group. Two (2.8%) thrombotic events were observed in the subset affected by major congenital thrombophilia and 4 (4.3%) in the non-thrombophilic group (p 0.4). Five (6.8%) minor bleedings were reported in the group of major thrombophilia; 13 (14%) hemorrhagic adverse events were observed in the other group: 10 minor and 3 clinical relevant non-major bleedings (p 0.14).

Table I. Population Characteristics

Patients under DOAC 167	Patients with thrombophilia	Control Patients	p value*
Number of patients	72	94	
Sex (Male/Female)	39/33	62/32	0.12
Body Mass Index (median)	24,6 (range 16.8-45)	27 (range 20-39)	0.007
Age at start of therapy (median years)	42,4 (range 18-91)	55,9 (range 18-94)	<0,0001
Platelets at start of therapy (Median10^3/mmc)	228 (range 148-380)	234 (range 130-600)	0.24
Creatinine at start of therapy (median mg/dl)	0,8 (range 0.2-1.50)	0.93 (range 0.2-1.53)	0.005
DOAC administered			
Rivaroxaban	29 (40.3%)	26 (27.7%)	
Edoxaban	7 (9.7%)	20 (21.3%)	
Apixaban	28 (38.9%)	43 (45.7%)	
Dabigatran	8 (11.1%)	5 (5.3%)	
Thrombophilia			
Protein C Deficiency	7 (9.6%)		
Protein S Deficiency	20 (27.4%)		
Antithrombin Deficiency	12 (16.4%)		
FV Leiden Homozygous Mutated	18 (24.7%)		
FII G20210A Homozygous Mutated	5 (6.8%)		
Double Heterozygous mutation	10 (13.7%)		

*When appropriate, Chi-square and Mann-Whitney tests were performed

DOAC= direct oral anticoagulants; FV= factor V; FII= factor II

Summary/Conclusion: Although major thrombophilia predisposes to a higher incidence of VTE, our data suggest that in this setting of patients, DOACs are effective and safe, with comparable results to non-thrombophilic patients.

EP1320 COMPARISON OF DIFFERENT CLINICAL RISK ASSESSMENT MODELS (RAMS) FOR THROMBOSIS IN AMBULATORY CANCER PATIENTS RECEIVING CHEMOTHERAPY FROM THE SECOND COHORT ONCOTHROMB 12-01 STUDY

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Background: The identification of ambulatory patients with cancer at a high-risk of thrombosis and candidates for thromboprophylaxis remains challenging as several risk assessments models (RAMs) have been developed but none of them are routinely used in clinical practice by oncologists.
Aims: To evaluate in a prospective validation cohort (Oncothromb12-01) the predictive capacity of the Khorana, PROTECHT, CONKO, Vienna-CATS modified without P-selectin and Pabinger's nomogram risk scores.

Methods: Multicenter, prospective, observational cohort study in Spain. The second cohort started in 2018 and includes outpatients with lung, central nervous system, colorectal, pancreatic, biliary tract, and gastric cancer naïve for systemic anti-tumor therapy and scheduled for initial treatment. The primary endpoint was the diagnosis of a symptomatic or incidental VTE episode within 12 months of follow up. The predictive power of each RAMs was analyzed by means of calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios, and area under the ROC curve (AUC).
Results: 126 patients, median age 64 y.o. Gender male/female 54/72. Tumor types: pancreas 42,1 %, colorectal 21,4%, gastric 11,9%, biliary tract 9,5%, lung 9,5%, CNS 3,2%, esophagus 1,6% and pancreas + colorectal 0,8%. 57,9% stage IV, 10,3% ECOG ≥ 2. Thirty-four (27%) developed VTE during follow-up. PE 12 (35,3%), DVT 8(23,5%), central venous catheter thrombosis 1 (35,3%), visceral VTE 15 (44,1%). Incidental VTE 24 (70,5%). Overall mortality rate at 12 months 43%. Mortality rate of patients with VTE 65%. 79% of patients with VTE had tumor persistence within 12 months. The positive threshold of 3 points was determined for high-risk category in the RAMs (> 10% for Nomogram). Performance of clinical RAMs is summarized in Table 1.

Table 1. Performance of clinical RAMs

	Khorana			PROTECHT			CONKO			Viena-CATS (D-dimer)			Nomogram		
	All	Inc	Sympt	All	Inc	Sympt	All	Inc	Sympt	All	Inc	Sympt	All	Inc	Sympt
AUC	0,522	0,51	0,52	0,551	0,60	0,57	0,515	0,50	0,53	0,53	0,50	0,58	0,60	0,54	0,71
P value	0,598	0,66	0,72	0,311	0,05	0,33	0,735	0,91	0,60	0,591	0,95	0,37	0,06	0,43	0,01
Sensitivity	79,4%	79,2%	80%	55,9%	66,7%	70%	75,8%	73,9%	80%	38,4%	33,3%	50%	38,5%	27,8%	62,5%
Specificity	25%	25%	25%	54,3%	54,3%	45,7%	27,3%	27,3%	27,3%	64,7%	67,4%	67,4%	81,4%	81,4%	81,4%
LR+	1,06	1,06	1,07	1,22	1,46	1,29	1,04	1,02	1,1	1,18	1,02	1,54	2,07	1,49	3,36
LR-	0,82	0,83	0,8	0,81	0,61	0,6	0,89	0,96	0,73	0,91	0,99	0,74	0,76	0,89	0,46

All= all VTE events; Inc = incidental; Sympt= Symptomatic

Summary/Conclusion: All clinical RAMs tested in this study performed poorly in this high-risk population. We suggest the inclusion of other parameters in the RAMs as genomic o molecular variables to improve the predictive capacity.

EP1321 NON-THROMBOTIC COMPLICATIONS OF ANTIPHOSPHOLIPID SYNDROME

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Background: Currently, antiphospholipid syndrome (APS) is recognized as one of the most important causes of acquired immune thrombophilia. Vascular accidents associated with the presence of antiphospholipid antibodies contribute greatly to morbidity and mortality. In addition, it is expected that APS, as an autoimmune disease, can lead to the development of a number of severe complications not associated with the risk of thrombosis.
Aims: To assess the nature of non-thrombotic complications of antiphospholipid syndrome.
Methods: The study included 55 patients aged from 14 to 61 years diagnosed with APS. The average age of patients was 36 ± 7.92 years, women predominated - 85.45%. The follow-up period ranged from 6 months to 7 years. The diagnosis was verified in accordance with the Sydney classification criteria of APS (2006). Antibodies (AB) to cardiolipin and to β2-glycoprotein-1 (β2-GP-1) of the IgM and G classes were determined by enzyme-linked immunosorbent assay (ELISA). Plasma hemostasis indicators and lupus anticoagulant were determined using an ACL Elite pro coagulometer. In order to exclude congenital thrombophilia, the activity of antithrombin III, proteins C and S, and the level of homocysteine were assessed. Molecular genetic testing (by PCR) for the presence of thrombogenic mutations was also carried out.
Results: The primary APS was identified in 90.9%. Among the clinical manifestations, obstetric pathology prevailed - 60% of cases. 23.6% of patients were diagnosed with thrombosis of various localization was diagnosed in: thromboembolism of the pulmonary arteries - 30.8%; vein thrombosis of the lower extremities - 30.8%; thrombosis of atypical localization (transverse sinus of the brain, portal vein) - 7.7%; ischemic cerebral circulation disorder - 16.5% of cases. In 4 patients (7.3%), the APS manifested with immune thrombocytopenia. Antibodies to β2-GP-1 of Ig M class were detected more often (36.4%); in 16.3% - antibodies to cardiolipin of the Ig M class and to β2-GP-1 of the IgG class. Highly positive APS was diagnosed in 27% of patients (n = 15), 60% of them developed complications within 2 to 3 years of follow-up, mainly due to the autoimmune mechanism of APS development. The most severe of them are aplastic anemia and aseptic necrosis of the heads of the pelvic bones, diagnosed in one patient at the age of 32 years. In two cases, the course of APS was complicated by the renal-cutaneous form of hemorrhagic vasculitis with the development of glomerulonephritis. The most common complication (44%) was autoimmune coagulopathy with pronounced decrease in plasma coagulation factors FVIII and FIX due to the presence of inhibitors to them. In one case, autoimmune hemolytic anemia was diagnosed against the background of APS.
Summary/Conclusion: The course of APS can be clinically manifested not only by thrombotic, but also by severe hematological complications, such as aplastic anemia, autoimmune coagulopathy, hemorrhagic vasculitis, autoimmune hemolytic anemia, and immune thrombocytopenia. In this regard, the diagnosis of primary APS should be considered much wider than the range of acquired thrombophilia.

EP1322 HIGH RATE OF BLEEDING AND ARTERIAL THROMBOSIS IN COVID-19: SAUDI MULTICENTER STUDY

A. al Raizah [1,*], A. Hejazi [1], M. Al Zahrani [1], N. Shaheen [2], K. Aldosari [1], M. Alnahdi [1], M. Luhanga [1], A. Basendwah [3], T. Alshuaibi [4], E. Alrayes [5], M. Almegren [6], A. Al Askar [1]

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Background: Several observational studies have reported the rate of venous and arterial thrombotic events in patients infected with COVID-19, with conflicting results.
Aims: The aim of this study was to estimate the rate of thrombotic and bleeding events in hospitalized patients diagnosed with Coronavirus disease 2019 (COVID-19).
Methods: This was a multicenter study of 636 patients admitted between 20 March 2020 and 31 May 2020 with confirmed COVID-19 in four hospitals. Patients were excluded if they were transferred in or out from one of these four hospital to another hospitals. Patients also excluded is they were admitted for less than 24 hours. Venous thromboembolism (VTE) included all symptomatic or incidentally diagnosed cases of pulmonary embolism (PE), deep vein thrombosis (DVT) and thrombosis in unusual sites (cerebral, mesenteric, portal, splenic, hepatic, and renal veins). All VTEs were confirmed radiographically by appropriate imaging. Screening for VTE in asymptomatic patients was not performed. Arterial events included cerebrovascular accidents (CVAs), mesenteric ischemia, limb ischemia and myocardial infarction (MI) were confirmed by the appropriate clinical, laboratory and imaging modality. Bleeding events were classified as major and nonmajor based on the definition of International Society of Thrombosis and Haemostasis (ISTH). The rates of VTE, bleeding, arterial are summarized as proportions, with the corresponding 95% confidence intervals (CIs). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Informed consent was waived.
Results: The majority of patients (90%, n=573) and more than 99% of those in the ICU group received pharmacological prophylaxis according to local hospital practice. The most frequently prescribed regimen was enoxaparin (40 mg once daily) (59.2%). Over a median length of stay in the non-ICU group of 7 days and of 19 days in the ICU group, twelve patients were diagnosed with Venous thromboembolism (VTE) (1.8%) (95% CI, 1.1–3). The rate in the non-ICU group was 0.19% (95% CI, 0.04–0.84), and that in the ICU group was 10.3% (95% CI, 6.4–16.2). Two patients were not on prophylaxis prior to the event, 3 were on enoxaparin (40 mg once daily), 3 were on UFH (5000 IU twice daily), 2 were on UFH (5000 IU TID), one was on enoxaparin (40 mg twice daily), and one was on fondaparinux (2.5 mg once daily).The overall rate of arterial event is 2.2% (95% CI, 1.4–3.3). The rates in the non-ICU and ICU groups were 0.94% (95% CI, 0.46–0.1.9) and 8.4% (95% CI, 5.0–14.0). The overall rate of bleeding is 1.7% (95% CI, 1.0–2.8). The bleeding rate in the non-ICU group was 0.19% (95% CI, 0.04–0.84),

and that in the ICU group was 9.4% (95% CI, 5.7–15.1). At the time of bleeding, six patients were on enoxparin 40 mg once, 2 were on UFH(Unfractionated heparin)5000 IU TID, 1 was on enoxparin 40 BID, 1 was on asprin and one was on full dose UFH.

Table 1. Demographics and Baseline Characteristics of the Population

	Overall n=636	Non-ICU n=530	ICU n=106	p-value
Age (mean ±SD)	49±16	47±16	59±14	<0.0001
Male n (%)	456 (71.7)	371 (70)	85 (80.2)	0.033
BMI (mean ±SD)	28.4±6.0	28.1±5.5	17.3±7.8	0.075
^^Any comorbidities n (%)	303(47)	205(38)	98(92)	<0.0001
Active Cancer n (%)	12 (1.9)	9 (1.7)	3 (2.8)	0.432
History of Thrombophilia n (%)	3 (0.47)	1 (0.19)	2 (1.8)	0.073
History of DVT/PE n (%)	6 (0.94)	5 (0.95)	1 (0.94)	1.00

^^ Comorbidities: DM, hypertension, coronary artery disease, stroke, bronchial asthma, COPD, heart failure, and ESRD.

Table 2. Outcome Data

Variable	Overall	Non-ICU	ICU	P value
VTE % (95% CI)	1.8 (1.1–3)	0.19 (0.04–0.84)	10.3 (6.4–16.2)	<0.0001
PE n	8	0	8	
DVT n	5	0	5	
Proximal upper n	1	0	1	
Proximal lower n	4	0	4	
Other VTE n	2	1	1	
Arterial % (95% CI)	2.2 (1.4–3.3)	0.94 (0.46–1.9)	8.4 (5.0–14.0)	<0.0001
CVA n	10	4	6	
MI n	4	1	3	
Bleeding % (95% CI)	1.7 (1.0–2.8)	0.19 (0.04–0.84)	9.4 (5.7-15.1)	<0.0001
Major bleeding n	5	1	4	
Other bleeding n	6	0	6	

Summary/Conclusion: In this study, we found that the VTE rates in hospitalized patients with COVID-19 might not be higher than expected. In contrast to the risk of VTE, we found a high rate of arterial and bleeding complications in patients admitted to the ICU. Given the high rate of bleeding, the current study suggests that the intensification of anticoagulation therapy in COVID-19 patients beyond the standard of care be pursued with caution and would best be evaluated in a randomized controlled study.

1. *Moores, Lisa K., et al. Chest 158.3 (2020): 1143-1163.*
2. *Spyropoulos, Alex C., et al. Journal of Thrombosis and Haemostasis 18.8 (2020): 1859-1865.*

EP1323 PLATELET COUNT AND MEAN VOLUME IN ACUTE STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Incidence of stroke in Europe is 95 to 290/100,000 per year and it is the fourth cause of death in the United States. The important role of platelets in the pathogenesis of the acute stroke (AS) (atherothrombosis and ischemic) has been documented. Mean platelet volume (MPV) is regarded as a marker of platelet turnover. More immature, thereby larger platelets usually contain more granules, thus releasing more chemokines promoting further platelet aggregation as well as activation. Elevated MPV simultaneously with the elevated PC increases the risk of thrombosis. Significant increased MPV in patients with deep vein thrombosis and isolated elevated platelet count (PC) in patients with pulmonary embolism has been revealed.
Modification of platelet function and consequently a hypercoagulable state has been suggested in patients with both ischemic and hemorrhagic strokes. It has been shown that PC and MPV are independent predictors for poor outcome in primary intracerebral hemorrhage (PICH). There has also been a body of interest for PC and MPV in stroke patients. However, these studies have yielded inconsistent findings. Some groups reported that patients with AS had significantly increased MPV or PC compared with controls, whereas other studies found decreased MPV or PC values in AS patients. Additionally, some studies have observed no association between these parameters and AS.
Aims: Taking these inconsistent findings into consideration, we undertook a meta-analysis to investigate the association between MPV, PC and AS.
Methods: Studies were included in accordance with Patient Population or Problem, Intervention, Comparison, Outcomes, and Setting framework. The PRISMA strategy was used to report findings. Risk of bias was assessed with the Newcastle-Ottawa Scale.
Results: We included 34 eligible articles retrieved from the literature. PC was significantly lower in AS patients [standardized mean difference (SMD) = – 0.30, (95%CI: – 0.49 – – 0.11), N = 2492, P = 0.002] compared with controls (N = 3615). The MPV was significantly higher [SMD = 0.52, (95%CI: 0.28 – 0.76), N = 2739, P < 0.001] compared with controls (N = 3810). Subgroup analyses showed significantly lower PC in both ischemic stroke (Difference SMD = – 0.18, 95%CI: – 0.35 – 0.01) and hemorrhagic stroke (– 0.94, – 1.62 – – 0.25), but only samples by citrate anticoagulant showed significantly lower result for patients compared to controls (– 0.36, – 0.68 – – 0.04). Ischemic stroke patients had higher MPV (0.57, 0.31 – 0.83), and samples by Ethylenediaminetetraacetic acid (EDTA) anticoagulant showed significantly higher result for patients compared to controls (0.86, 0.55 – 1.17).
Summary/Conclusion: PC and MPV appeared to be significantly different between patients with AS and control populations. MPV was significantly higher in ischemic stroke and PC was significantly lower in both ischemic and hemorrhagic strokes. These characteristics might be related to AS and associated with it. It is advisable to pay attention to elapsed time between phlebotomy and hematology analysis, anticoagulant and hemocytometer types in AS.

EP1324 PROGNOSTIC VALUE OF SONORRHEOMETRY IN COAGULOPATHY IN COVID-19 PATIENTS.

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Background: COVID-19 is a severe respiratory disease caused by the SARS-CoV-2 that manifests severely in a high number of patients, leading to hospitalization of many of them and in the worst case to death. Recent studies have shown a high incidence of thrombotic complications in these patients, especially in those with poor prognosis, and confer special interest to D-dimer as an indicator of poor prognosis. However, the diagnostic value of D-dimer is limited by the long analysis times and that it only reflects the final part of the physiological process of hemostasis. Therefore, the identification of other parameters is needed to allow a rapid and reliable characterization of the hemostatic status of the patient. Viscoelastic testing allows a global analysis of coagulation and have already proven their usefulness in the study of other infectious diseases. The application of viscoelastic tests in COVID-19 patients would therefore be very useful to quickly determine the hemostatic status of patients and thus identify predictors of poor prognosis.
Aims: To characterize the hemostatic status of COVID-19 patients with standard and viscoelastic testings, and identification of poor prognosis variables.
Methods: Prospective, observational, single-centre study. A total of 50 patients requiring hospitalization were included in the study. The next-generation viscoelastic testing "Quantra Hemostasis Analyzer" (HemoSonics) was used to determine the coagulation profile of patients. Blood samples at the time of hospitalization were taken to determine the parameters reported by Quantra (QStat and QPlus cartridges). Correlation study using a heat map of our Spearman partial correlation matrix with a confidence interval of 95%.
Results: As described, a high percentage of COVID-19 patients admitted to hospital showed increased levels of fibrinogen (81.6%), D-dimer (61.9%), IL-6 (70.3%) and increased clot stiffness measured by CS, FCS and PCS parameters (63.6%), while clotting times were normal in almost 100% of patients. Age (>65 years), together with elevated levels of D-dimer, LDH and clot firmness were associated with the presence

of an adverse event during admission, including the need for mechanical ventilation, ICU admission or death (p=0.007/0.030/0.010/0.002). Increased D-dimer levels were significantly recurrent in patients >65 years (p=0.031). A significant difference was observed between the median of these parameters between patients who experienced an adverse event and those who did not: fibrinogen (750 vs 532, p=0.010), D-dimer (779 vs 560, p=0.005), LDH (309 vs 227, p=0.027), CTH (131.5 vs 123, p=0.042), CS (38.15 vs 25, p=0.042), PCS (30.85 vs 20.7, p=0.042) and FCS (7.45 vs 3.9, p=0.027). Multiple correlation study using HeatMap representation revealed independence between clot firmness, age, LDH and D-dimer levels.

Summary/Conclusion: The study of global hemostatic status using Quantra can be a powerful tool for the analysis of COVID-19 patients at admission and thereby predict risk by identifying markers of poor prognosis. Increased levels of parameters measuring clot stiffness are associated with the presence of an adverse event in patients and can be considered as new independent prognostic markers.

EP1325 THROMBOTIC EVENTS AND THE PROFILE OF HEREDITARY THROMBOPHILIA FACTORS IN COVID-19 PATIENTS

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Background: The leading cause of mortality in more than 2.5 million COVID-19 patients is the development of acute respiratory distress syndrome and multiple organ failure associated with thrombotic events (TE). However, information on the nature of TE and the pathogenetic significance of hereditary thrombophilia factors in patients with COVID-19 is still not completely understood.

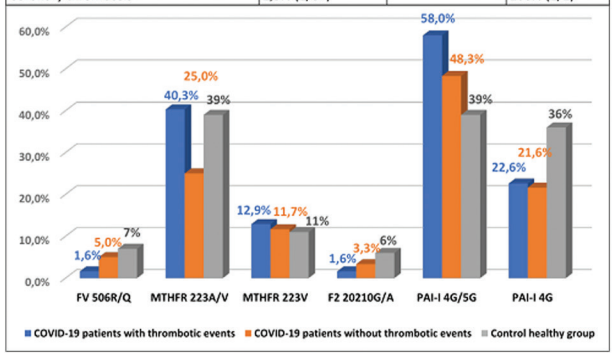
Aims: To study possible correlation of TE with the profile of FV 506R/Q, MTHFR 223A/V, F2 20210G/A, and PAI-1 4G/5G mutations in patients with COVID-19.

Methods: Autopsy studies of 179 COVID-19 patients were performed from April to July 2020. Median age of the patients was 73 (range 37 to 99).Control healthy group was 71 individuals with median age of 56 (range 25 to 71). DNAs were isolated from formalin-fixed and paraffin-embedded spleen tissues using a QIAamp DNA FFPE Tissue Kit (QIAGEN, USA) according to the manufacturer's instructions. FV 506R/Q, MTHFR 223A/V, F2 20210G/A, and PAI-1 4G/5G alleles were assessed by an allele-specific real-time polymerase chain reaction.

Results: According to the results of postmortem examinations, 87 patients with TE were identified (see Figure 1). Pulmonary artery thrombosis was detected in 37.9% (33/87) of cases. Pulmonary embolism (PE) was detected in 27.6% (24/87) of cases, of which 87.5% (21/24) PE was combined with deep vein thrombosis (DVT) of the lower extremities, in two patients - with intracardiac thrombi, and in one case - both with DVT and intracardiac thrombi. The frequency of PE in women was twice as high. The incidence of pulmonary vein thrombosis was 18.4%, with a predominance in men (62.5% vs. 37.5%). Isolated intracardiac thrombi were found in 11.5% (10/87) of patients, with a predominance in women. Hepatic vein thrombosis was 4.6% (4/87) of cases. Cerebral artery, coronary vessels, and mesenteric veins thrombosis was detected in 2.3% (2/87) of cases. FV 506R/Q, MTHFR 223A/V, F2 20210G/A, and PAI-1 4G/5G allele patterns were identified for 122 cases 62 of which had TE (see Figure 1). The group of patients with TE revealed a higher incidence of heterozygous genotypes MTHFR 223A/V compared to those without TE (40.3% versus 25%), but relatively similar to the control healthy group (40.3% vs. 39%), and higher incidence of heterozygous PAI-1 4G/5G compared to both groups (58% vs. 48.3% vs. 39%). On the contrary, the incidence of FV 506R/Q and F2 20210G/A heterozygotes was lower compared to the group without TE, and control healthy group. The incidence of homozygous MTHFR 223V and PAI-I 4G did not differ significantly between COVID-19 patients groups, however the latter genotype incidence was lower compared to control healthy group.

Figure 1. Types and frequencies of vascular TE, and profile of the hereditary thrombophilia factors

Vascular TE	General (n=87)	Males (n=38)	Females (n=49)
Pulmonary artery thrombosis	37,9% (33/87)	48,5% (16/33)	51,5% (17/33)
Pulmonary embolism (PE)	27,6% (24/87)	29,2% (7/24)	70,8% (17/24)
PE associated with deep vein thrombosis	21/24	33,3% (7/21)	66,7% (14/21)
PE associated with intracardiac thrombi	3/24	33,3% (1/3)	66,7% (2/3)
Pulmonary vein thrombosis	18,4% (16/87)	62,5% (10/16)	37,5% (6/16)
Isolated intracardiac thrombi	11,5% (10/87)	40% (4/10)	60% (6/10)
Hepatic vein thrombosis	4,6% (4/87)	75% (3/4)	25% (1/4)
Cerebral artery thrombosis	2,3% (2/87)	100% (2/2)	-
Mesenteric venous thrombosis	2,3% (2/87)	-	100% (2/2)
Coronary thrombosis	2,3% (2/87)	-	100% (2/2)



Summary/Conclusion: Thrombosis and thromboembolism of arteries and veins of vital organs are detected in about half of patients who died from COVID-19. No significant trends in the distribution of genotypes of predisposition to thrombophilia between groups of COVID-19 patients with TE and without them, and the control healthy group have been revealed. This is quite unexpected that patients who died from thrombotic complications do not show any signs of hereditary predisposition to thrombophilia. Especially concerning no bias in PAI-4G allele incidence. Probably we do not have enough sample strength to reveal possible differences. Therefore, establishing the role of hereditary thrombophilia factors in the development of COVID-19 associated TE requires further studies with an extended cohort of patients.

EP1326 ROTATIONAL THROMBOELASTOMETRY (ROTEM) PROFILING OF COVID–19 PATIENTS

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Background: Thrombosis is frequently diagnosed in patients with Coronavirus disease (COVID - 19), despite the use of a standard-dose thromboprophylaxis in all hospitalized. Since conventional coagulation tests (CCTs) reflect only limited parts of the coagulation system and are insufficient to assess hypercoagulability, rotational thromboelastometry (ROTEM) could be more effective in identifying hypercoagulable pattern and patient in high-risk of thrombosis.

Aims: 1. To analyze ROTEM parameters across the entire clinical COVID-19 pneumonia spectrum, from moderate to critical. 2. To determine the incidence of hypercoagulable ROTEM patterns and improve risk stratification.

Methods: We evaluated coagulation abnormalities via CCTs and ROTEM in a group of 94 patients with confirmed SARS-CoV-2 infection and different severity of pneumonia (34 moderate, 25 severe, 35 critical). Shorter than normal clotting time (CT) and higher than normal maximum clot firmness (MCF) in both extrinsic pathway (EXTEM) and fibrinogen pathway (FIBTEM), as well as shorter than normal EXTEM clot formation time (CFT) and higher than normal α-angle were classified as markers of hypercoagulable state.

Results: At least one hypercoagulable ROTEM parameter had 62 (66%) patients. Increment in the number of patients with ≥ 2 hypercoagulable parameters, higher EXTEM MCF (P = 0.0001), higher FIBTEM MCF (P = 0.0001) and decrement in maximum lysis (P = 0.002) were observed

with increment in disease severity (P = 0.0001). Significant positive correlations between interleukine - 6 (IL6) and CT EXTEM (P = 0.003), MCF EXTEM (P = 0.033), MCF FIBTEM (P = 0.01) as well as negative with ML EXTEM (P = 0.006) were seen. Contrary to hypercoagulable ROTEM pattern which was not predictive for death, hypocoagulability represented by prolonged EXTEM CT (P = 0.0001) and CFT (P = 0.0001), smaller α angle (P = 0.014) and a prolonged FIBTEM CT (P = .0001) was a predictor.

Summary/Conclusion: Our findings confirmed that a hypercoagulable ROTEM pattern characterized by clot formation acceleration, high clot strength, and reduced fibrinolysis was more frequent in advanced disease groups and patients with high IL6. These results support the need for different thromboprophylaxis approaches for different severity groups.

EP1327 INCIDENCE OF THROMBOHAEMORRHAGIC COMPLICATIONS IN THE PERIPROCEDURAL OF ORAL ANTICOAGULANT TREATMENT WITH VITAMIN K ANTAGONISTS

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Background: During the follow-up of oral anticoagulation therapy (OAT) with vitamin K antagonists (VKA), the patient undergo invasive procedures. The decision wether to withdraw or maintain the OAT, as well as the needing or not to implement low molecular weight heparin (LMWH) as bridge therapy, will be determined by the patient's thrombotic risk (TR) and the haemorrhagic risk (HR) of the surgery.

Aims: To determine the incidence of thrombohemorrhagic complications in the periprocedural of the patient with OAT, limiting the use of LMWH to patients at high TR looking for decreasing bleeding events related to surgery.

Methods: Prospective, unicentric and observational study including 200 patients with OAT who had had surgery between December 2019 and February 2021, with a subsequent follow-up of 4 weeks. The periprocedural management of the OAT was carried out in the anticoagulation consultation according to the hospital protocol approved in the Thrombosis Committee, which classifies patients according to TR (High TR: Prosthetic heart valves, atrial fibrillation (AF) with CHA2DS2-VASc score 7-9, Severe rheumatic mitral valvulopathy, Venous Thromboembolism less tan 3 months ago and Severe thrombophilia, define as Leyden's factor V in homozygosis, 20210 prothrombin mutation, protein C, S or antithrombin III deficiency, múltiples deficiencys or Antiphospholipid Syndrome), and surgeries in three groups according to HR. Thus, the VKA is suspended 3 days before the intervention and resumed 24 hours after. The use of LMWH as bridge therapy (BT) is reserved for patients with high TR or suspected active cancer. It starts the moment OAT is suspended and it is reintroduced along with it 24 hours after surgery for 3 days (if there are no bleeding complications). The dose of LMWH is therapeutic (as patients requiring BT are high TR).

Given the coagulopathy inherent to COVID infection, no positive COVID patients were included.

Results: The median age of the population is 73 (range 33-93). The main reason for anticoagulation is AF (64.5%). Most patients are low TR and HR on the CHADs-VASc and HAS-BLED scales (76% and 64% respectively). 26.5% of the patients had personal history (PH) of thrombosis and 5.5% had PH of Hemorrhagic Diathesis.

Table 1 shows the interventions performed and clinical events during the follow-up period. 10 post-surgical haemorrhagic events (5%) are described. Three of them (hemoperitoneum after cholecystectomy, hemoperitoneum after laparoscopic tubular gastrectomy, and haematoma of the anterior rectus abdominis muscle with secondary anemization after ventral hernia repair) required hospitalisation for management, all of which were solved with conservative treatment. The other 7 were mild events that were handled outpatiently. In addition, intra-procedure bleeding during bronchoscopy is described in patient with BT, that was controlled on the spot with amchafibrin and adrenaline. No thrombotic events were recorded. Generally, OAT was re-induced the day after surgery in patients undergoing minimal and low HR interventions, being the percentage somewhat lower in patients undergoing high HR interventions, both in high or low TR patients.

Table 1. Incidence of haemorrhagic and thrombotic complications according to the TR of the patient and the HR of the intervention.

Thrombotic Risk of the patient		Haemorrhagic risk of the surgery		Haemorrhagic Complications	Thrombotic Complications	OAT re-induced the day after surgery
High TR: Bridge therapy with LMWH	72 (36%)	Hihg/moderate HR	25 (12.5%)	5 (2.5%)	0%	19 (76%)
		Low HR	18 (9%)	1 (0.5%)		17 (94.4%)
		Minimum HR	29 (14.5%)	0 (0%)		28 (96.6%)
Low RT: Without bridge therapy	128 (64%)	Hihg/moderate HR	59 (29.5%)	3 (1.5%)		49 (83.1%)
		Low HR	25 (12.5%)	2 (1%)		23 (92%)
		Minimum HR	44 (22%)	0 (0%)		42 (95.4%)

TR: thrombotic risk; HR: haemorrhagic risk; LMWH: low molecular weight heparin.

Summary/Conclusion: Standardization by means of a periprocedural management protocol of the OAT that adjusts BT with LMWH according to the risk factors of each patient, results in a reduction of the incidence of haemorrhagic complications without secondary increase of thromboembolic events. This study demonstrates the importance of centralizing unified periprocedural management using an established protocol.

EP1328 PLATELET ADHESION, VON WILLEBRAND FACTOR ACTIVATION AND LEUKOCYTES RECRUITMENT AT HIGH SHEAR RATES

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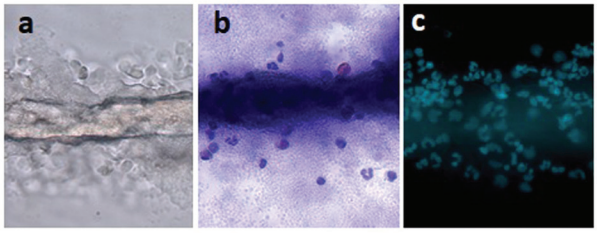
Background: Platelet adhesion is an important process in primary haemostasis and thrombus formation. Von Willebrand factor (VWF) is a key mediator of platelet adhesion at sites of vascular injury under high shear rates. Recent studies showed that VWF becomes highly reactive with platelets and leukocytes upon unfolding into a stretched conformation, at shear rates above the critical value, which occur at sites of arterial stenosis and injury. Activated VWF and platelets, adhered to injured vessel wall, may serve as sites of leukocyte recruitment under flow conditions and predispose to the propagation of inflammation and thrombosis.

Aims: The aim of the study was to investigate platelet adhesion and leukocyte recruitment in whole blood under high shear rates.

Methods: Venous blood from 7 healthy volunteers was collected from the cubital vein into PPACK solution at final concentration of 100 μM or into EDTA (1.6 mg/ml). To study the kinetics of cell adhesion to collagen we developed a laser optical system that utilizes special optical and microfluidic techniques. The microfluidic optical system consists of a cell assembly with a disposable flow chamber, a specialised optical prism system with a semiconductor laser and a photodetector. Shear stress-induced adhesion of blood cells to type I collagen-coated surface of a perfusion chamber was registered during 15 minutes of circulation of whole blood samples at shear rate of 2300 s^{-1}. After 15 minutes of perfusion flow chambers were fixed with 1% formalin solution, stained by Giemsa staining and 4′,6-diamidino-2-phenylindole (DAPI). Platelet GP Ib and GP IIb/IIIa receptors were blocked using monoclonal antibodies.

Results: Cell adhesion was quantified by measuring the intensity of scattered light after 15 min of perfusion and was 0.35±0.10 V in control samples, 0.25±0.08 V in samples after addition of anti-GP Ib and 0.07±0.03 V after addition of anti-GP IIb/IIIa antibodies (p=0.002). In blood samples with EDTA the intensity of scattered light was 0.06±0.02. Microscopy of perfusion chambers revealed large protein structures in the form of long strands. They were attached to a collagen surface and stretched along the streamline (Fig. 1a). Microscopy of perfusion chambers after Giemsa staining revealed that the protein structures were co-localized with leukocytes and platelets (Fig. 1b). Fluorescence microscopy of samples after staining with DAPI confirmed that there are leukocytes in this structure (fig. 1c).

Figure 1. Platelet adhesion and leukocyte recruitment to a collagen-coated surface at shear rate of 2300 s-1. (a) Transmitted optical microscopy; (b) Microscopy with Giemsa staining; (d) staining with 4′,6-diamidino-2-phenylindole (DAPI).



Summary/Conclusion: Our data demonstrate that platelet adhesion and leukocyte recruitment to collagen coated surface at high shear rates is mediated by the complex interaction of von Willebrand factor and platelet GP receptors.

EP1329 EXPERIENCE WITH DIRECT ORAL ANTICOAGULANTS (DOACS) FOR THE TREATMENT OF CANCER ASSOCIATED THROMBOSIS

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Background: Low molecular weight heparins (LMWH) have long been the gold standard of the treatment of cancer associated thrombosis (CAT). However the growing use of DOACs as currently recommended by most international guidelines is gradually changing the treatment paradigm in this setting

Aims: To report some real-world experience on the efficacy and safety of DOACs for the treatment of CAT in a community hospital in Spain

Methods: Patients evaluated had been diagnosed with CAT, were referred from the Oncology to the Haematology Department for management of anticoagulant treatment and agreed to start on a DOAC. All patients had active cancer and underwent regular outpatient follow-up in order to make decisions on DOAC treatment duration, perform dose adjustments as required and evaluate any episodes of recurrent VTE or bleeding. DOACs are licensed but not reimbursed in Spain for the treatment of venous thromboembolism (VTE)

Results: Twenty three patients (12 male/11 female) fulfilled criteria mentioned above. Patients were affected by cancers as shown in Table 1. Over 60% (60.8%; 14 patients) had metastatic disease and almost 2 out of 3 (65.2%) were on some type of chemotherapy when VTE was diagnosed. Median age and duration of DOAC therapy were 68 years (range 49-87) and 103 days (range 27-740) respectively; 43.4% (10 cases) were treated for over 6 months. Twenty three patients had received a LMWH (tinzaparin 13, enoxaparin 7) following diagnosis of CAT for a median of 3 months (range 0-15) before switching to a DOAC. Rivaroxaban was the most commonly prescribed DOAC (20 patients; 87%). Edoxaban (2 cases) and apixaban (1 case) accounted for the rest of DOAC prescriptions. Most cases (69.5%) were sorted as having low thrombotic risk according to Khorana score 0-1 and the diagnosis of VTE was incidental in 14 cases (60.8%), this is, all cases of PE and 1 of portal/mesenteric venous thrombosis (Table 1). Only 2 individuals (8.7%) had a prior history of VTE.

Two patients (8.7%) with lung cancer showed thrombotic recurrence during follow-up in association with recurrent and/or locally advanced tumor progression.

No major bleeding episodes (ISTH criteria) were reported throughout the follow-up period. Four patients (17.3%) presented with some episode of clinically relevant non-major bleeding at a median of 2 months (range 1-4) from DOAC start: 3 cases of haematuria (1 patient on rivaroxaban with a urine bladder tumour, and 2 cases of lung cancer) and 1 case of haemoptisis (in a patient on edoxaban with lung metastases of a gynaecological cancer; incidence 1.2 per 100 patients-year). Nine patients (39.1%) died during the follow-up after a median of 88 days of DOAC therapy (range 54-740); in all cases cancer progression was the cause of death

Summary/Conclusion: Our real-world experience in an unfavourable-profile cancer patient setting confirms that DOACs are efficient and safe for the treatment of CAT even when prescribed for longer periods than those reported in clinical trials. Although initial treatment with a LMWH before patient referral and DOAC start may bias our results these are clinically applicable. Thus, incidence of thrombotic recurrence was consistent with that reported in pivotal trials of direct factor Xa inhibitors for the treatment of CAT and linked to cancer progression in our experience. Bleeding was always easily manageable with no major bleeding episodes being reported; incidence of other bleeding complications was also consistent with that reported in clinical trials of DOAC treatment for CAT

EP1330 THE EFFECTS OF AMBIENT PARTICULATE MATTER AIR POLLUTION ON HEMOSTASIS: A REPEATED-MEASURES ANALYSIS

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Background: High level of ambient air pollution significantly increases thrombotic risk, stroke, myocardial infarction and mortality rates. Furthermore, fine particulate matter size less than 2.5 and 10 microns ($PM_{2.5}$ and PM_{10}) were associated with disseminated intravascular coagulation (DIC) in animal models. This study describes the hemostatic changes in adults during the seasonal variations of air pollution.

Aims: This study aims to evaluate the short-term effects of high levels of $PM_{2.5}$ and PM_{10} on the coagulation tests in the same healthy individuals across the seasonal variations of ambient air pollution.

Methods: This is a prospective study. The data were collected from 30 platelet apheresis donors, during February and July 2020 at The Blood Bank Center, Maharaj Nakorn Chiang Mai Hospital, Thailand. The blood samples were obtained repeatedly at the time of donation, once every 4 weeks for 4 visits. The complete blood count and various coagulation tests, including PT, aPTT, vWF antigen, ristocetin cofactor assay, P-selectin and platelet function analysis, were done. Data of the ambient air pollution was recorded at the central air-quality monitoring station, one kilometer from the hospital center. Mixed effect model was used to analyze the impact of high $PM_{2.5}$ and PM_{10} on the blood cell count and the hemostatic tests.

Results: There were 30 healthy volunteers, 29 (96.7%) were men. Mean age was 38.9±8.2 years old. The median levels of $PM_{2.5}$ at the first, second, third and the fourth visits were 68.4, 35.25, 14.36 and 6.21 µg/m^3, and the PM_{10} levels during each visit were 98.09, 52.13, 25.92 and 15.96 µg/m^3, respectively. The hematocrit value was correlated with the $PM_{2.5}$ and PM_{10} levels. The white blood cell and platelet count were not affected. P-selectin was significantly associated with the levels of $PM_{2.5}$ and PM_{10}. The platelet function showed no correlation with the particulate matter level. The elevated $PM_{2.5}$ and PM_{10} levels were associated with the shortening of prothrombin time. This effect was not seen in aPTT. The values of $PM_{2.5}$ and PM_{10} markedly correlated with the increased von Willebrand function, whereas the von Willebrand antigen remained unchanged.

Summary/Conclusion: The elevated $PM_{2.5}$ and PM_{10} levels affect coagulation tests, including the shortening of prothrombin time and increased von Willebrand function. These findings wound play a key role in pathogenesis of ambient air pollution-related thrombosis.

EP1331 VALUE OF LABORATORY PARAMETERS IN THE CLINICAL MONITORING OF PATIENTS WITH SARS-COV-2 INFECTION (COVID-19).

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Background: Association between some analytical parameters and clinical evolution of patients infected by SARS-COV-2 is a controversial issue.
Aims: Review the relationship between laboratory parameters and severity and/or lethality of the COVID-19.
Methods: Observational, cross-sectional and retrospective study. Data obtained from electronic health record of patients over 18 years of age admitted in our hospital, between March and May 2020 with suspected SARS-COV-2 infection. After descriptive statistical study, we did an inferential analysis using Mann-Whitney U test for independent samples, in order to verify association between the results of analytical parameters and the clinical severity (defined by hospitalization in conventional ward vs. intensive care units (ICU)) and/or lethality (alive vs. death at the end of the study).
Results: 668 patients were included, 345 men (52%) and 323 women (48%), with a median age of 70 years. 80% of patients had previous comorbidities, 10% were admitted to the ICU, and 17% died.
Differences were found in hematimetric parameter between the different groups: leukocytes (10^3/µl): 8.3 in ICU patients vs. 6.5 in those admitted to the ward; platelet count (10^3/µl) of 182l in death patients vs. 223 in survivors; hemostasis parameters: D-dimer (DD) (µg/L) of 1379 and 1236 in deceased and admitted to the ICU respectively, compared to 734 and 786 in survivors and not admitted to ICU; and biochemical figures (increase in C-reactive protein (CRP), lactate dehydrogenase (LDH) or cardiac enzymes, the latter, especially, in patients who were deceased, with a median ultrasensitive troponin I (ng/L) of 34.75 vs. 7.1 in survivors. The differences were statistically significant (p value <0.01).

Figure 1. ICU vs. Ward admitted/ Defeated vs survival. *Inferential Statistics.*

	R.V.[1]	U.[2]	Total	ICU	Ward admitted	p value	Defeacted	Survival	p value
Blood count									
Haemoglobin	(12-16.5)	g/L	13.1 (1.77)	12.55 (2.27)	13.1 (1.76)	0.211	12.4 (2.22)	13.1 (1.73)	0.014
Leukocytes	(3.6-10.5)	10^3/µl	6.6 (6.97)	8.3 (4.72)	6.5 (7.2)	0	8.35 (7.29)	6.5 (6.86)	0
Neutrophils	(1.5-7.7)	10^3/µl	4.7 (5.04)	7.25 (4.4)	4.5 (5.06)	0	7.2 (4.55)	4.45 (5.05)	0
Linfocytes	(1.1-4.5)	10^3/µl	1 (2.34)	0.7 (0.4)	1.1 (2.46)	0	0.7 (5.45)	1.1 (0.67)	0
Platelets	(140-370)	10^3/µl	217 (140.9)	229 (129.9)	214 (143.1)	0.507	182 (97.25)	223 (147.31)	0
Haemostasia									
DD[3]	(0-500)	µg/L	821 (7035.58)	1236 (4781.19)	786 (7201.16)	0	1379 (4426.68)	734 (7428.4)	0
PT[4]	(9,5-14,3)	seg	12,9 (8,05)	13,1 (2,84)	12,9 (8,47)	0,121	13.4 (15.72)	12.9 (4.85)	0.013
APTT[5]	(25-37,9)	seg	30 (5,7)	30,35 (6,5)	30 (5,73)	0,197	31.25 (8.75)	29.7 (4.84)	0
Biochemistry									
LDH[6]	(0-248)	U/L	279 (143.03)	480.5 (181.02)	270 (127.11)	0	392 (195.04)	270 (119.4)	0
Ferritin	(15-300)	ng/ml	617 (6109.7)	1579.8 (2071)	600 (6372.04)	0	766.9 (1444.17)	599.6 (6557.9)	0.006
IL-6[7]	(0-7)	pg/ml	29.1 (950.92)	78.15 (465.34)	26.77 (990.9)	0.05	65.23 (2243.64)	24.43 (173.07)	0.09
CRP[8]	(0-0.5)	mg/dl	7.8 (9.42)	15.24 (12.29)	7.2 (8.66)	0	13.67 (11.32)	6.75 (8.45)	0
PCT[9]	(0-0.5)	ng/ml	0.11 (12.25)	0.325 (15.54)	0.1 (11.79)	0	0.3 (28.58)	0.09 (2.13)	0
TnI[10]	(0-19.8)	ng/L	8.3 (404.43)	14.1 (51.4)	8.1 (420)	0.002	34.75 (732.46)	7.1 (306.1)	0

All analytical data expressed as median (standard deviation). 1. Reference values in our laboratory 2. Units of measurement. 3. D-dimer. 4. Prothrombin time. 5. Activated partial thromboplastin time. 6. Lactic dehydrogenase. 7. Interleukin 6. 8. C-reactive protein. 9. Procalcitonin. 10. Troponin I.

Summary/Conclusion: Correlation exist between severity of infection and the increase in leukocytes, neutrophils, DD, CRP and LDH, and lymphopenia, in our sample. Decrease in the platelet count and the increase in cardiac enzymes were associated with an increased risk of mortality.

EP1332 FACTOR XII 46 C/T GENE POLYMORPHISM COULD BE ASSOCIATED WITH THE RISK OF LATE-ONSET VENOUS THROMBOEMBOLISM IN PATIENTS FROM THE NORTH-WESTERN RUSSIA

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Background: The Hageman factor (factor XII, FXII) is involved in initiation of internal blood coagulation pathway, regulation of fibrinolysis and kallikrein-kinin system, and activates coagulation factors VII and XI. The 46 C/T polymorphism in the gene coding for FXII is associated with decrease of both level and activity of this factor in blood plasma. However, the role of the FXII 46 C/T polymorphism in venous thromboembolism (VTE) development is not yet clear.
Aims: To assess the role of the FXII 46 C/T polymorphism in VTE development in patients from the North-Western region of Russia.
Methods: We examined 600 patients (294 men and 306 women, mean age – 43.6±15.3 years) with VTE. In 400 patients, the first episode of VTE was diagnosed at age 45 years or less. Other 200 patients composed the group with late-onset VTE. The control group (CG) consisted of 200 age- and sex-matched healthy individuals. All individuals originated from the North-Western region of Russia and gave informed consent for participation in the study. Genotyping for the FXII 46 C/T polymorphism was performed by PCR-RFLP. The differences in genotypes distribution between the groups were estimated by Fisher`s exact test.
Results: Comparative analysis of gene variants distribution for the FXII 46 C/T polymorphism in VTE patients and CG did not reveal any statistically significant difference. Frequencies for the CC, CT and TT genotypes were 48.2%, 43.0%, 8.8% in patients, and 48.0%, 45.5%, 6.5% in controls, respectively. Interestingly, the presence of 46T allele was more frequently detected in patients with late-onset VT (58.0% vs. 48.8% in young patients; OR=1.5; 95% CI: 1.0-2.0; p=0.038). Homozygosity for the 46T allele was found in 24 (12.0%) patients with late-onset VT and 29 (7.3%) young patients (OR=1.7; 95% CI: 1.0-3.1; p=0.066). When compared to CG, the frequency of 46TT genotype was almost 2-fold increased in patients with VT manifested after 45 years old (12.0% vs. 6.5%, respectively; OR=2.0; 95% CI: 1.0-4.0; p=0.083).
Summary/Conclusion: Our data suggest that the FXII 46 C/T gene polymorphism could influence the risk of late-onset VT development in patients from the North-Western region of Russia. Further studies are needed to confirm this association.

EP1333 VKORC1 -1639AA GENOTYPE COULD BE A POSSIBLE PROTECTIVE FACTOR FOR VENOUS THROMBOEMBOLISM DEVELOPMENT IN PATIENTS WITH FII G20210A MUTATION FROM NORTH-WESTERN RUSSIA

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Background: Vitamin K plays a crucial role in hemostasis by activating both procoagulant (FII, VII, IX, X) and anticoagulant (proteins C, S, Z) factors. Vitamin K-epoxide reductase 1 (VKORC1) G-1639A gene polymorphism is known to affect an enzyme activity and bioavailability of vitamin K. To date, there is a little data on the role of VKORC1 G-1639A variation in venous thromboembolism (VTE) development, in particular, in patients with inherited thrombophilia.
Aims: To assess effect of the VKORC1 G-1639A gene polymorphism on the risk of VTE development in patients from North-Western Russia.
Methods: We included 600 VTE patients (294 men and 306 women, mean age 43.6±15.3 years) originated from the North-Western region of Russia in the study. The control group (CG) consisted of 200 healthy individuals of the same origin. Genotyping for the VKORC1 G-1639A, FII G20210A and FV G1691A variations was performed by PCR-RFLP. Odds ratios (OR) with 95% confidence intervals (CI) and p-values were determined by Fisher's exact test to characterize intergroup differences in distributions of genotypes and their combinations. The study was approved by the local ethical committee.
Results: Allele and genotype frequencies for the VKORC1 G-1639A polymorphism were similar in both VTE patients and controls. At the same time, we observed significant differences for the VKORC1 genotypes distribution between the groups of VTE patients with or without classical markers of inherited thrombophilia. The frequency of the -1639AA genotype in patients with FV 1691A variant (FV Leiden)

was 4-fold higher than in those having FII G20210A mutation (19.6% vs. 4.4%, respectively; OR=5.2; 95%CI: 1.2-23.6; p=0.021). In the group of patients without FII and FV gene mutations, the frequency of the VKORC1 -1639AA genotype was almost equal to that in CG (17.1% vs. 16.5%, respectively). When compared to CG, the VKORC1 -1639AA variant was significantly underrepresented in patients with the FII G20210A gene mutation (4.4% vs. 16.5%, respectively; OR=0.2; 95%CI: 0.1-1.0; p=0.035).
Summary/Conclusion: Genotype VKORC1 -1639AA could have protective effect on VTE development in patients with FII G20210A mutation from North-Western Russia. Further studies are needed to confirm this finding.

EP1334 GENES OF THROMBOPHILIA AND PROTHROMBOTIC CONDITIONS BY WOMEN WITH REPRODUCTIVE FAILURE IN ANAMNESIS

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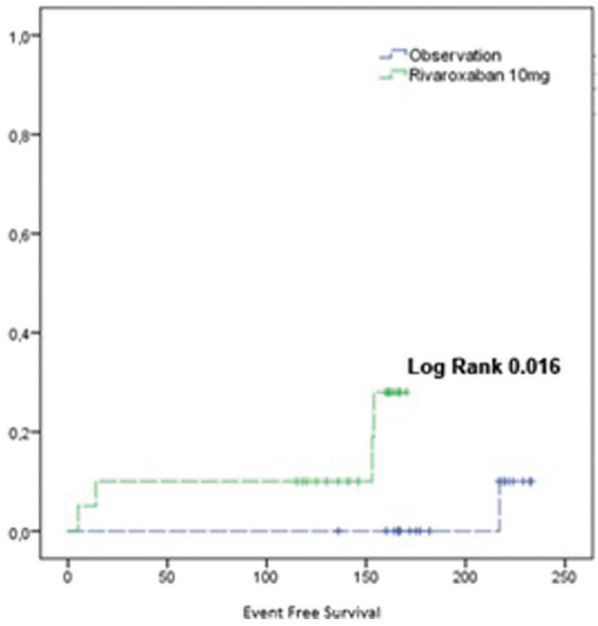
Background: Inherited thrombophilia is one of the leading causes of coagulating disorders. Prothrombotic disorders are considered to be risk factors for many obstetric complications of placental origin starting with the implantation process and ending with the formation of the placenta (stillbirth, intrauterine growth retardation, severe preeclampsia, and placental abruption, recurrent pregnancy loss).
Aims: To assess the distribution of genes of thrombophilia and prothrombotic conditions (*F2: 20210 G>A, F5: 1691 G>A, F7: 10976 G>A, F13: 103 (163) G>T, FGB: -455 G>A, ITGA2: 807 C>T, ITGB3: 1565 T>C, PAI-1: -675 5G>4G*) by women with reproductive failure in anamnesis and by healthy women.
Methods: Genes of thrombophilia and prothrombotic conditions genes were carried out by polymerase chain reaction in real time on the detecting amplifier DT-96 (DNA Technology, Russia). The crtiterion X2 was used for statistical data processing. Depending on the diagnosis eastablished in the hospital on the basis of the international classification of diseases (ICD-10), 367 examined women were devided into such groups: group 1 - female infertility, unspecified (ICD-10: N97.9), n=9; group 2 - female infertility of other origin (ICD-10: N97.8), n=175; group 3 - two complete or unspecified abortions, without complications (ICD-10: O03.9), n=19; group 4 - habitual aborter (ICD-10: N96), n=59; comparison group - no problems with the onset and gestation of pregnancy, two or more children, n=105.
Results: The data of the performed study showed, that the C allele of the *ITGB3: 1565 T>C* gene was more common in women with other forms of female infertility (ICD-10: N97.8) (34.9% to 22.9% in the comparison group, p<0.05). Polymorphism of the remaining genes (*F2: 20210 G>A, F5: 1691 G>A, F7: 10976 G>A, F13: 103 (163) G>T, FGB: -455 G>A, ITGA2: 807 C>T, PAI-1: -675 5G>4G*) was detected with comparable frequency in women with and without pathology of pregnancy.
Summary/Conclusion: The presence of the allele C of the ITGB3:1565 T>C gene predosposes to female infertility.

EP1335 EFFECT OF RIVAROXABAN (10MG) VERSUS OBSERVATION ON THE RISK OF THROMBOSIS AT DISCHARGE IN INDIVIDUALS WITH COVID-19.

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Background: Coagulopathy associated with COVID-19 is one of the main complications, especially in individuals with risk factors. Simultaneously, the use of low molecular weight heparin is the recommended strategy in hospitalized individuals, but the usefulness of other strategies such as DOACs in outpatients is still unknown.
Aims: Describe the benefit of the use of rivaroxaban at discharge on the risk of thrombosis in patients discharged from COVID-19.Identify the behavior of Dimero-D at discharge and its modification with anticoagulant therapy.
Methods: Randomized 1: 1 study (Rivaroxaban 10mg for 14 days versus observation) at discharge in individuals with COVID-19 who have not required mechanical ventilation. D-dimer was evaluated at 14 and 30 days after discharge in conjunction with a CT angiography at four weeks after hospital discharge. The protocol was developed in the Hospital Regional de Alta Especialidad de Ixtapaluca, authorized by the ethics committee with registration number NR-19-2020. The study is identified in ClinicalTrials.gov with the following registry NCT04508439
Results: Forty individuals were evaluated (20 in each arm) with follow-up greater than 100 days. Gender distribution was equitable in each arm, with a mean age of 50 years (21 to 74 years), 40% (n = 16) were older than 55 years, 27.5% (n = 11) had hypertension and 20% (n = 8) had diabetes. The mean length of hospital stay was 10.5 days (6 to 23 days) treated with oxygen and low molecular weight heparin. At discharge, treatment was started with rivaroxaban 10mg x 14d vs. observation; in the rivaroxaban group, four events were identified (3 hemorrhages / 1 thrombosis), this difference being significant (Log Rank 0.016). Only one thrombosis event (pulmonary embolism) was identified in the rivaroxaban group at eight treatment days. Compared to the diagnosis, DD levels were lower at both 14 and 30 days (p = 0.000, 95% CI, 440.8-1164.9) without finding a difference in those treated with rivaroxaban or observation (p = 0.721, 95% CI, -68.48 to 241.18).



Summary/Conclusion: The use of DOACs at discharge does not benefit from an increased risk of hemorrhagic events; the anticoagulant strategy should be individualized, focused only on those patients at very high risk of thrombosis.

Transfusion medicine

EP1337 RAVULIZUMAB AND ECULIZUMAB REDUCE TRANSFUSIONS IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: EVIDENCE FROM THREE REAL-WORLD DATABASES: TRINETX US EMR, TRINETX US CLAIMS AND KOMODO HEALTH

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Background: Results from the International PNH Registry have shown that eculizumab reduced the number of transfusions by 50% in patients (pts) with PNH with transfusion history. Ravulizumab, the new standard of care for PNH, was non-inferior to eculizumab in 2 large clinical trials; 77% and 87% of pts treated with ravulizumab achieved transfusion avoidance at 1 year. Collecting real world data on the proportion of pts with PNH requiring transfusions whilst on ravulizumab, or after switching from eculizumab to ravulizumab (E-R switch) is important

and valuable. Electronic medical records (EMR) and claims databases provide valuable real-world insight.
Aims: Determine proportion of pts with PNH receiving transfusions before and after initiating treatment with eculizumab, ravulizumab or E-R switch by using large-scale US EMR and claims databases.
Methods: TriNetX is a global health research network that integrates data from a variety of sources to create longitudinal real-world data, which can be sourced from EMR or claims. KOMODO Health is a comprehensive claims database in the US. The study population was identified using records with ICD-10 codes for PNH. Pts were grouped into three cohorts: received eculizumab but never ravulizumab (eculizumab-only), received ravulizumab but never eculizumab (ravulizumab-only), and an E-R switch. The TriNetX platform was used to access data up to 10/Feb/21 from two TriNetX networks: the US EMR and US Claims networks. Analyses for these databases were conducted at 6-month intervals: 6-months (mos) to 1 day pre-treatment, 0-6-mos post-treatment and continued at 6-month intervals thereafter until 18-24 mos in ravulizumab and E-R switch cohorts, and 42–48 mos in the eculizumab cohort. From the KOMODO Health database, claims data were sourced from 01/Jan/15 to 31/Dec/19. Analyses were conducted at 3-month intervals: 3 mos to 0-days pre-treatment, day of treatment (index date) to 3 mos post-treatment and at 3-month intervals until 6 mos for the ravulizumab and E-R switch cohorts, and 24 mos for the eculizumab cohort. Proportion of pts receiving transfusions at each interval was assessed.
Results: A total of 295, 804 and 231 pts with PNH that met the analysis criteria were identified from TriNetX EMR, TriNetX Claims and KOMODO, respectively (**Figure 1**). Proportion of pts receiving transfusions prior to index date in the eculizumab-only cohort was higher in all 3 databases. In the eculizumab-only cohort, the proportion of pts receiving transfusions decreased from 23–37% pre-treatment to 8–15% at the end of the study period. In the ravulizumab-only cohort, proportion of pts receiving transfusions decreased from 10–15% pre-treatment to 0% in the TriNetX Claims and KOMODO cohorts, and 8% in the TriNetX EMR cohort at the end of the study period. In the E-R switch cohort, proportion of pts receiving transfusions decreased from 9–17% pre-switch, to 0% in TriNetX Claims and TriNetX EMR cohorts and 8% in the KOMODO cohort at the end of study period after switching to ravulizumab. A limitation of this study was the small ravulizumab sample size.

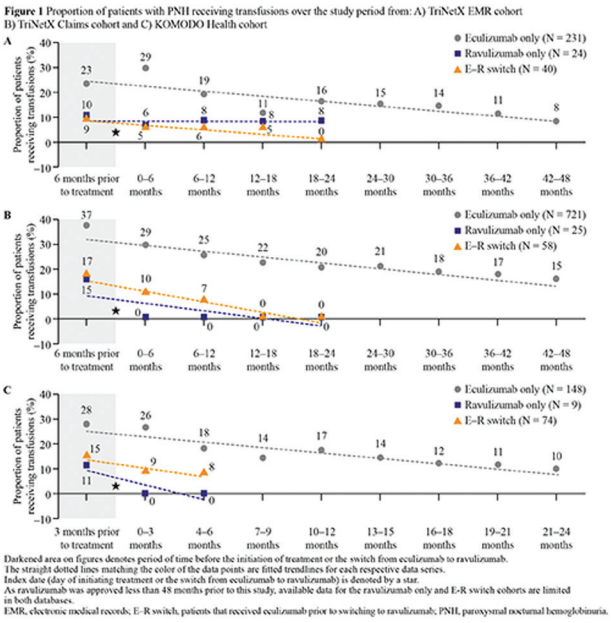


Figure 1 Proportion of patients with PNH receiving transfusions over the study period from: A) TriNetX EMR cohort B) TriNetX Claims cohort and C) KOMODO Health cohort

Darkened area on figures denotes period of time before the initiation of treatment or the switch from eculizumab to ravulizumab.
The straight dotted lines matching the color of the data points are fitted trendlines for each respective data series.
Index date (day of initiating treatment or the switch from eculizumab to ravulizumab) is denoted by a star.
As ravulizumab was approved less than 48 months prior to this study, available data for the ravulizumab only and E-R switch cohorts are limited in both databases.
EMR, electronic medical records; E-R switch, patients that received eculizumab prior to switching to ravulizumab; PNH, paroxysmal nocturnal hemoglobinuria.

Summary/Conclusion: Results of this real-world study demonstrate that the proportion of pts with PNH requiring blood transfusions was substantially reduced with eculizumab or ravulizumab monotherapy or after the E-R switch, with similar trends noted between treatment groups. This real-world data demonstrates the low transfusion dependence in pts with PNH treated with eculizumab or ravulizumab, or pts switched to ravulizumab.

EP1338 EVALUATION OF RED BLOOD CELL AUTOANTIBODIES AND ASSOCIATED THROMBOTIC RISK IN A TERTIARY CARE CENTRE IN SPAIN

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Background: Autoimmune hemolytic anemia (AIHA) is characterized by the presence of anti-red blood cell (RBC) autoantibodies with active hemolysis. Several studies have described a higher thrombotic risk compared to healthy subjects, possibly related to a combination of autoimmune features and hemolysis. However, the relationship between presence of anti-erythrocyte autoantibody and risk of thrombosis has not yet been explored.
Aims: The aim of this study is to identify whether the elevated thrombotic risk in AIHA could be associated with anti-RBC autoantibody presence regardless of the existence of active hemolysis.
Methods: We conducted a retrospective research in a single-center cohort selecting patients with an identified anti-RBC autoantibody and then evaluating the presence of hemolysis and the incidence of thrombotic events.
Laboratory methods to identify autoantibodies included direct antiglobulin test (polyspecific and monospecific anti-IgG and C3d, Menarini reagents) and elution tests (acid glycine elution with ELU-KIT Immucor or 56ºC elution) were also undertaken. Measured parameters for hemolysis were indirect bilirubin, LDH and reticulocytes.
Patients with AIHA were recorded from 2009, and those without active hemolysis were registered during part of this follow-up period. We also assessed associated diseases and features of the autoantibody. Prothrombotic characteristics (elderly, active cancer, previous VTE, known thrombophilic condition, recent trauma/surgery, infection/rheumatologic disorder and hormonal treatment) were registered in order to identify bias. Reduced mobility could not be evaluated due to lack of data.
Results: 105 patients with an anti-RBC autoantibody were identified, 5 were excluded due to lack of information. Among these 100 patients, 59 showed active hemolysis (AIHA). There was no difference in gender, age or associated diseases (idiopathic, lymphoproliferative, autoimmune disorders or others) between both groups. Patients without hemolysis showed more frequently warm autoantibody features (p=0.025) and less commonly mixed characteristics (p=0.039). Median follow up in AIHA patients was higher (33 vs 16 months; p=0.025). Prothrombotic factors were comparable among both groups, except for recent trauma/surgery (p=0.008), which was more frequent in patients without hemolytic features. We found a thrombosis incidence in AIHA patients of 17.2%; which is consistent with previous studies and comparable to those without hemolytic features (17.2% vs 9.8%; p=0.39. We dismissed the presence of confounding factors (trauma/surgery, warm or mixed autoantibodies) through stratified analysis, finding no statistical significance (p>0.14) on the incidence of thrombosis between AIHA and patients without hemolysis.
Median time to thrombosis from autoantibody identification was shorter in AIHA patients (2 vs 19 months; p=0.16) as 4 of them presented venous thromboembolism (VTE) at diagnosis. VTE in AIHA and patients without hemolysis were pulmonary embolism (5 vs 2); deep vein thrombosis (3 vs 2); and portal vein thrombosis (2 vs 0).

Table 1. Baseline characteristics of patients with an identified anti-RBC autoantibody.

	AIHA (n=59)	Autoantibody without hemolysis (n=41)	p
Baseline characteristics			
Gender, female; n (%)	34 (57.6)	23 (56.1)	.879
Median age (IQR)	72 (56-82)	67 (55-81)	.950
Median follow up, months (IQR)	33 (7-83)	16 (8.5-36)	**.025**
Associated disease, n (%)			
Idiopathic	28 (47.5)	25 (61)	.322
Lymphoproliferative	14 (25.7)	7 (17.1)	.546
Autoimmune disease	10 (16.9)	8 (19.5)	.634
Others (Immunodeficiency, neoplasm)	7 (11.9)	1 (2.4)	.136
Autoantibody characteristics, n (%)			
Warm autoantibodies	48 (81.4)	40 (97.6)	**.025**
Mixed autoantibodies	7 (11.9)	0 (0)	**.039**
Cold agglutinin	2 (3.4)	1 (2.4)	1
Others	2 (3.4)	0 (0)	.511
Prothrombotic characteristics; n (%)			
Elderly age (≥70 years)	30 (50.8)	19 (46.3)	.658
Active cancer	12 (20.7)	8 (19.5)	.886
Previous VTE	1 (1.7)	5 (12.2)	.079
Known thrombophilia	1 (1.7)	3 (7.3)	.304
Recent (≤1 month trauma/surgery)	1 (1.7)	7 (17.1)	**.008**
Acute infection/rheumatologic disorder	12 (20.7)	9 (22)	.880
Obesity (BMI≥30)	16 (27.6)	12 (29.3)	.855
Ongoing hormonal treatment	0 (0)	1 (2.4)	.414
Complications			
Thrombosis; n (%)	10 (17.2)	4 (9.8)	.385
Median time to thrombosis, months (IQR)	2 (0-45)	19 (17.5-21.5)	.161

Summary/Conclusion: Thrombotic events among patients with anti-RBC autoantibody were similar, regardless of the presence of active hemolysis (AIHA). Despite AIHA features and even in the absence of hemolysis, patients with anti-RBC autoantibodies may benefit from a closer follow up in order to prevent thrombosis. Further studies are needed to clear the significance of these autoantibodies in the pathogeny of AIHA related thrombosis.

EP1339 THE CONSEQUENCES OF UNNECESSARY REQUESTING AND REPORTING OF THE DIRECT ANTIGLOBLIN TEST IN NEONATES.

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Background: BSH (British Society of Haematology) guidelines recommend that the Direct Antiglobulin Test (DAT) is only requested when clinically indicated in neonates. Prophylactic anti-D (PAD) administered routinely to Rh D Negative mothers during pregnancy can cause a positive DAT in the neonate that is not clinically relevant as PAD does not cause significant haemolysis (Dillon *et al.*, 2011, Maayan-Metzger *et al.*, 2001). However, it is common practice for clinicians to request 'Group and DAT' on all cord/heel prick samples that they send to the Transfusion Laboratory.
Aims: To analyse data on DAT testing in neonates performed by the Transfuision Laboratory Service at St Helens and Knowsley Teaching Hosptials NHS Trust (STHK) over a 12 month period. The aim was to establish if the test was clinically indicated and what further intervention a positive result prompted.
Methods: A list of all DATs performened on neonates (< 4 months of age) by the STHK transfusion service from 1st January 2020 to 31st December 2020 was retrospectively gathered. Postive DATs were further investigated to establish the impact of the positive result; clinical indication, additional blood tests, phototherapy, length of stay, folic acid administration and pardiatric consultation/review.
Results: During the audit period, 1745 DATs were performed on neonates at STHK. Of these, 10% (n=169) were postiive. In 80 of the postive cases (47%), the DAT was clinically indicated due to maternal antibodies or neonatal anaemia/jaundice. In over half of the positive DATs (53%) a clinical indication for the tests could not be found in the patients notes yet the mother was Rh D Negative and had recieved PAD during pregnancy. A vast majority of these DAT results were very weakly positive (97%). Half of the neonates with a non-clinically indicated but postive DAT recieved at least one intervention. Interventions included SBR and FBC teasting, folic acid administration, phototherapy, paediatric consult or 2 week review at a paediatirc out patient department.
Summary/Conclusion: The reporting of non-clinically indicated DATs in neonates of mothers who have recieved PAD is a financial burden and leads to unnecessary interventions, such as additional venepuncture and folic acid administration in non-syptomatic neonates. Additional teaching sessions and better policies need to be introduced to reduce this practice. Laboratory staff should also be empowered to question the clinical relevance of DATs if requesters fails to provide clinical details.

EP1340 FACILITATED IMMUNOGLOBULIN (FSCIG) USE IN PATIENTS WITH SECONDARY IMMUNODEFICIENCY DISEASES: TWO-YEAR INTERIM RESULTS FROM THE FIGARO STUDY

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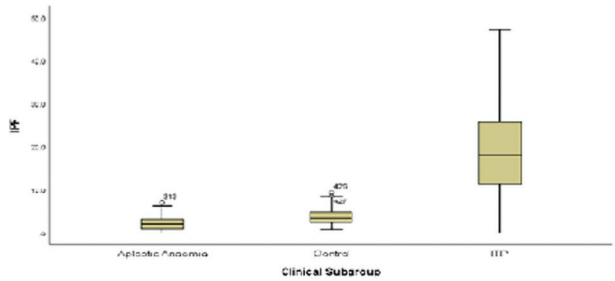
Background: Secondary immunodeficiency diseases (SID) commonly affect patients with hematological malignancies such as chronic lymphocytic leukemia (CLL) and lymphoma. Immunoglobulin replacement therapy (IGRT) is an important therapeutic option for preventing severe, recurrent, or persistent infections in patients with hematologic malignancies and SID. Facilitated subcutaneous immunoglobulin (fSCIG) is a dual-vial unit of immunoglobulin G (IgG) 10% and recombinant human hyaluronidase (rHuPH20) approved in the European Union as an IGRT for patients with SID. rHuPH20 depolymerizes hyaluronan in the extracellular matrix to transiently increase local subcutaneous tissue permeability, allowing for fSCIG infusion at rates, volumes, and frequencies comparable to intravenous immunoglobulin (IVIG) with better systemic tolerability.
Aims: To assess fSCIG usage and tolerability over time in patients with SID treated in routine clinical practice.
Methods: FIGARO (NCT03054181) is a European multicenter, prospective, observational study. Patients were eligible if they received ≥1 fSCIG infusion for primary immunodeficiency diseases or SID and provided informed consent. Patients are being followed for up to 3 years. An interim analysis (data cut-off date: February 2, 2021) was conducted to evaluate fSCIG usage and tolerability over the first 2 years of follow up in the subgroup of patients with SID.
Results: Of the 156 patients enrolled, 31 (mean [range] age: 61 [3–88] y) had SID and are included in the baseline (inclusion visit) analysis. At interim analysis, 1- and 2-year follow-up data were available for 23 and 12 patients, respectively. Indications for IGRT were CLL (n=20), non-Hodgkin lymphoma (n=6), SID due to immunosuppressive therapy (n=3), and Hodgkin lymphoma (n=2). At the inclusion visit, fSCIG (median total monthly dose: 30.0 g) was most recently infused at home (61%) or at a hospital (36%) by the patient (58%) or a nurse (42%). Most patients received fSCIG every 4 weeks (68%), infused into a single site. The median maximum infusion rate was consistent over the 2-year follow up: 290 mL/h at inclusion, 268 mL/h at 1 year, and 300 mL/h at 2 years. The median infusion volume was 300 mL across all visits to 2 years, with all patients receiving the full dose as planned. Two patients each reported 1 adverse drug reaction (ADR; erythema and headache) at the inclusion visit, with no ADRs reported at any of the follow-up visits. One patient changed to IVIG by 12 months.
Summary/Conclusion: In patients with SID primarily due to hematologic malignancies, fSCIG was tolerated over 2-years' follow up in routine clinical practice and offered the flexibility of administration at home or in a hospital setting, either by the patient or a nurse. Infusion parameters remained consistent over time.

EP1341 ASSESSMENT OF IPF% AS A PREDICTIVE BIOMARKER AND ITS USE IN PREDICTING PLATELET RECOVERY IN THROMBOCYTOPENIC PATIENTS

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Background: Patients with haematological malignancies more commonly present with thrombocytopenia than any other cohort. Early identification of the cause of thrombocytopenia is important to provide timely intervention to decrease the risk of life-threatening bleeding. Sysmex XN analysers allow for the measurement of immature platelet fraction (IPF%), differentiating mature from immature platelets. IPF% has the ability to distinguish between the causes of thrombocytopenia, differentiating decreased platelet production from increased platelet destruction. IPF% also has the ability to predict platelet recovery, reducing unnecessary platelet transfusions in patients where the platelet count would recover without intervention.
Aims: The aim of this project was to determine the efficacy in IPF% in determining the cause of thrombocytopenia and to determine the ability of IPF% to predict platelet recovery in thrombocytopenic patients in UHW.
Methods: 87 thrombocytopenic patients were included over a 13-month period. Patients were divided into two groups; decreased platelet production (n=53) and increased platelet destruction (n=34). Patients with normal FBC parameters (n=100) were included to establish a reference range for IPF%, represented using the 2.5th and 97.5th percentile. Comparison of IPF% amongst each group was carried out using Mann-Whitney U test. Reproducibility of IPF% was assessed by coefficient of variation (CV%) analysis. 14 patients were followed daily through platelet count and IPF% to determine the ability of IPF% to predict platelet recovery. ROC curve analysis was performed to determine the diagnostic cut off point of IPF% in differentiating between ITP and aplastic anaemia. ROC curve analysis was also used to determine the optimal value of IPF% for the prediction of platelet recovery.
Results: IPF% was assessed in patients with ITP, aplastic anaemia and a control group. A statistically significant different in IPF% between ITP and AA patients ($p<0.05$) and the control group ($p<0.05$) was found. ROC curve analysis determined a cut of point of 6.8% for differentiating ITP from AA with a sensitivity of 87% and specificity of 92.9%. To determine the sensitivity and specificity of IPF% in predicting imminent platelet recovery, ROC curve analysis was used. The increase in IPF% for ROC curve analysis was defined as the increase in IPF% from platelet nadir to the peak IPF% prior to platelet recovery. An increase of 2.1% was found to have a sensitivity and specificity of 92% and 96% respectively in predicting platelet recovery within 2 days of increase in IPF%.



Summary/Conclusion: Extensive analysis of the data obtained for this study has shown the benefits to IPF% as a clinical biomarker. Implementation of IPF% as a routine parameter would be beneficial to clinicians in UHW. As a non-invasive biomarker, IPF% would allow clinicians to gain an insight into the cause of thrombocytopenia allowing for prompt decisions regarding treatment strategies without the need for invasive procedures. IPF% as a predictive biomarker would also allow clinicians to defer platelet transfusion if platelet recovery is imminent, avoiding unwarranted platelet transfusions.

EP1342 PEDIATRIC TRAUMA: BLOOD PRODUCT TRANSFUSION CHARACTERISTICS IN A PEDIATRIC EMERGENCY DEPARTMENT

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Background: Trauma is the leading cause of preventable death in children. Severely injured cases may require transfusion of blood products but no consensus exists regarding optimal blood product use and clear indications for pediatric massive transfusion (MT) activation.
Aims: In this study, it was aimed to investigate clinical and laboratory data, management, and outcomes of pediatric trauma patients who initially received blood product transfusion.
Methods: Children aged 0 to 18 years who presented to the pediatric emergency department due to trauma and underwent and blood product transfusion within 24 hours of arrival between January 2011 and January 2021 were included. Demographics, initial vital signs, clinical findings, laboratory, and radiologic results were recorded. Injury Severity Score (ISS), total volume of transfused blood products and crystalloid boluses in 24 hours were calculated. Patients were divided into two groups according to the fresh frozen plasma (FFP): packed red blood cell (PRBC) ratio: low ratio group as <1:2 and high ratio group as ≥1:2. Massive transfusion was defined as transfusion of ≥40 mL/kg of all blood products in 24 hours. Length of stay in the pediatric intensive care unit (PICU), stay in the hospital and 30-day mortality were recorded.
Results: Thirty-two patients [median age 8.8 years (IQR 2.0-15.1), 20 males (62.5%)] were enrolled. In addition to crystalloid boluses and PRBC transfusion, 19 (59.3%) cases received FFP and among them, 12 cases were transfused with high and 7 cases with low FFP: PRBC ratio. Eight (25.0%) patients met MT threshold criteria. Length of PICU stay, length of mechanical ventilation (MV) and transfusion complication rates were higher for cases who received MT although there was no difference for age, ISS scores, the volume of crystalloid boluses, length of hospital stay, and 4 h, 24 h or 30-day mortality between MT (+) and (-) groups. Children who received transfusion with a high FFP: PRBC ratio were older in age and had a higher ISS score than those who received a low ratio but there was no difference for length of hospital stay or mortality rates between groups. Total volume of crystalloid boluses was higher in patients who died than those who survived but the volume of blood products was similar for two groups. To predict 30-day mortality, multivariable analysis was performed and among parameters of a Glasgow Coma Scale (GCS) score of ≤8, an ISS score of ≥25, having received MT and crystalloid bolus ≥40 mL/kg, a GCS score of ≤8 was identified as a predictor (OR = 21.700, 95% CI: 1.951-243.498, p: 0.012). When we added activated partial thromboplastin time (APTT) to these parameters, then an APTT value of >37.5 seconds was identified as a predictor of 30-day mortality (OR = 48.000, 95% CI: 3.704-621.998, p: 0.003), respectively.
Summary/Conclusion: Children who received MT had longer duration of MV and PICU stay, and higher transfusion complication rates than those who did not receive but there was no significance for ISS scores, the volume of crystalloid boluses, hospital stay or mortality between two groups. Total volume of crystalloid boluses was higher in patients who resulted in death than those who survived although the volume of blood products was similar for two groups. The GCS score and APTT can be used to predict 30-day mortality in pediatric trauma patients.

EP1343 RELATION OF ABO BLOOD GROUP WITH SURVIVAL IN COVID-19 PATIENTS ADMITTED IN HOSPITAL CENTRAL DE LA DEFENSA, MADRID, SPAIN.

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Background: There are some papers reporting a possible link between blood group type and susceptibility to SARS-CoV2 (COVID-19) infection and perhaps even with mortality. They describe a higher risk to develop COVID-19 in individuals with blood type A, whereas those with blood type O would have a lower susceptibility to COVID-19 infection.
Aims: To describe the distribution of the blood groups among the COVID-19 patients admitted in our hospital during the worse pandemic months in our country (March to May) and their relation with survival.
Methods: From March 1st to May 31st 1299 Covid-19 patients were admitted in our hospital (a 520-bed institution); a 27% died. We had the

blood group testing performed in 297 out of the 1299 patients. Those records were in our blood bank software (Delphy®) because of a previous transfusion or a transfusion during the COVID-19 hospitalization. We examined the ABO types among these patients and we compared this data with the frequency observed in the Spanish healthy population according to the Red Cross records of blood donors. Statistical study was performed using the Chi square test (χ^2) and Kaplan-Meier survival curves, by SPSS software.
Results: In the 297 COVID-19 patients admitted in our Hospital with ABO blood type recorded, the 55.2% were men, 44.8% women; median age was 79 (21-103).
We found a higher percentage of blood type A and a lower of O among the COVID-19 patients, compared with the prevalence of those blood groups in Spanish healthy population, but that difference was not statistically significant. Regarding survival curves among different blood groups, we found a decreased mortality in patients with O blood type (25.2%) compared with the rest of groups (34.5%). That difference was close to be statistically significant (p 0.08), showing a clear tendency that could be maybe significant with a bigger group of patients.
Summary/Conclusion: The distribution of the blood group in COVID-19 admitted patients in our hospital is similar to data already published: a higher rate of COVID-19 infection in patients with blood type A and a lower rate of type O. We also found lower mortality in our patients with O blood type; with a special signification when we compare O with the rest of blood groups together. There are some literature describing that anti-A antibodies could be protective against COVID-19 infection; this could explain the tendency we found of better survival in patients with O blood type.

EP1344 BLOOD DONATION AND IRON SUPPLEMENTATION IN NIGERIA THE RANFERON STUDY

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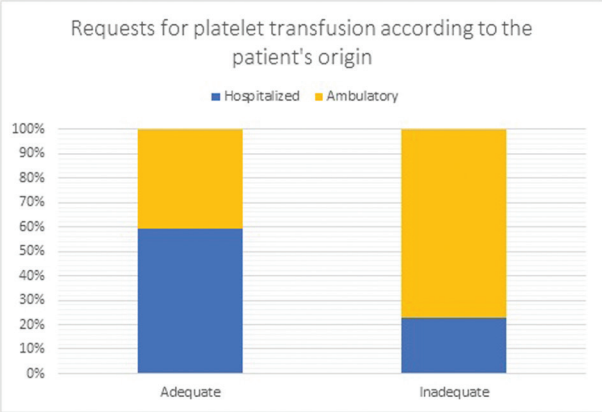
Background: Regular blood donation depletes Iron. Uncompensated iron loss may eventually lead to iron deficiency anaemia. Approximately 25 to 35% of blood donors who donate blood 3-4 times yearly become iron depleted. Iron deficiency anaemia is an important limiting factor to a sustainable supply of blood units especially in LMIC. Blood transfusion practice in Nigeria is poorly developed and structured with paucity of non-remunerated blood donors and high rate of donor deferrals resulting from transfusion transmitted infections and low haemoglobin levels. There is need to protect the donor pool to meet the blood needs in resource poor countries.
Aims: We aimed to assess the effect of daily supplementation of iron using Ranferon-12 on RBC indices, Iron level, ferritin level and Hb recovery in blood donors in Nigeria.
Methods: We carried out an interventional study at the University of Nigeria Teaching Hospital blood transfusion center from March to July 2020. Study participants (blood donors) were randomized into two groups. Group A (control group): blood donor who did not donate a unit of blood and did not receive iron supplementation. Group B (experimental group): blood donors who donated a unit of blood and received iron supplementation (Daily Ranferon capsules containing 100mg elemental iron; iron fumarate) and 100mg of tablet vitamin C for 6 weeks. The primary outcome measure were levels of Haemoglobin (Hb), Packed cell volume (PCV), red cell indices (Mythic 22 haematology analyzer) Serum ferritin (Abbott 1000isr), Total body iron Beckman Coulter AU680) Soluble transferrin receptor (sTfR), and percentage iron saturation was calculated
Secondary outcome measure were adherence/compliance and tolerance to daily iron supplementation using Ranferon using Modified Morisky scale and investigator designed pretested, pre validated questionnaire, respectively.
The study was approved by UNTH REC with ethical approval number NHREC/05/01/2008B-FWA00002458-1RB00002323
Results: A total of 90 blood donors participated in the study, 30 was randomized to the control group and 60 to the experimental group. Majority (52.2%) were less than 24 years and Most (95.6%) were males. Only the mean difference in mean cell haemoglobin concentration (MCHC) and soluble transferrin receptor (sTfR) before and after iron supplementation were statistically significance with p values of 0.030 and<0.001, respectively.
The relationship between only the mean difference in red cell count (RCC), packed cell volume PCV), red cell indices, % iron saturation and soluble transferrin receptor (sTfR) and iron supplementation were statistically significant with p values <0.001.
Percentage recovery of the parameters after 6 weeks of daily Ranferon range from 89 to > 100%. The percentage recovery of Hb level was 89% while others were more than 89%.
Six participants (10%) were iron replete before the intervention with daly Ranferon with only one participant (1%) remaining iron replete after the intervention.
Only one participant (1.7%) reported GIT intolerance while on daily iron supplementationwith Ranferon. Majority, (95%), (93.3%) responded NO to "the participant takes less/more medicine than instructed" and NEVER to "The participant alters the dose of his/her medicine."
Summary/Conclusion: Iron supplementation using Ranferon capsule daily for 6 weeks enhanced the recovery of haemoglobin (Hb), red cell indices post blood donation with attainment of benchmark haemoglobin levels for donation.

EP1345 AUDIT OF PLATELET TRANSFUSION IN A LARGE UNIVERSITY HOSPITAL: HOW CAN WE IMPROVE PLATELET TRANSFUSION?

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Background: According to the literature, up to 20% of platelet transfusions are considered inadequate, increasing platelet consumption and exposure to patients at risk.
Aims: The objective of this study is to know the incidence of inadequate platelet transfusion in our center and to determine areas of improvement.
Methods: Platelet transfusions performed in November 2020 at our center were reviewed retrospectively. Each transfusion was considered independently. Intra-operating room requests were excluded. Criteria of appropriate platelet transfusion set in the Guide on the Transfusion of Blood Components and Plasma Derivatives of the Spanish Society of Blood Transfusion and Cell Therapy (5th ed) were used: stable patients with central thrombocytopenia and platelet <10x10^9/L, platelets <20x10^9/L in non-stable patients (> 38 Celsius degrees fever, signs of ≥ WHO grade 2 haemorrhage), platelets < 50x109/L in patients who will undergo major surgical and/or invasive procedures or have signs of ≥ WHO grade 3 bleeding and platelets is < 80x10^9/L in case of central nervous system or eye involvement.
Results: Our center is a tertiary University Hospital with a large Stem Cell Transplantation program and important cardiac surgery department. 335 transfusion episodes were reviewed in 86 patients with mean age of 55 years (0-90). It involved 476 units of platelets. 49.4% were women (165/335), 78.5% (263/335) were indicated by the Hematology service and 11.4% (38/335) because of surgical procedures. 283 transfusions (84.4%) were performed in hospitalized patients compared to 52 (15.5%) outpatients. In 5 patients (5.8%) tranexamic acid was associated. 86% (288/335) of platelet transfusions were correctly indicated while 14% (47/335) did not meet the criteria described above, 29 patients (33%) were inadequately transfused with 49 platelet units (10,6% of total). No significant differences were found with respect to the requesting service. The main indication of platelet transfusion was stable thrombocytopenias with platelet values between 10x10^9/L and 20x10^9/L and it is this indication that has the highest frequency of inadequate transfusion. A significant difference was observed in the percentage of units suitable indications in outpatients versus admitted (40% vs 12%, p <0.005).



Summary/Conclusion: There is a high percentage of inadequate platelet transfusions, similar to the incidence referred in the literature. The main area of improvement is transfusion in outpatients. The development of training programmes and prescription aid systems can help to improve these outcomes.

EP1346 CONVALESCENT PLASMA FOR COVID-19. OUR EXPERIENCE.

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Background: Passive immunotherapy has been widely used previously to treat severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, Influenza A and Ebola virus disease with encouraging results. The use of convalescent plasma against SARS-CoV-2 has been suggested as one of the treatments of patients with coronavirus disease 19 (Covid-19), specially as an early intervention.
Aims: We assess the security and efectivity of the treatment with CP in severe or potentially severe covid-19 disease.
Methods: We collect the data of all patients with Covid-19 who were treated with covalescent plasma (CP) in our hospital from April 2020 to February 2021. First of all, we assess the security of CP transfusion and then, we assess the efectivity of the CP transfusion.
We assess the mortality rate in this patients by precocity of plasma transfusión, sex and WHO Ordinal Scale for Clinical Improvement.
Results: Between April 2020 and February 2021, a total of 44 patients with Covid-19 were treated with CP in our hospital. 77.27% (n=34) were male and 22.73% (n=10) were female with a median age of 65 (28-92). Mortality rate by sex was 32.35% (n=11) in male and 30% (n=3) in female. In terms of security one of the patiens developed a mild rash that was managed with antihistamine and had a complete resolution.
In terms of precocity of CP administration we separated the patients into two different groups. The first one, with those patients who had an early CP transfusion (ten days or less after symptom onsent) and the second one, with patients who had a late CP transfusion (more than ten days after symptom onsent). 56.80% (n=25) had and early CP administration, while 43.20% (n=19) of the patients had a late one. Mortality rate in the first group was 16% (n=4) and 52.63% (n=11) in the second one. According to the WHO Ordinal Scale for Clinical Improvement, patients with a score of 6 (intubated or mechanical ventilation) or higher were 12; patients with a score of 5 (non-invasive ventilation or high-flow oxygen) were 13, and patients with a score of 4 (oxygen by mask or nasal prongs) were 19. In our center, the mortality rate of these groups of patients was 50% (n=6), 38% (n=5) and 16% (n=3) respectively.
Summary/Conclusion: In this 44 patients group, the administration of CP has had an adverse event rate very low, similar to non convalescent plasma trasfusion adverse event rate.
In those patients who had an early CP transfusion, the mortality rate is much lower than those who had a late CP transfusion. Possibly the elapsed time from symtom onset is the most important factor to assess efectivity.
Mortality rate by WHO Ordinal Scale for Clinical Improvement shows differences between groups. Those patients with a higher score present higher mortality rates, probably similar to patients with Covid-19 treated with other therapeutic options.
The mortality rate by sex was similar in both groups as we can observe in other studies.
An early CP administration could be a therapeutic option in severe patients with Covid-19 considering that is a safe procedure that can improve survival rates.

EP1347 THE RESULTS OF SCREENING AND IDENTIFICATION OF RED BLOOD CELLS ANTIBODIES IN HEMATOLOGICAL PATIENTS AND BLOOD DONORS

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Background: Alloimmunization to antigens of red blood cells (RBC) can cause the development of post-transfusion complications and hemolytic disease of the fetus and newborn. Prevention of the emergence of alloantibodies during transfusion of blood components consists in the selection of RBC that are compatible with the recipient by phenotype. Since 2013, the Russian Federation has regulated the selection of RBC for all patients with diseases of the blood system for antigens ABO, RhD, C, c, E, c, K.
Aims: Determine the level of RBC alloimmunization of the healthy population (donors of blood components) and patients of the hematological hospital; to establish the value of donor selection for Rhesus antigens for the prevention of alloimmunization of recipients.
Methods: The analysis of the results of screening and identification of RBC antibodies was carried out in 2546 donors who first came to the blood center and 2729 patients who were first admitted to the hematology clinic in 2014-2020. Non-Hodgkin lymphoma (NHL) was diagnosed in 560 patients, acute leukemia (AL) - in 472, multiple myeloma (MM) - in 398, chronic lymphocytic leukemia (CLL) - in 188, aplastic anemia (AA) - in 100, chronic myeloid leukemia (CML) - in 92, MDS - in 78, hemophilia - in 65, other hematological diseases - in 776. Immunohematological studies were performed using equipment and reagents from BioRad (USA).
Results: RBC alloantibodies were detected in 0.98% of blood donors: in 0.24% of men and in 1.69% of women ($p < 0.01$). Alloantibodies were distributed according to specificity as follows: anti-D (0.27%) > -Le^a (0.20%) > -DC (0.16%) > -C^w(0.08%) > Jk^a (0.04%), -Jk^b (0.04%), -Fy^a (0.04%), -M (0.04%), -S (0.04%), -P_1 (0.04%).
Specific alloantibodies were diagnosed in 1.80% of hematological patients: in 1.26% of men, in 3.14% of women, and in 0.50% of children ($p < 0.01$). Alloimmunization was established in 5.43% of patients with CML, in 4.62% - hemophilia, in 3.85% - MDS, in 2.75% - OL, in 1.76% - MM, 1.61% - NHL, 1.06% - CLL, 0% - AA, in 0.9% of patients with other blood diseases.
The scale of the occurrence of specific antibodies in patients is as follows: anti-E (0.26%) > -M (0.22%)> -K (0.18%) > -DC (0.15%), -Le^a (0.15%) > -D (0.11%), -Jk^a (0.11%), -Lu^a (0.11%) > -C (0.07%), -c (0.07%), -Fy^a (0.07%), -S (0.07%), -Le^b (0.07%) > -Jk^b (0.04%), -C^w (0.04%), -s (0.04%), -P_1 (0.04%).
When comparing the data obtained with the results of our previous studies, a decrease in the level of alloimmunization of patients of the hematological clinic was found from 2.31% (in 2007 - 2013) to 1.80% (in 2014 - 2020), which is associated with the beginning of the mandatory selection of RBC for hematological patients for antigens C, c, E, c of the Rhesus system since 2014.
Summary/Conclusion: The frequency of detection of alloantibodies in patients of the hematology clinic remains high, twice as high as the level of alloimmunization in healthy individuals. Phenotypic selection of RBC is an effective method of preventing the formation of antibodies, which reduces the percentage of alloimmunization in hematological patients.

EP1348 REMOTE MONITORING OF VITAL AND ACTIVITY PARAMETERS IN CHRONIC TRANSFUSION DEPENDENT PATIENTS – A CASE-CROSSOVER PILOT USING WEARABLE BIOSENSORS

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Background: Optimising red cell transfusion requires an understanding of both the risks and the benefits. Adverse events of red cell transfusions, like transfusion reactions and iron overload are reasons for considering a restrictive transfusion strategy. However, there are no completed trials in the outpatient setting for chronic transfusion-dependent patients, and little data in general about the value of outpatient transfusions. With no objective parameters to measure the benefits of red cell transfusions, a restrictive transfusion strategy may not be optimal for patients who require RBCT on a regular basis. Transfusions are ordered primarily based on haemoglobin concentrations and a subjective interpretation of symptoms of anaemia. Endpoints that may be more clinically relevant include quality of life measurements, vital signs, functional activity and cognition. To date, there has been little systematic assessment of tools that assess these measures and no published trials that have examined the impact of transfusions on functional outcomes in transfusion-dependent patients.
Aims: The aim of this study is to understand how wearable devices and web-based testing can be used to measure physiological changes and functional activity in a cohort of transfusion-dependent patients.
Methods: We monitored 5 patients who chronically receive transfusions during one transfusion cycle with the VitalPatch® and Withings Steel HR. Patients completed CANTAB cognitive tasks, QUALMS and PROMIS quality of life questionnaires through web-based testing. Outcomes were first the quality and usability of data. Second, we leveraged mixed models to evaluate transfusion-induced changes in 1) heart rate, 2) activity, 3) sustained attention, and 4) patient-reported quality of life.
Results: Captured data was 97,8% high quality and usable for the VitalPatch; 98,9% for the Withings Steel HR. The sent out web-based CANTAB tasks and questionnaires were all completed on the appointed days. Heart rate and sustained attention are significantly and reversibly affected by RBC transfusions, corrected for predefined confounders (Fig. 1): Mean daytime heart rate was 76.5±2.8 bpm before and 72.3±2.8 after transfusion (*P*=0.002). Sustained attention (RVPA) increased from 8586±140 to 9141±183 after transfusion (*P*=0.004). Activity and quality of life measures did not yield transfusion-induced changes. The measured activity data may not be representative as the study was conducted during the COVID-19 induced lockdown.

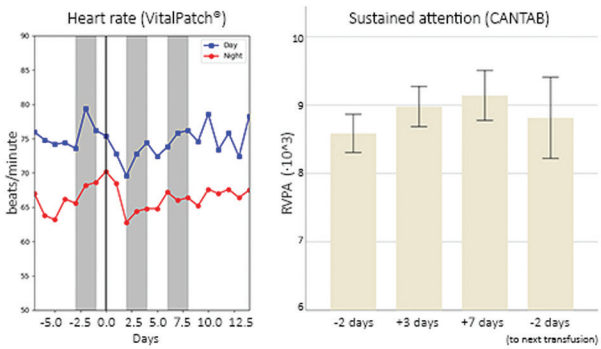


Figure 1. Mean heart rate as measured by the VitalPatch® per day/night (left) and mean RVPA per visit (right). A reversible transfusion-induced effect on heart rate and cognition is depicted. No data beyond day 14 is shown because 2/5 patients received another transfusion at day 15. Data summarized as visits for mixed models are shown as grey areas, transfusion is at day 0. CANTAB web-based cognitive tests (RVPA) were completed on the 4 appointed visits.

Summary/Conclusion: AccelerateIQ™, Withings Steel HR and the CANTAB platform are usable for extracting and analysing data. Red cell transfusions significantly and reversibly decrease heart rate and increase sustained attention in our cohort of 5 red cell transfusion-dependent patients.

EP1349 PHENOTYPIC AND FUNCTIONAL AGGREGATION FEATURES OF LEUKOCYTE-DEPLETED PATHOGEN-REDUCED PLATELETS OBTAINED BY AUTOMATIC APHERESIS

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Background: Any technological procedure influences the functional activity of platelets. Therefore, to standardize the quality of platelet components (PLTCs), it is important to assess its phenotypic and aggregation properties. According to the immunophenotypic profile of platelets, one can judge its structural integrity and functional activity.
Aims: To study some phenotypic and functional features of leukocyte-depleted (LD) pathogen-reduced platelets obtained by automatic apheresis.
Methods: Phenotypic and functional characteristics were studied on 64 samples obtained from 32 donors of PLTCs. Platelet samples obtained from wholeblood before apheresis, prepared with 3.8% sodium citrate (n = 32) and obtained by automatic apheresis, pathogen-reduced LD (INTERCEPT (n = 23) and MIRASOL (n= 9)) were studied. The expression of adhesion molecules CD 62P, integrin complex (CD41 / CD61) and platelet activation marker CD36 was assessed using flow cytometry. The studies of the functional aggregation activity of platelets were carried out by theturbidimetric method. Statistical analysis was performed using the STATISTICA v.10software. To assess the quality of the functional aggregation activity of platelets by an opticalturbidimetric method, LD pathogen-reduced PLTCs obtained by automatic apheresiswere diluted to a standard platelet concentration (200-250 thousand / μL) with a poolof platelet-free universal plasma obtained from male donors AB (IV) blood groupRhesus (D)-negative in a ratio of 1: 3 (PLTCs: AB (IV) Rh (D)-negative (diluent))and incubated for 20-30 min.
Results: The ADP-induced (2.5 μM; 5 μM) platelets aggregation activity before apheresis was 48.1 (36.5; 65.8)% and 66.9 (55.6; 75.7)% respectively, which was significantly higher ($p < 0.05$) than one on the 1st day in LD pathogen-reduced platelets obtained by the method of automatic apheresis. The ADP-induced platelets aggregation activity of that PLTC was 7.5 (1.2; 12.3)% for plain and 10 (7.0; 15.4)% for diluted PLTC in case of 2.5 μM ADP and 15.7 (7.1; 20.1)% for plain and 19.4(14.3; 27.1)% for diluted PLTC in case of 5 μM ADPA statistically significant positive correlation was found in platelet samples from whole blood before apheresis between indicators of the ADP-induced (5 μM) platelet aggregation activity 66.9 (55.6; 75.7)% and the relative number of cells expressing CD62P 13.1 (6.4; 20.7)% ($R = 0.82$, $p = 0$). A similar positive correlation was determined in LD pathogen-reduced PLTCs afterapheresis which were stored for one day in a thermal shaker at 22 ± 20 C diluted with plasma. In that case ADP-induced (5 μM) platelet aggregation activity was 19.4(14.3; 27.1))% and the relative number of cells expressing CD62P 13.9 (8.0; 19.1)% ($R = 0.36$, $p = 0.003$)
Summary/Conclusion: Thus, a positive statistically significant correlation was revealed in ADP-induced (5 μM) platelet aggregation activity and the relative number of cells expressing P-selectin (CD62P) for LD pathogen-reduced PLTCs after apheresis after dilution with plasma and one day storage. The data obtained allow us to consider indicators for assessing the aggregation activity of platelets as one of thecharacteristics of quality control of platelet components.

Acute lymphoblastic leukemia - Biology & Translational Research

PB1350 NRF2 AS A THERAPEUTIC TARGET IN ACUTE LEUCEMIA – IN VITRO STUDIES WITH OLTIPRAZ

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Background: Acute leukemias are a group of hematological neoplasias characterized by a dysregulation in cell proliferation and/or an arrest in the differentiation process of hematopoietic stem cells. Oxidative stress (OS) has been referred as one of the mechanisms involved in the pathophysiology of these diseases. The OS state consists in an unbalance between the production of reactive oxygen species (ROS) and the ability to neutralize them by antioxidant defenses. The nuclear factor erythroid 2–related factor 2, NRF2, is a transcription factor (TF) that regulates the expression of several antioxidants and detoxification systems and works as a protective mechanism in normal cells against malignant transformation. However, during the tumorigenic process, NRF2 protects tumor cells from OS effects compromising the therapeutic efficacy. Based on this, the modulation of this transcription factor may represent a therapeutic approach in acute leukemias.
Aims: The aim of this study was to investigate the therapeutical potential of the NRF2 modulator Oltipraz (Olt) in acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) cell lines.
Methods: To this propose, 3 ALLs cell lines, two from T lineage (CEM and MOLT-4 cells) and one B lineage (KOPN8 cells), and two AML (HEL and NB4 cells) were incubated in the absence and presence of Oltipraz in several concentrations for 72h. Metabolic activity was evaluated by resazurin assay. Cell death was assessed by flow cytometry (FC), using the Annexin V and 7-AAD double staining, and by optic microscopy (May-Grünwald-Giemsa staining). Cell cycle analysis was evaluated by FC using a PI/RNAse solution. The intracellular levels of ROS and GSH were quantified by FC (DCFH2-DA, DHE, and MO probes). JC-1 probe was used to determine the mitochondrial membrane potential (Y_{mit}) by FC. The statistical analysis was performed, considering a significance level of 95%.
Results: Oltipraz reduced metabolic activity in a time, dose, and cell line-dependent manner. After 72h of incubation, B-ALL cell line was the most sensitive to Olt (KOPN8 IC_{50}= 4.5µM) comparing to T-ALL (MOLT-4 IC_{50}= 87.4µM; CEM IC_{50}= 40.4µM) and AML (HEL IC_{50}= 63µM, NB4 IC_{50}= 21µM) models. This drug induced a cytotoxic effect mediated by apoptosis in AML cells. It was also observed a cytostatic effect in B-ALL cells, with a cell cycle arrest in G_0/G_1 phase, and in AML cell lines with a cell cycle arrest in S phase. Moreover, Olt increased the intracellular levels of ROS and ROS/GSH ratio and decreased the mitochondrial membrane potential (□mit) in all cell lines. These results support the role of OS and mitochondria dysfunction in the therapeutic effects mediated by Oltipraz in acute leukemias.
Summary/Conclusion: Our results demonstrate that lymphoid and myeloid acute leukemias were sensitive to NRF2 modulation using Oltipraz, suggesting that this drug may constitute a new therapeutic approach in these hematological neoplasms. However, the drug efficacy is cell type dependent and could be also related with molecular/genetic characteristics of the leukemia.
This work was supported by FMUC, CIMAGO and FCT (SFRH/BD/145531/2019).

PB1351 THE ROLE OF CASPASE-8 (CASP8) AND -10 (CASP10) GENE POLYMORPHISMS IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: In the past 50 years great advances have been achieved in the management and prognosis of Acute Lymphoblastic Leukemia (ALL) in children, resulting in improved treatment outcome of up to 90%. However ALL still remains a major cause of morbidity and mortality in children, specially in disease relapse.Major progress has been made in the last decade in understanding the biology of ALL, the genetic basis of leukemogenesis and the response to treatment. Epidemiological studies of possible risk factors in acute leukemia, proved that genetic factors play a crucial role in leukemogenesis. Alterations in the regulation of apoptosis and the deregulation of expression or function of caspase antagonists' pathways seem to play an important role in the pathogenesis and progression of hematological malignancies. Caspases are a family of cysteine proteases whose functions are strongly associated with programmed cell death. Polymorphisms in the apoptotic genes may enhance the risk of disease, as implicated by the strong link between genetic diversity and susceptibility to ALL. Caspase 8 plays an important role in apoptosis and several studies have been performed to identify the relationship between polymorphisms in *Casp8* gene and different types of cancer. Caspase 10 is the only caspase that shares homologous death–effector domains with caspase 8, while somatic mutations in *Casp10* gene have been observed in many cancers.
Aims: The purpose of the present study was to investigate the incidence of rs1045485 polymorphism in exon 10 of the caspase 8 gene and rs13006529 in exon 10 of the caspase 10 gene in children and adolescents with Acute Lymphoblastic Leukemia compared with healthy individuals.
Methods: The patient group consisted of 50 children and adolescents (1.5 to 17.5 years) with ALL and the control group consisted of 100 healthy individuals. Genomic DNA was isolated from periphral blood of participants and the genetic regions harboring the single nucleotide polymorphisms (SNPs) under investigation were amplified with Polymerase Chain Reaction. The PCR product was then digested with the appropriate restriction enzymes (*BstU*I for rs1045485, *Ssp*I for rs13006529). Statistical analysis was performed by using the GraphPad Prism (GraphPad Software, San Diego, CA, USA) program.
Results: Statistic analysis showed an association between the G allele of *Casp8* rs1045485 SNP and ALL (p=0.0002, OR=0.381, 95% 0.229-0.633). Statistically significant differences were found between AT and TT genotypes of rs13006529 SNP of *Casp10* and ALL (p=0.011, OR=4, CI 95% 1.382-11.380 and p=0.048, OR=0.346, CI 95% 0.127-0.937, respectively), as well as between T allele of the same SNP and ALL (p<0.0001, OR=0.345, CI 95% 0.205-0.578).
Summary/Conclusion: The present study showed that both rs1045485 SNP of *Casp8* and rs13006529 SNP of *Casp10* are associated with the diagnosis of ALL. Further study of these polymorphisms in children and adolescents with ALL would be of great interest, in order to confirm whether they are associated with the disease in the population of Greece.

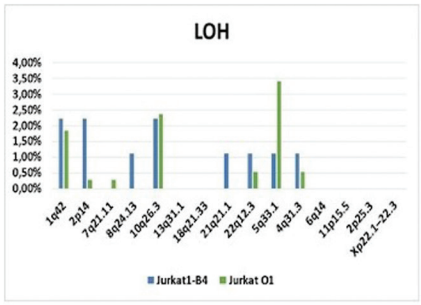
PB1352 ¬HIGH FREQUENCY OF SPONTANEOUS LOSS OF HETEROZYGOSITY AND ELEVATED MICROSATELLITE ALTERATION AT SELECTED TETRANUCLEOTIDES IN LEUKEMIA CELLS STR-PROFILES: IN-VITRO TESTING OF LYMPHOBLASTOID CELL LINES

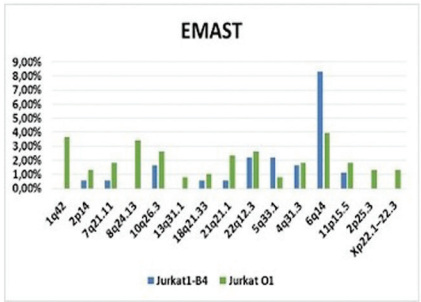
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Background: The frequency of spontaneous mutagenesis of tetranucleotide microsatellites (STR) in the human population is less than 0.3% for most of STR loci [https://strbase.nist.gov/str_fact.htm]. The frequency of these events during leukemia cell development could hardly be measured by means of testing clinical specimens. However, these data could be assessed

by in vitro culturing and cloning experiments with common lymphoblastoid cell lines and could be useful for investigating possible associations of instability in certain chromosomal loci with the disease features in ALL.
Aims: To evaluate frequency of STR profile mutations during long term culturing of Jurkat and WIL2-S cell lines after cloning by limiting dilutions.
Methods: Jurkat is an immortalized T lymphocyte cell line originally obtained from the peripheral blood of T cell leukemia patient. WIL2-S is an immortalized B lymphoblast cell line derived from the spleen of the patient with hereditary spherocytosis. Cell lines were cultured in RPMI 1640 medium. Cells were cloned by the method of limiting dilutions; 21 individual clones of WIL2-S and 18 Jurkat clones were taken for STR profiling. Clone WIL2-S #11 was karyotyped, further cloned and 350 subclones were STR profiled. Jurkat1-B4 clones (with stable STR-profile comparing with STR-profile of Jurkat cell line) and Jurkat-O1 (Y loss and 12p13.2 LOH in relation to Jurkat cell line) were also karyotyped, further cloned and 180 subclones of Jurkat1-B4 and 381 subclones of Jurkat-O1 were STR profiled. STR-profiles were assessed by PCR with COrDIS Plus multiplex kit for amplification of 19 polymorphic STR-markers and amelogenin loci (Gordiz Ltd, Russia). The fragment analysis was performed on ABI 3130 Genetic Analyzer. The data processing was accomplished using GeneMapper v.4-0 software.
Results: Out of 18 Jurkat clones, 7 have marker loss on Y-chromosome (amelogenin locus); 5 have LOH on 12p13.2 (3 of these clones also have amelogenin Y loss) one clone - LOH on 4q; one — on 5q33.1; and one - on 8q. Elevated Microsatellite Alteration at Selected Tetranucleotides (EMAST- change in the length of STR markers) was found in 10 clones. Only 4 clones retained exactly the same STR profile of initial Jurkat stock sample. Out of 21 WIL2-S clones, EMAST was found in 4 clones only. One clone lost the amelogenin Y marker. Out of 350 subclones of WIL2-S STR-stable clone #11, only two (0.57%) were found to lose the Y-chromosome amelogenin marker. One LOH at 10q26.3 was seen in one of 350 clones (0.29%) only. For Jurkat line LOH was seen in 26 from 180 Jurkat1-B4 subclones (14.4%) and in 35 from 381 Jurkat-O1 clones (9,1%). EMAST was found in 45 from 180 (25%) B4 and 111 from 381 O1 subclones (29%) respectively. While EMAST appears uniformely along different STR-markers, LOH frequency for distinct STR-loci differs and seems to be a feature of certain acute T-cell leukemia (See Fig.1 LOH and EMAST frequencies for different loci in Jurkat 1-B4 and Jurkat-O1 subclones. *STR loci at 3p21.31, 5q23.2, 16q24.1, 12p13.31 are homozygous in Jurkat cell line). Only 60% of Jurkat1-B4 and 64% Jurkat-O1 subclones were found STR-stable. No significant difference was found in mutation frequencies in stable initially Jurkat1-B4 and mutated Jurkat-O1 clones.





STR-marker	Locus
D1S1656	1q42
D2S441	2p14
D3S1358	3p21.31
D5S818	5q23.2
D7S820	7q21.11
D8S1179	8q24.13
D10S1248	10q26.3
D12S391	12p13.2
D13S317	13q31.1
D16S539	16q24.1
D18S51	18q21.33
D21S11	21q21.1
D22S1045	22q12.3
CSF1PO	5q33.1
FGA	4q31.3
SE33	6q14
TH01	11p15.5
TPOX	2p25.3
VWA	12p13.31
Amelogenin X	Xp22.1–22.3
Amelogenin Y	Yp11.2

Summary/Conclusion: Jurkat T lymphocyte leukemia cell line demonstrated a high level of spontaneous LOH in selected loci and EMAST spreading equally through genome. More detailed STR profile testing on extended samples of in vitro cultured cell clones might identify more detailed patterns of spontaneous chromosomal instability in lymphoblastoid cells.

PB1353 PATHOGENETIC ROLE OF TUMOR NECROSIS FACTOR (TNF) AND TRANSFORMING GROWTH FACTOR B1 (TGFB1) IN THE CHANGING OF ADHESIVE PROPERTIES OF VASCULAR ENDOTHELIUM (VE) IN ACUTE LEUKEMIA (AL)

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Background: Adhesion of acute leukemic cells (blasts) to the VE was significantly influenced by TNF and TGFβ1. TNF and TGFβ1 often accumulated in the blood of AL pts and correlated with the negative course of the AL. The pathogenetic role of cytokines in the spread of the AL has not been definitively established.
Aims: The aim of our investigation was to determine the role of TNF and TGFβ1 in changing the adhesive properties of the VE in 9 primary patients (pts) with AL (6 pts with ALL and 3 - AML).
Methods: Median of pts age was 68 years. The number of blasts in peripheral blood - 58,62±10,53%. We identified the attachment of labeled by ^{3}H-thymidine cells lines K562, L1210 to the monolayer of human umbilical vein endothelial cells (HUVECs) *in vitro* after treated of plasma or 24 h-conditional mediums (CM) of blasts from blood pts, and to compare obtained data with concentration of TNF and TGFβ1 in the experimental samples. We also evaluated the effect of different doses of rhTGFβ1, rhTNF on the adhesive properties of HUVECs. Doses of rhTNF and rhTGFβ1 were selected according to the determined in plasma and CM of blasts from AL pts. The level of TNF and TGFβ1 was detected by bioassays using L929 and CCL64 in accordance. The attachment of K562, L1210 to HUVECs was estimated by the index of adhesion (IA). K562, L1210 were not activated before the investigation.
Results: TNF and TGFβ1 levels in plasma of AL pts were higher than in healthy donors (p<0,001). Plasma showed more strong influence on adhesion to HUVECs of K562 cells (IA=2,37±0,24), in comparison to L1210 (IA=1,28±0,8; p<0,05). Nevertheless TGFβ1 levels in CM of blasts AL pts was two-fold higher than in plasma of AL pts and inversely correlated with blasts number (r= - 0,40). Blasts of AL pts influenced on adhesive activity of HUVECs to K562 and L1210 (IA=1,99±0,38 and 1,92±0,24, respectively). CM of blasts secreted higher level of TGFβ1, than it was in plasma pts (p<0,05) We found that low concentrations (0,01 up to 2,40 ng/ml) of rhTGFβ1 stimulated significantly the adhesive properties of HUVECs. rhTGFβ1 in the ranges from 3,60 ng/ml up to 8,30 ng/ml inhibited adhesion of K562 cells (IA<1,00) but in the higher doses it stimulated adhesive properties of HUVECs again (IA>1,00). On the other hand we found that low concentrations of rhTNF (0,001 up to 0,01 ng/ml) correlated inversely with adhesion of K562 to HUVECs (IA from 4,33 to 1,0). rhTNF in the range 0,01 up to 0,1 ng/ml didn't stimulate the attachment of K562 to HUVECs. Incubation of HUVECs with rhTNF in concentrations 0,8 up to 4,1 ng/ml resulted in significant increase of K562 adhesion (IA>1,0). After influence of rhTNF (0,001 up to 0,024 ng/ml) HUVECs demonstrated considerable adhesiveness to L1210 (IA from 1,42 to 3,02). rhTNF in range 0,03 up to 0,06 ng/ml diminished the attachment of L1210 (IA<1,0), but in the range (0,07 up to 2,03 ng/ml) it significantly induced the adhesion of L1210 again. Pretreatment of HUVECs by rhTNF more than 3,12 ng/ml didn't induce any adhesion, perhaps via its cytotoxic influence on EC monolayer.
Summary/Conclusion:.
Blasts were the powerful source of cytokines secretion that was able to modulated the adhesive properties of VE and may pathogenetically influence on spreading of AL.
TNF and TGFβ1 can affect different types of leukemia cells in different ways. On the other hand rhTNF and rhTGFβ1 *in vitro* changes the adhesive properties of HUVECs in a dose-dependent manner. Therefore, the adjustment of cytokine levels in the blood of AL pts may be an important step in the treatment of AL.

PB1354 EVALUATION OF BIOMATRICA'S RNASTABLE (BRS) AND NOVEL STABILIZER (CPHD1) TO PRESERVE IVT-RNA AT ROOM TEMPERATURE(RT) TO BE USED FOR CALIBRATION OF THE CEPHEID XPERT® BCR-ABL ULTRA P190 PROTOTYPE‡ ASSAY

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Background: Reliance on RNA usage is integral in many scientific fields. For many applications, RNA integrity is required and must be maintained during storage. Current gold standard for RNA storage at -80°C[1] may still jeopardize RNA integrity due to ribozyme activity[2]. An alternative method for RNA preservation is essential in these growing fields, where the use of RNA is imperative. BRS (Biomatrica, San Diego, CA), is a unique RNA preservative that has demonstrated RT stability for up to 12 years in accelerated aging studies[3].
Aims: BRS has shown excellent stability at 50°C for total RNA; however, BRS IVT-RNA stability data has not been published. We evaluated preservation of e1a2 IVT-RNA in BRS and CPHD1 for calibration of the Cepheid Xpert BCR-ABL Ultra p190 Prototype Assay, which is designed as a ≤ 2.5 hour test, to monitor minimal residual disease in Ph+ ALL patients.
Methods: e1a2 IVT-RNA was prepared in DEPC-treated water or in CPDH1 at 200pg/µL in *E.coli* tRNA. 10 µL of the IVT-RNA mixture was added to BRS or CPDH1 and dried in a laminar flow hood for ~24 hours. Completely dried IVT-RNA tubes were placed into moisture barrier bags with desiccant packets, heat sealed, and stored at RT (19°C-23°C) or 50°C. The IVT-RNA in DEPC-treated water controls were aliquoted into microfuge tubes and stored at -80°C. At designated time points, aliquots from each condition were diluted in assay buffer and tested with the Xpert BCR-ABL Ultra p190 Prototype Assay and with digital droplet PCR (ddPCR) on the BioRad QX-200 ddPCR systems (BioRad, Hercules, CA).
Results: Storage of IVT-RNA in BRS at RT and 50°C show excellent stability, comparable to the gold standard (-80°C) through the duration of the study. A general linear model (GLM) was fit to evaluate the effect of time, storage temperature, and IVT-RNA input level on measured e1a2 transcript (a2 Ct). Significant value was set at 0.01, according to Bonferroni correction method. All non-significant two-factor interaction and second-order terms were dropped from the analysis, yielding a general regression equation which predicts an increase of 0.43 Ct over 36 weeks. The reduced model ANOVA table showed no significant difference in e1a2 Ct between storage temperature with p-value = 0.73. E1a2 copy number was monitored in parallel, for the two lowest input levels (0.1fg and 1fg) with ddPCR. A GLM was similarly run to generate a regression equation to predict copy number (CN). Reduced model ANOVA from Design Of Experiment for CN show non-statistically significant for storage temperature with p-value = 0.296. At 36 weeks, e1a2 IVT-RNA performs remarkably well at 50°C, comparable to T0 baseline. Cycle threshold, endpoint fluorescent and CN comparability are indicators of excellent stability (Table 1). Preliminary data for the CPHD1 RNA show promising results after dried storage at RT for 20 days + 16 days at 50°C.

Table 1: RT-PCR data from Xpert BCR-ABL Ultra p190 and BioRad ddPCR data for e1a2 IVT-RNA stored in BRS for RT and 50°C and stored in DEPC-treated water for -80°C at 36 weeks compared to Time 0 week (T0).

Timepoint (Week)	IVT-RNA storage cond	IVT-RNA input per test (fg)	Xpert BCR-ABL Ultra p190 RT-PCR (10ul per test)							RT-ddPCR data (1ul per test)	
			a2 Ct	a2 EP	ABL Ct	ABL EP	dCt (ABL-a2)	e1a2 slope and R^2	ABL slope and R^2	RT-ddPCR a2 CN	RT-ddPCR ABL CN
T0	CTRL	0.1	not tested							203	187
		1	19.0	617	18.6	664	-0.4	y = -3.2725x + 18.94 R^2 = 0.9958	y = -3.2575x + 18.505 R^2 = 0.9938	2047	1953
		10	15.7	635	15.3	656	-0.4			21053	20047
		100	12.3	647	11.8	757	-0.6			219333	214000
		1000	9.2	619	8.9	702	-0.3			not tested	
36 weeks	-80°C Wet Ctrl	0.1	not tested							244	213
		1	19.2	547	18.7	643	-0.5	y = -3.2225x + 19.065 R^2 = 0.9924	y = -3.1575x + 18.455 R^2 = 0.9912	2407	2140
		10	15.5	588	14.9	684	-0.6			not tested	
		100	12.8	515	12.3	573	-0.5				
		1000	9.4	553	9.0	618	-0.4				
	RT Dried	0.1	not tested							277	234
		1	19.1	554	18.5	631	-0.6	y = -3.2775x + 19.085 R^2 = 0.9979	y = -3.215x + 18.435 R^2 = 0.998	2240	2153
		10	15.8	584	15.2	699	-0.6			not tested	
		100	12.5	609	11.9	746	-0.6				
		1000	9.3	585	8.9	714	-0.4				
	50°C Dried	0.1	not tested							247	209
		1	19.4	561	18.8	622	-0.7	y = -3.43x + 19.508 R^2 = 0.9957	y = -3.365x + 18.823 R^2 = 0.9946	2120	2053
		10	16.2	553	15.5	612	-0.7			not tested	
		100	12.7	609	12.1	658	-0.5				
		1000	9.2	544	8.7	616	-0.5				

Summary/Conclusion: BRS is an effective IVT-RNA storage formula at 50°C for up to the evaluated duration of 36 weeks, equivalent to 5 years at RT based on accelerated aging. Future timepoints up to 24 months will be monitored. The study goal was to determine storage stability of e1a2 IVT-RNA for usage in the Xpert BCR-ABL Ultra p190 Prototype Assay. However, during the initial evaluation, BRS production was discontinued and Cepheid has consequently developed an alternative formula (CPHD1) to store IVT RNA at RT. Preliminary data for CPHD1 show promising results. Further studies will need to be performed to elucidate the effectiveness of the CPHD1 RNA stable reagent for storage at RT.

PB1355 DEVELOPMENT OF ASSAY CALIBRATION MEHTHODOLOGY FOR CEPHEID XPERT® BCR-ABL ULTRA P190 PROTOTYPE‡ ASSAY

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Background: Currently, no International Standards are available for the quantitation of the e1a2 p190 transcript for both CML and ALL, posing a challenge when developing a quantitative assay to monitor the e1a2 p190 transcript levels.
Aims: Implementation of a primary control material, containing *in vitro* transcribed RNA (IVT-RNA) of ABL and BCR-ABL e1a2, for standardization of ABL and BCR-ABL e1a2 quantifications through copy number (CN) calibration was used to develop an assay calibration methodology at Cepheid. This process allows generation of in-house RNA control materials as secondary standard (SS) mimicking clinical samples, for calibration and standardization of the Xpert BCR-ABL Ultra p190 Prototype Assay.
Methods: Titration studies were performed with Cepheid's IVT-RNA, containing e1a2 and ABL, to derive CN calibration curves of the target genes relative to the corresponding Cycle Threshold (Ct) for both e1a2 and ABL in the background of PAXgene human whole blood. The calibrated standard curves assigned the BCR-ABL e1a2/ABL% values to a 4-member in-house control material (SS) ranging from ~10% to 0.02% generated by spiking BCR-ABL e1a2 total RNA and ABL total RNA (HL60) in PAXgene blood. A lot-specific curve of delta Ct vs BCR-ABL e1a2/ABL% value was generated from the secondary standard for the BCR-ABL p190 Prototype Assay providing an Efficiency Value ($E_{\Delta\Delta Ct}$) and a lot-specific scaling factor (*SF*). The BCR-ABL e1a2/ABL% value of any given clinical sample was calculated with $E_{\Delta\Delta Ct}$ and *SF*. A 4-assay comparison study was performed to validate the assay calibration methodology with contrived clinical samples.
Results: Based on the observation of constant delta Ct between e1a2 and ABL from IVT-RNA, the ABL standard curve was generated by BCR-ABL e1a2 standard curve. Through the BCR-ABL e1a2 and ABL calibration curves generated from IVT-RNA PAXgene blood background, the BCR-ABL e1a2/ABL % value of the SS was assigned. The $E_{\Delta\Delta Ct}$ and *SF* of 4 lots of BCR-ABL Ultra p190 kit were generated. BCR-ABL e1a2/ABL % values of contrived clinical samples in EDTA whole blood and PAXgene whole blood from BCR-ABL Ultra p190 Prototype Assay were consistent with those from three other comparator assays, RT-ddPCR, Asuragen, and Ipsogen (Table 1).

Table 1: Four assay comparison data for the same EDTA sample and PAXgene blood sample.

Sample background	Assay	Reported BCR-ABL/ABL %
EDTA Blood	BCR-ABL Ultra p190	2.69
	RT-ddPCR	N/A
	Asuragen	2.80
	Ipsogen	2.380
PAXgene Blood	BCR-ABL Ultra p190	0.026
	RT-ddPCR	0.020
	Asuragen	0.025
	Ipsogen	0.037

Summary/Conclusion: In conclusion, implementing a primary control material of IVT-RNA, allowed linkage of known RNA CN to corresponding Ct, thus providing a methodology to assign BCR-ABL e1a2/ABL % value to a human whole blood-based secondary standard. A lot-specific $E_{\Delta\Delta Ct}$ and *SF* for BCR-ABL Ultra p190 Prototype Assay was generated from the secondary standard and was utilized to calculate the BCR-ABL e1a2/ABL % value for a given clinical sample. Data from 4-assay comparison suggested that we achieved the goal of establishing a successful assay calibration methodology with IVT-RNA in human blood background as primary standard and the BCR-ABL e1a2/ABL % value reported by BCR-ABL Ultra p190 Prototype Assay was compatible with other comparator assays.

PB1356 BCR-ABL P190 QUANTITATION EVALUATED BY COMMERCIALLY AVAILABLE ASSAYS AND THE CEPHEID XPERT® BCR-ABL ULTRA P190 PROTOTYPE‡ASSAY

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Background: BCR-ABL is a constitutively active tyrosine kinase formed by the t(9;22) reciprocal translocation, with the p190 transcript being the most frequent variant in Ph+ ALL[1]. Tyrosine kinase inhibitor (TKI) resistance develops in a significant number of Ph+ ALL patients over the course of treatment[2,3,4]. As 15-20% of children, and about half of adults treated for Ph+ ALL ultimately relapse, there is need for a more sensitive and easier to use molecular test with a shorter time-to-result (TTR) for the monitoring of MRD and treatment response in p190-positive patients[3,5,6].
Aims: The objective of this study was to compare the performance of the novel Cepheid Xpert BCR-ABL Ultra p190 Prototype Assay to the Asuragen QuantideX® qPCR BCR-ABL minor Kit, the Qiagen ipsogen® BCR-ABL1 mbcr Kit, and an in-house developed reverse transcriptase digital droplet PCR (RT-ddPCR) assay using samples contrived using Philadelphia chromosome-positive (Ph+) ALL patient peripheral blood. Our goal was to create a fast and easy to use quantitative assay with higher sensitivity than currently available assays for use in the monitoring of treatment efficacy and minimal residual disease (MRD) in Ph+ ALL patients.
Methods: Three p190-positive ALL total RNA samples were spiked into p190-negative EDTA whole blood lysate matrix diluents and serially diluted to target %BCR-ABL p190/ABL outputs from approximately 25% (LR [log reduction] 0.60) to near the assays expected limit of detection (LoD), approximately 0.005% (LR 4.30). A subset of each level underwent sample preparation, total RNA extraction, and RT-qPCR all in the Cepheid GeneXpert automated cartridge system, and another subset had total RNA extracted using the Zymo Direct-zol™ RNA Miniprep Plus Kit. RNA was qualified and quantified using the Thermo Scientific NanoDrop™ 2000 Spectrophotometer before being tested per the comparator assay vendors' recommendations. The Cepheid Prototype assay utilized 4.5mL of lysate, whereas the Asuragen assay used 1-2 µg of RNA per test, and the Qiagen and RT-ddPCR assays used 1 µg of RNA per test. The Cepheid Prototype assay was evaluated against the three comparator assays using Deming regressions with regression confidence intervals determined using jackknife resampling. Bland-Altman plots were utilized to evaluate bias between assay quantitation outputs. Hit-rates were assessed to compare the LoD between assays.
Results: Deming regressions and associated Bland-Altman plots showed a high degree of correlation and agreement between comparator assays and the Cepheid Prototype assay. Replicates that did not detect p190 were not included in this analysis. Dropout rates at low target %BCR-ABL p190/ABL levels were compared between assays. The Cepheid Prototype assay had the best performance in terms of hit-rate, followed by the Asuragen, RT-ddPCR, and Qiagen assays (**Table 1**).

Table 1. For levels containing at least one drop-out in any given assay, hit rate is given by %BCR-ABL p190/ABL level, as determined by the mean RT-ddPCR output ratio for the corresponding level. Misses were only included in this analysis if sufficient ABL background was detected.

Assay	Hit Rate by RT-ddPCR Determined %BCR-ABL p190/ABL Levels				
	0.006%	0.013%	0.020%	0.041%	0.068%
Xpert BCR-ABL Ultra p190 Prototype Assay	3/3	3/3	3/3	3/3	3/3
Asuragen QuantideX® qPCR BCR-ABL minor Kit	2/3	3/3	3/3	3/3	3/3
Qiagen ipsogen® BCR-ABL1 mbcr Kit	0/4	0/4	3/4	3/4	3/4
RT-ddPCR	2/3	2/3	3/3	3/3	3/3

Summary/Conclusion: The novel Cepheid Prototype assay showed a high level of agreement with the three comparator assays and gave the lowest LoD overall in this study using samples contrived from Ph+ ALL patient peripheral blood. TTR was minimized in the Cepheid Prototype assay to 130 minutes, while the comparator assays all had a TTR of approximately five hours or greater. While RNA extraction is performed within Cepheid Prototype assay cartridge and is included in the 130-minute TTR, the comparator assays require additional expensive and labor-intensive extraction steps that can last one-hour to multiple days, which are not included in the five-hour TTR estimate.

PB1357 CGH ARRAYS REVEAL ADDITIONAL CLINICALLY RELEVANT CHROMOSOME ABNORMALITIES IN POSITIVE PHILADELPHIA ACUTE LIMPHOBLASTIC LEUKEMIA: A CASE STUDY

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Background: Screening at onset for BCR-ABL1 fusion gene by FISH/RT-PCR and chromosome banding analysis is mandatory and routinely tested for a rapid diagnosis in Acute Limphoblastic Leukemia (ALL). Philadelphia chromosome in adult ALL patients was associated with an unfavorable prognosis before the introduction of tyrosin kinase inhibitors. However, a proportion of patients still have an unfavorable prognosis, suggesting that additional biological mechanisms, like additional chromosomal abnormalities (ACAs), other than the BCR-ABL1 driver lesion, are involved. The application of high-resolution genome wide methods is useful for understanding the molecular bases of these mechanisms.
We report the case of a 42 years old male with Ph+ ALL confirmed by RT-PCR ($p190^{BCR-ABL}$) with a normal karyotype in all the observed metaphases and an abnormal FISH signal pattern (four fusion signals) detected only in nuclei.
Aims: To assess the real nature of an atypical cytogenetically undetectable rearrangement of BCR-ABL1 in a ALL patient we investigated his bone marrow sample with a microarray-based approach.
Methods: DNA obtained from bone marrow of the patient was analyzed by Comparative Genomic Hybridization (CGH) 60K oligonucleotide array. Fluorescence in situ hybridization (FISH) was performed to confirm the result obtained.
Results: CGH array detected a clone (20% of cells) with an additional X chromosome, trisomy of chromosomes 4, 5, 20, and 21 and a 3.8 MB interstitial deletion of short arm of chromosome 9. This region contains several genes including CDKN2A/2B, recently emerged as very strong prognostic marker in Ph+ ALL adult patients. Moreover, our analysis showed a gain of two copies of 9q34-qter and 22pter-q11.2 regions suggesting the presence of two additional Philadelphia chromosomes. This abnormal clone was confined to nuclei, as confirmed by FISH. Karyotype analysis needs the presence of mitotic cells that have been arrested in the metaphase. In this case probably only normal cells were actively dividing. This explains the normal karyotype displayed by the cytogenetic analysis. At the present time the patient, at day 45 from therapy start, is responding to the induction therapy with imatinib and prednisone, with minimal residual disease persistence.
Summary/Conclusion: Most of ACAs, frequently observed in Ph+ ALL, are detectable by chromosome analysis. The presence of ACAs in adult Ph+ ALL seems to negatively influence the prognosis and consequently the efficacy of TKI combined with chemotherapy and hematopoietic stem cell transplantation.
When a normal karyotype is detected, screening for recurrent fusion genes and rapid diagnosis for clinically relevant anomalies by FISH or RT-PCR represent the gold standard methods in genetic analysis of ALL. Anyway, these methods may not be able to detect cryptic genetic lesions. It is well known that a normal karyotype can hide a more complex condition. This is due to the low resolution of the cytogenetic analysis and to the different clone proliferation leading to cell selection. This case underlines that to overcome these limitations may be useful to include microarray-based genome wide test in the diagnostic workup that could provide insight into the molecular pathogenesis of Ph+ ALL and help to define more accurately prognostic groups.
In particular, CGH array can easily identify small and very often cytogenetically undetectable CDKN2A/2B deletions that recently emerged as a new strong and independent prognostic marker in Ph+ ALL adult patients.

PB1358 CHROMOSOMAL ABNORMALITIES DURING THE CLINICAL COURSE OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Using conventional cytogenetics, an abnormal karyotype can be detected in 60-85% of adult acute lymphoblastic leukemia (ALL) patients. Taking into consideration the identified cytogenetic abnormalities ALL patients are currently classified into three risk groups: favorable, intermediate and adverse. These genetic abnormalities are the most important factors in determining response to chemotherapy as well as outcome in ALL.
Aims: Aim of this study was to detect the diagnostic and prognostic significance of chromosomal abnormalities in leukemic cells at different

phases of ALL and to determine the frequencies of clonal evolution at ALL relapse.
Methods: Cytogenetic investigations of bone marrow and/or peripheral blood cells from 54 adult patients were performed during clinical evolution of ALL: in newly diagnosed patients, in remission and at relapse. The methods of conventional cytogenetics (GTG) and fluorescence *in situ* hybridization (FISH) were used. Cytogenetic methods were performed using standard techniques and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.
Results: Cytogenetic investigations of 50 adult ALL patients were performed in newly diagnosed patients, in remission and at relapse. Structural (t(9;22)(q34;q11), 11q23 rearrangements, t(12;21)(p13;q22), del(17p), del(7q) and others) and numerical (monosomies, trisomies, tetrasomies, hyperdiploidy, hypodiploidy) chromosomal abnormalities in leukemic cells were found. Some genetic abnormalities (*BCR/ABL* and *AF4/MLL* fusion genes) were detected by molecular genetic methods (FISH). Spectrum of cytogenetic abnormalities had an important diagnostic and prognostic significance. Diagnosis of ALL was possible due to the presence of specific genetic markers that can confirm some types of ALL (ALL with t(9;22)(q34;q11), *BCR/ABL* gene, t(4;11)(q21;q23), hyperdiploidy, hypodiploidy). Taking into consideration the identified cytogenetic abnormalities ALL patients were classified by risk groups: the group of patients with adverse cytogenetic markers (hypodiploidy, t(4;11)(q21;q23), t(9;22)(q34;q11), multiple changes (≥3)), the intermediate risk group without significant prognostic markers and the group with favorable prognostic factors (t(12;21)(p13;q22), high hyperdiploidy). In remission cytogenetic investigations showed a normal karyotype without cytogenetically visible changes in all patients. Cytogenetic investigations at relapse were performed in 9 of 50 ALL cases. Presence of the additional/secondary chromosomal aberrations in leukemic cells or new cells clones with multiple structural and numerical changes at relapse was detected in 5 (56%) patients. This is the one sign of clonal evolution and progression of the disease.
Summary/Conclusion: Cytogenetic investigations had an important significance for diagnosis, prognosis and selection the optimal treatment strategy of ALL. Besides the analysis of chromosome banding patterns it is necessary for patients with ALL to apply molecular genetic studies, namely FISH and polymerase chain reaction (PCR). Taking into consideration the identified cytogenetic abnormalities ALL patients were classified by risk groups. Presence of the additional/secondary chromosomal aberrations in leukemic cells or new cells clones with multiple structural and numerical changes at ALL relapse is the one sign of clonal evolution and progression of disease.

Acute lymphoblastic leukemia - Clinical

PB1360 MAINTENANCE TREATMENT WITH LOW-DOSE DECITABINE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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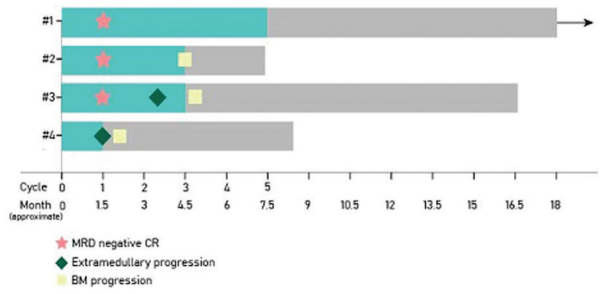
Background: Post-transplant relapse and graft-versus-host disease (GVHD) remain to be the principal leading causes of failure after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with adult acute lymphoblastic leukemia (ALL), especially relapse. The degree of methylation of tumor suppressor genes is closely related to the subtypes and prognosis of ALL. Decitabine is one of hypomethylating agents inducing leukemic differentiation and re-expression of epigenetically silenced tumor antigens. The aim of this study was to investigate the safety and efficacy of maintenance treatment with low-dose decitabine after allo-HSCT for adult ALL.
Aims: The aim of this study was to investigate the safety and efficacy of maintenance treatment with low-dose decitabine after allo-HSCT for adult ALL.
Methods: We enrolled 34 patients with ALL who underwent allo-HSCT from August 2016 to April 2020 and gave them low-dose decitabine maintenance treatment after transplantation. GVHD, relapse and overall survival (OS) were observed, and the safety of the regimen was evaluated.
Results: Among the 34 patients enrolled, 32 patients (94.1%) developed only grade I-II myelosuppression, 6 patients relapsed and 6 patients died. The 2-year cumulative incidence of relapse rate (CIR), OS and disease-free survival (DFS) were 20.2%, 77.5% and 73.6%, respectively. The 2-year CIR, OS and DFS of 12 patients with T-ALL/Lymphoblastic Lymphoma (LBL) were 8.3%, 90% and 81.5%, respectively. Among the 7 patients with T-ALL, no one relapsed. During maintenance treatment, only 1 patient (2.9%) developed grade IV acute GVHD and 4 (11.8%) patients had severe chronic GVHD.
Summary/Conclusion: Maintenance treatment with low-dose decitabine after transplantation was associated with good tolerance, a low relapse rate without significantly affecting GVHD, and satisfactory survival in patients with ALL, especially patients with T-ALL.

PB1361 BLINATUMOMAB FOR HLA LOSS RELAPSE AFTER HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Loss of patient-specific HLA after haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is considered as a relapse mechanism for lacking the incompatible molecule to elicit alloreactivity, which extensively diminishing graft versus leukemia (GVL) effects. Blinatumomab, as a CD3/CD19 bispecific antibody, can yield a profound response via redirecting T cells towards malignant lymphoblasts in B-cell acute lymphoblastic leukemia (B-ALL). We aimed to assess whether blinatumomab could result in a considerable response by regenerating immunological engagement in patients with HLA loss relapse after haplo-HSCT.
Aims: As there are no clinical data on blinatumomab for posttransplantation HLA loss relapse, we herein report the preliminary results of blinatumomab in treating B-ALL with HLA loss recurrence after haplo-HSCT.
Methods: We recruited patients with B-ALL at the First Affiliated Hospital of Zhejiang University School of Medicine. Eligible patients were diagnosed with HLA loss relapse after haplo-HSCT. One cycle of blinatumomab treatment lasted for 6 weeks, including a 4-week continuous i.v. infusion period and a 2-week treatment-free interval. During the first induction cycle, an initial dose of 9 μg/day was used for the first 7 days and the dose was increased to 28 μg/day starting on day 8 (week 2) and continuing through day 29 (week 4). The 28 μg/day dose was used for all subsequent cycles. Patients received up to 5 cycles of blinatumomab, with efficacy follow-up at 3, 6, 9, 12, 18, and 24 months after treatment initiation. The primary endpoint was CR/CRh rates in the 2 cycles of blinatumomab treatment.
Results: Between January 2017 and July 2019, 4 eligible patients relapsed HLA loss relapse after haplo-HSCT were enrolled in the study. Four patients achieved a CR/CRh with three MRD-negative response within the first 1 cycle of treatment. Three of the four met a primary endpoint with CR/CRh and MRD-negative response within 2 cycles of treatment. One patient developed new EM sites of skin after the first cycle (Fig 1). Cytokine release syndrome was observed in one patient. Cytopenias, as well as elevated alanine aminotransferase and aspartate aminotransferase, were two common adverse effects during treatment.



Summary/Conclusion: Blinatumomab can induce rapid and robust remission in B-ALL patients undergoing HLA loss relapsed after haplo-HSCT. By *redirecting* lysis of CD19-positive lymphoblast who losing the incompatible HLA, blinatumomab is a potential strategy to eradicate malignant cells via restoring GVL effects. A randomized clinical trial assessing blinatumomab in patients with HLA loss relapse after HSCT is warranted.

PB1362 INCIDENCE OF HEMATOLOGICAL MALIGNANCIES AT THE NATIONAL CANCER INSTITUTE IN PERU. A 19 YEARS' EXPERIENCE.

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Background: Cancer is a public health problem that affects the whole world, is divided into 2 major groups, solid tumors and hematological malignancies (HM). International studies mainly from developed countries report that HM account for 10% of all cancers, being the most frequent lymphoma followed by multiple myeloma (MM). National Cancer Institute (NCI), the leading public institution in Peru treats almost the 20% of cancer patients in the country.
Aims: To determine the incidence of HM by sub-type in the leading cancer center in Peru and its association with sex and age group.
Methods: We reviewed the database at the NCI Epidemiology Department in Peru from 2000 to 2018. The classification was based on the International Classification version 10 (ICD-10) and the ICD for Oncology version 3 (ICD-O 3) and divided into the main subtypes: Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), Chronic Myeloid Leukemia (CML), Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), MM, other leukemias (OtL), and other HM (oHM). Baseline characteristics (BLC) as age, age group, sex and sub-type of HM were collected. The age group was divided as follows: 0-14 years, 15-39 years (Adolescent and Young Adult, AYA), 40-64 years, and >64 years. BLC were compared using Chi-square test. The Stata software version 16 was use for the analysis.
Results: During the study period 12.4% (n= 23,795) were HM. The median age was 43 (range 0-103). 53.7% (n=12,798) were male. The most frequent HM was NHL with 44.1% (n=10,502), followed by ALL with 23.9% (n=5,684) and AML with 12.9% (n=3,072). MM and HL were 5.7% and 5.5% (n=1,351, and n=1,316), respectively. CLL was presented in 0.95% (n=225). The most frequent age group was those 40-64 years old with 32.1% (n=7,642), follow by the AYA group with 24.4% (n=5,812), the less common groups were 0-14 years group with 21.5% (n=5,113) and >64 years with 21.97% (n=5228). In the 0-14 group the most frequent HM was ALL with 63.1% (n=3,226) followed by AML with 13.5% (n=689). In the AYA group the most frequent HM was NHL with 31.5% (n=1,833) followed by ALL with 29.7% (n=1,727). In the 40-64 group the most frequent HM was NHL with 58.5% (n=4,497) followed by AML with 11.6% (n=889) and in the > 64 years group was NHL with 69.5% (n=3,632) followed by MM with 9.8% (n=514). There was a statistically significant difference between the subtypes and age ranges (p<0.001) (see table 1). In the first three age groups the most frequent sex was male, with 58.9%, 56.7% and 51%, respectively. However, in the > 64 years group the predominant sex was female with 50.6%. The difference between sex and age ranges was statistically significant p<0.001.

Table 1: Sub-types of HM according to age ranges.

Types of HM	Total n (%)	0-14 y n (%)	15-39 y n (%)	40-64 y n (%)	>64 y n (%)	p-value
ALL	5,684 (23.9)	3,226 (63.1)	1,727 (29.7)	616 (8.1)	115 (2.2)	<0.001
CLL	225 (0.95)	0	8 (0.14)	92 (1.2)	125 (2.4)	
AML	3,072 (12.9)	689 (13.5)	1,032 (17.8)	889 (11.6)	462 (8.8)	
CML	896 (3.8)	39 (0.8)	417 (7.2)	354 (4.6)	86 (1.6)	
NHL	10,502 (44.1)	540 (10.6)	1,833 (31.5)	4,497 (58.5)	3,632 (69.5)	
HL	1,316 (5.5)	422 (8.3)	515 (8.9)	246 (3.2)	133 (2.5)	
MM	1,351 (5.7)	0	72 (1.2)	765 (10.0)	514 (9.8)	
Other leukemias	673 (2.8)	146 (2.9)	196 (3.4)	173 (2.3)	158 (3.0)	
Other HM	76 (0.3)	51 (1.0)	12 (0.2)	10 (0.1)	3 (0.1)	
Total	23,795 (100)	5,113 (100)	5,812 (100)	7,642 (100)	5,228 (100)	

Summary/Conclusion: HM account for 12% of cancers. Most of patients are male. The most affected group was 40-64 years. The most frequent HM is NHL. Unlike developed countries the second most frequent HM was ALL, being this latter the most frequent HM in the 0-14 years group and the most frequent leukemia in AYA group. AML was the second most frequent HM in 0-14 years group and the most frequent leukemia in ≥ 40 years group. Also, unlike developed countries CLL was rare. MM ranked fifth in incidence. There was a statistically significant difference between the subtype and the age range.

PB1363 OUTCOME OF ADOLESCENTS AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH PEDIATRIC PROTOCOL

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Background: Several retrospective studies have confirmed that adolescents and young adults (AyA) with acute lymphoblastic leukemia (ALL) treated with pediatric protocols have better outcomes than similarly aged patients treated with adult protocols.
Aims: We reported feasibility and results of a pediatric-based protocol (EORTC 58951) in adolescents and young adults.
Methods: From January 2000 to December 2019, 87 patients aged 16 to 30 years with newly diagnosed ALL were treated, in the department of hematology of Hedi Chaker Hospital, according to the pediatric protocol EORTC 58951. Further leukemia characteristics (Sex, White Blood cell count, Blasts phenotype, Cytogenetic results), we studied the protocol results: response to prophase), risk group stratification (average: AR1 and AR2, very high: VHR), remission rate, death rate, relapse rate and survivals (overall OS and event free EFS).
Results: Eighty-seven AyA ALL were treated with the pediatric protocol. The patients were 56 males (64%) and 31 females. WBC counts more than 100 Giga/l was noted for 25 patients (19%). Immunophenotyping was performed in all patients: 44 B-ALL (51%), 43 T-ALL (49%).
Twenty five patients (29%) were corticoresistant. Seventy eight patients (89%) achieved CR. Five patients failed to respond after 2 courses of chemotherapy and died and 4 patients died during induction chemotherapy as a result of infectious complications. Eleven patients (13%) were treated according AR1 arm, 48 patients (55%) according AR2 arm and 28 (32%) according VHR arm. Twenty eight patients (51.7%) with VHR arm protocol were eligible for allogeneic stem-cell transplantation but, only 10 were allograft: 4 were alive in complete remission and 6 died (by GVH for 2 patients and relapse for 4 patients). Relapse was observed in 22 patients (29%), among them 12 during the first year of treatment. The mean follow up was 128 months. The 10 years OS and EFS were respectively 50% and 49%.
Summary/Conclusion: The results of this pediatric-based study show that response to therapy and prognostic in adolescent and young adults were better than those treated with adult protocols and tolerability of chemotherapy is acceptable. However OS and EFS, were better than adult ALL treated by adult protocol (OS and EFS at 5 years = 35%: local study) but were not satisfactory. Our results were less than those described in the literature (OS ~ 80% and EFS ~ 70%). To further improve our results, it is necessary to expand donor sources such as matched unrelated.

PB1364 A SINGLE-ARM, OPEN-LABEL PHASE 2 PILOT STUDY OF VYXEOS (CPX-351) IN ADULTS WITH RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA.

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Background: Vyxeos is a liposomal formulation employing a 1:5 molar ratio of daunorubicin:cytarabine. Clinical trials in high risk acute myeloid leukemias demonstrated a significant benefit in CR rates and median OS, culminating in FDA approval August 2017. Emerging pediatric data suggest this benefit may extend to acute lymphoblastic leukemia (ALL).
Aims: The following pilot trial was performed to better understand the activity and toxicity profile in adults with relapsed and refractory ALL.
Methods: Adults with ALL or mixed phenotype leukemia were eligible if ≥5% lymphoblasts and/or extramedullary disease >1x1cm. Induction

consisted of Vyxeos 100 units/m^2 on days 1, 3 and 5. Those with clinical benefit could receive up to 3 cycles of consolidation delivered at 65 units/m^2 on days 1 & 3 after recovery of neutrophils (>500 cells/μL) and platelets (>50,000 cells/μL).

Results: Ten patients have been treated to date, with median age of 40y (22-74y), 8 male, and 3 caucasian. Six had B-ALL, including 1 B-myeloid. Three of 4 T-ALL had early t-cell precursor (ETP) phenotype. NGS was available in 9, and include TP53 mutation (n=4), and PH-like changes (n=2). Median prior lines was 3, with 6 showing primary refractory disease. Prior blinatumomab, inotuzumab, CAR-T cell therapy, and allogeneic transplant were noted in 5, 2, 1, and 2 patients.

Pancytopenia was uniform during induction, with febrile neutropenia noted in 8. One passed from pneumonia after moving to comfort measures in lieu of intubation 20 days after Vyxeos, and is non-evaluable for response. A second patient developed grade 3 sepsis. The remainder of infections were grade 1-2. One had grade 3 gastrointestinal bleed, and 3 had grade 1 spontaneous subdural bleeding. One case of veno-occlusive disease was observed in a patient with prior allogeneic transplant and inotuzumab. Median time to ANC recovery was 32 days among 9 evaluable. Two with refractory disease failed to recover platelets; among the remaining 7, median time to platelet recovery was 30 days. Adverse events were uncommon during consolidation, and include foot cellulitis and myopericarditis, each in 1.

Among 9 evaluable patients, 3 achieved CR/CRi, including 2 ETP T-ALL and one B-ALL. Two with TP53 mutation demonstrated >50% blast reduction with hematologic recovery, allowing for prolonged time to subsequent therapy. Three received 1-3 cycles consolidation. One was bridged to donor leukocyte infusion. Responses were noted in only 2 after progression following Vyxeos. Median PFS was 28 days, time to next therapy 76 days, and OS 189 days.

Summary/Conclusion: Vyxeos in high risk refractory adult ALL was overall well tolerated and active, with median OS of approximately 6mo. A second induction course or the addition of novel agents may further improve on remission rates and duration of response.

PB1365 L-ASPARAGINASE HYPERSENSITIVITY AND SURVIVAL RELATIONSHIP IN TURKISH PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMİA PATIENTS TREATED WITH MODIFIED ST. JUDE TOTAL XV TREATMENT PROTOCOL

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Background: Hypersensitivity is the most common side effect of L-Asparaginase (L-Asp), which is used in the treatment of acute lymphoblastic leukemia (ALL), most common malignancy of childhood with a survival rate of up to 90%. The irritating formulation is discontinued and replaced with other formulations, due to allergic reactions. Also, anti-asparaginase antibodies in patients who develop hypersensitivity may lead to decrease in drug efficacy, relapse and survival disadvantage.

Aims: In this study, we aimed to demonstrate the adverse effect of L-Asp hypersensitivity on the survival of children with newly diagnosed ALL by evaluating the survival of patients with and without L-Asp hypersensitivity comparatively.

Methods: 182 newly diagnosed ALL patients whose mean age at diagnosis was 6.7 ± 4.4 years (1-18 years) treated with Modified St. Jude Total XV Therapy between 1 January 2008 and 30 January 2016. The survival of patients who showed a clinical allergic reaction to L-Asparaginase (Group A) and those who did not (Group B) were comparatively evaluatedretrospectively. Besides, in order to evaluate the effectiveness of High Dose Methylprednisolone (HDMP) treatment, patients were randomized consecutively and HDMP (maximum 1000 mg / day) of 20 mg/kg/day (n = 65) and 10 mg/kg/day (n = 90) were administered for 7 days prior to Modified St. Jude Total XV protocol induction therapy. MP at 10 mg/kg/day and 5 mg/kg/day were continued with induction therapy for initial 7 days, respectively. Then, MP at 2 mg/kg/day in both groups during day 8-21 of induction was given and discontinued. In patients with hyperleukocytosis at diagnosis (n=28), MP was started at lower doses (1 mg/kg/day) and gradually increased for 7 days.

Results: Clinical hypersensitivity reactions to L-Asp were observed in 43 (23%) patients (Group A), 40 (93%) during the maintenance and 3 (7%) during the induction, and desensitization was applied to the patients with antihistamine and steroid. The remaining 138 (%76) patients (Group B) did not show any clinical allergic reactions to L-Asp. The age, gender, leukocyte count, immunophenotype and risk group distribution at diagnosis of Group A and Group B were found to be similar (p = 0.553, p = 0.318, p = 0.079, p = 1,000, p = 0.431, respectively). In addition, no statistically significant difference was found between the rates of patients who developed L-Asp allergy in the two groups in which 10 mg/kg/day and 20 mg/kg/day YDMP treatment was initiated (p = 0.127). The 5-year event-free (EFS) and overall survival (OAS) rates of Group A and Group B were similar (p = 0.116 and p = 0.250, respectively). Although premedication was applied for subsequent doses, 21 (49%) of the patients with recurrent allergic reactions continued their treatment with PEG-Asparaginase and 16 (37%) with Erwinia L-Asp.

Table 1. Comparison of Characteristics and Treatment Results of Group A and Group B

	Group A (n=43) n (%)	Group B (n=138) n (%)	*p* value
Age (year) (mean± SD) (min-max)	6,28 ± 4,1 (0,94-15,37)	6,80 ± 4,5 (0,96-18)	0,553
Age (year)			
• 1-9,9	34 (%79)	105 (%76)	0,686
• 10-18	9 (%21)	33 (%24)	
Gender			
• Female	15 (%35)	60 (%43)	0,318
• Male	28 (%65)	78 (%57)	
Leucocyte Count			
• ≥ 50x10^9/L	12 (%28)	22 (%16)	0,079
• < 50x10^9/L	31 (%72)	116 (%84)	
Immunophenotype			
• Precursor B cell ALL	40 (%93)	126 (%91)	1,000
• T cell ALL	3 (%7)	12 (%9)	
Risk Groups			
• Low	18 (%42)	70 (%52)	0,431
• Standart	19 (%44)	53 (%39)	
• High	6 (%14)	25 (%9)	
Event-free Survival (5-year)	%90,7 (%86,3-95,1)	%84,6 (%81,5-87,7)	0,259
Overall Survival (5-year)	%94,7 (%91,0-98,4)	%88,1 (%85,3-90,9)	0,116

Summary/Conclusion: The incidence of allergic reaction, which is the most common side effect of L-Asp, has been reported in the literature in a wide range of 0-76% and mostly in the post-induction period. The rate of clinical allergic reaction to L-Asp found in our study was much lower compared to the St. Jude Total XV protocol (23% vs 40%). The observation of allergy in very few patients during induction can be explained by the suppression of hypersensitivity reaction due to the use of HDMP before and during the induction period. Additionally, no significant difference in the survival rates of patients who developed antibodies or allergies compared to patients who did not was revealed in accordance with our study.

PB1366 FERRITIN AS A MARKER FOR PROGNOSIS OF THYROID PATHOLOGY AND FEATURES OF THE AMINO ACIDS PROFILE IN THE LONG-TERM CARE OF CHILDREN WHO HAVE SUFFERED FOR ALL AFTER CHORNOBYL ACCIDENT

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Background: There are few data on metabolic changes in the body of children who have suffered from ALL and have a long-term EFS. The relationship between thyroid status, protein and iron metabolism has not been described under such conditions so far. The contact of described patients group with radiation factor has not been taken into account also.

Aims: To determine the influnce of ferritin on thyroid function and connection with amino acids (AC) profile in the urine of patients affected by the Chornobyl accident and who suffered from ALL in childhood.

Methods: There are 84 children living in radiation-contaminated areas and suffered from ALL in childhood (pro B - 8, common ALL - 66, pre-B - 6, T-ALL - 4) were examined. EFS of the patients ranged from 10 to 15 years. Ionising radiation dose for bone marrow of children were 5.31 ± 1.14 mSv. All children were examined after completing the full course of chemotherapy for ALL. The percentage and morphological characteristics of bone marrow erythroid cells, erythrocytes morphometric parameters, serum iron, serum ferritin (SF) and transferrin

levels, transferrin saturation coefficient, the percentage of bone marrow sideroblasts, urine AC levels: Lyz, Arg, O-Pro (oxyproline), Asp, Tre, Ser, Glu, Pro, Gly, Ala, Cys,Val, Met, Leu, Tyr, Phe; serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were stydied. We used generally accepted statistical methods (t-Student, Spearman's correlation coefficient, U-Test).
Results: In 53 children (63.1%) - SF was 285.4 ± 11.3 ng / ml, in 16 (19%) - 497.6 ± 13.6 ng / ml, in 15 (17.9%) - 783.7 ± 14.2 ng / ml. After 3-5 years of treatment end in 14 children (16.6%) thyroid pathology was detected: in 6 - hypothyroidism (SF 423.5 ± 12.1 ng / ml), in 7 - thyroiditis (SF 851.2 ± 15.5 ng / ml), one child had papillary thyroid cancer (SF - 489.6 ng / ml). A positive correlation between TSH and O-Pro (rs = 0.42) and negative correlation with FT4 (rs = -0.52) was found. In addition, SF was inversely correlated with TSH (rs = -0.46). In patients with serum iron levels higher than 27 µmol / l, the correlation was established between its amount and O-Pro (rs = -0.88) and the precursor O-Pro - Proline (rs = 0.86), which are markers of the collagen condition. The obtained results emphasize metabolic changes in ALL patients with excess iron in the body, which adversely affect the thyroid function in the remote period after chemotherapy.
Summary/Conclusion: Ferrokinetic processes affect the mechanisms of leukemogenesis and metabolic changes in children, which is associated with the development of multiorgan pathology and requires correction at the proper time.

PB1367 ACUTE LEUKEMIA AT ALEXANDRIA UNIVERSITY CHILDREN'S HOSPITAL: A SIX YEARS' EXPERIENCE

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Background: Acute leukemia (AL) is the most common form of pediatric cancer. Nowadays, it is curable in the majority of pediatric patients, with 95% achieving long-term remission. The two most common subtypes of AL in children are Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML).
Aims: to report the epidemiology and treatment outcome of children with AL in our center.
Methods: This was a retrospective study. The available data were retrieved from medical files of children newly diagnosed with AL during the period from 1st January 2013 to 31st December 2018 at Alexandria University Children's Hospital, a large tertiary care center in northern Egypt. The demographic, initial clinical, and laboratory data were collected, as well as the treatment protocol and outcome of included patients.
Results: A total of 413 patients was identified during the study period, of which 98 have been transferred to a central children's cancer hospital in Cairo, and 315 were treated and further analyzed. The patients' age ranged from 2.0 to 288 months, the majority of patients were from 1-10 years of age, 19 (6%) patients were more than ten years of age, and 13 (4.1%) patients were less than one year of age. One hundred sixty eight (53.3%) patients were males, while the females represented 147 (51.1%) patients. Two hundred fifty seven (81.6%) patients had ALL and 58 (18.4%) patients had AML. At presentation, the median total leucocytic count was 12.0 x10^3/µL, ranging from 0.2 - 989 x10^3/µL; 37 (11.7%) patients had hyperleukocytosis. From 2013 to 2016, ALL patients were treated according to the modified CCG-1991 standard risk protocol and CCG-1961 high-risk protocol, then Total study XV protocol was used starting in 2017. AML patients were treated according to the MRC 12 protocol. Regarding patients' outcome, 128 (49.8%) of ALL patients were in remission after treatment, 56 (21.8%) were on treatment, 57 (22.2%) have died, 9 (3.5%) died after relapse, 6 (2.3%) relapsed on treatment and 1 (0.4%) patient had a therapy-induced AML. Among the AML patients, 21 (36.2%) patients were in remission after end treatment, 3 (5.2%) still on treatment, 27 (46.6%) died, 6 (10.3%) died after relapse, and one (1.7%) patient has been lost to follow up, which significantly worse outcome than ALL patients, (p<0.001*). Only 6.7% of patients relapsed over the study period; hematological relapse was the most common form (71%). Using the Kaplan-Meier survival curve, the 3-years overall survival for all treated patients was 70.4%. Early deaths were more marked among infant leukemia and AML patients, and the most common cause of death among all categories was infectious complications. The 3-years overall survival for ALL patients was 76.4% versus 43.2% in AML patients (p<0.001*). Among ALL patients, B-ALL had a higher 3-year event-free survival (75.3%) compared to T-ALL (58.8%), p = 0.035.
Summary/Conclusion: This study showed the distribution of patients treated in our center, showing high mortality, especially early in the treatment of high-risk categories, identifying the areas where improvement of patient care can lead to improvement of survival rates. The relapse rate was not high but might be underestimated by the follow-up period's relatively short duration.

PB1368 CYTOGENETIC HETEROGENEITY IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND TRANSLOCATION T(12;21)(P13;Q22), TEL/AML1 (ETV6-RUNX1)

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Background: Translocation t(12;21)(p13;q22) and presence of the chimeric gene *ETV6-RUNX1* occurs more frequently (25-30%) in children with acute lymphoblastic leukemia (ALL), however only in 1-4% of adults. This translocation t(12;21)(p13;q22) cannot be detected through conventional cytogenetics, thus can only be diagnosed through FISH and RT-PCR methods and confers a favorable prognosis. However, 20% of the patients may relapse after years.
Aims: To study the frequency, type and long-term clinical impact of additional cytogenetic aberrations detected along with t(12;21)(p13;q22) in ALL patients.
Methods: We studied 41 B-ALL patients, 21 males and 20 females. Median age at diagnosis was 4 (range 2-24) years old. Flow cytometry revealed common ALL in 25 and pre-B ALL in 16 patients. Median WBC count at diagnosis was 6,7 K/µl (0,84-120). *ETV6-RUNX1* transcripts were detected in all patients. Further transcript study was performed in 31 patients. Type I (298 bp zone) and type II (259 bp) transcripts were found in 24 and 7 patients respectively. All patients underwent bone marrow cytogenetic analysis.
Results: Complete cytogenetic analysis was performed in 39/41 patient samples. Karyotype was normal in 12 and abnormal in 27 (69%) patients. Thirteen patients had diploidy, 7 had hyperdiploidy, 3 had hypodiploidy, 2 had hypotriploidy and 2 had hypotetraploidy. Structural chromosomal abnormalities were detected in 10/27 samples, numerical in 2/27 while both type of abnormalities in 15/27. Aberrations of chromosomes 12p or 21 or both (12p/21) were detected in ten, nine and one patient respectively. Deletion of 11q, and aberrations of 6q and 9p were detected in four, six and two patients respectively. Complex karyotype (three or more aberrations) was found in eighteen patients with median number of aberrations 5 (range 3-15). Ten patients had more than 4 aberrations. Clinical data was available for 40/41 patients. They all achieved hematologic remission. In a median follow up of 57.47 months (27-161), 10-year possibility of overall survival (OS) was 94% and 10-year disease free survival DFS was 92%. 10 year DFS was 86% for patients bearing abnormal karyotype and 100% for the normal karyotype group. Thirty-seven patients still remain in first remission, while two have relapsed. One of the relapsed patients died, while the other one is in second remission. One patient died in first remission. At the time of relapse the karyotype was abnormal in two relapsed patients. Clonal evolution with abnormalities as –Y, +21 and add(22)(q11) was detected in the one, whose diagnostic cytogenetic sample was available.
Summary/Conclusion: ALL with t(12;21)(p13;q22) is a disease with favorable prognosis and of wide heterogeneity. Additional aberrations involving chromosome 12, 21, 6, 9 and 11 as well as complex karyotype are frequently detected. Abnormal karyotype and clonal evolution is observed in relapse. Further study is needed in larger cohorts as well as with longer monitoring in order to investigate the biological and prognostic significance of additional chromosomal abnormalities.

PB1369 VALIDATION OF OPTICAL GENOME MAPPING FOR DIAGNOSIS OF ACUTE LEUKAEMIA IN PEDIATRIC PATIENTS

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Background: Cytogenetics has led to the discovery of multiple chromosomal anomalies associated with hemato-oncologic diseases in children and adolescents. From its beginning till now, and with the contribution of the molecular biology, there has been an improvement of the classic cytogenetic that allow cytogenetists to perform a more precise diagnosis. The introduction of next generation sequencing (NGS) has dramatically changed the way clinical molecular laboratories analyze their samples over the past 10 years, but for most clinical cytogenetic analyses a combination of karyotyping (KT), fluorescence in situ hybridization (FISH) and CNV-microarrays are still performed to detect genetic biomarkers of disease. Each of these tests has its own limitations such as maximum banding resolution (KT), knowledge of which loci to test and is limited in throughput (FISH) and lacking the ability to identify balanced chromosomal aberrations, to map gained material or nor are able to detect mosaicism lower than 5-20% (CNV-microarrays). These conventional cytogenetic techniques allow the detection of Structural variants (SV) significantly contributing to the discovery of disease causing genes are part of the routine diagnostic workflow in any tertiary hospital in the national health system. This is especially important in a center such as Hospital Infantil Universitario Niño Jesús, which cares for children and adolescents, populations in which rare genetic-based diseases are added to hemato-oncological pathology, for which genetic diagnosis is essential during the diagnostic phase. Recently, genome-imaging of extremely long linear molecules by optical genome mapping (OGM) to detect SVs and copy number variants (CNVs) has emerged as an efficient technology to replace the conventional cytogenetic diagnostic techniques improving the limitations mentioned above.
Aims: Our main objective was performed a clinical validation study of Acute lymphoblastic and myeloid leukaemia samples by (OGM) using Bionano Saphyr platform previously analysed using karyotyping, FISH and/or CNV-microarrays. Moreover, we proposed to identify new cytogenetic alterations related to paediatric diseases not previously detected by current methodologies.
Methods: Bone marrow aspirates and frozen cell samples at diagnosis of patients with leukaemia were processed for OGM with the Bionano Genomics Saphyr System. In brief, the ultra-high molecular weight (UHMW) gDNA from children and adolescent samples was extracted, labelled and loaded onto Bionano chip to perform a run in Saphyr platform. Then, the data collection was analysed and the results were validated and statistically analysed. Finally, novel findings by OGM were examined.
Results: We obtained not only a full concordance with previously diagnostic results obtained by conventional cytogenetic techniques but also we described novel structural variants missed by the other methods which could play an important role for the outcome of the leukaemia disease.
Summary/Conclusion: The analysis of SV and CNV by OGM emerge as a powerful tool in cytogenetic laboratories improving the pediatric routine diagnosis of Acute Leukemia both in children and adolescents.

PB1370 MANAGEMENT AND MORTALITY OF ACUTE LEUKEMIA DURING COVID-19 PANDEMIC: 8-MONTH FOLLOW-UP AT A SINGLE INSTITUTION IN PERU.

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Background: The COVID-19 pandemic is a global public health crisis. Most patients were affected on their active treatment, patients with acute leukemia are particularly vulnerable to any change in their curative therapy. It has been almost a year since the first reported case of COVID-19 in Peru. Our country had the highest mortality rates per one million population during the first wave. Since January 2021 we are on the second wave with the total excess deaths higher than the first wave.
Aims: The aim of this study was to report the management and mortality of acute leukemias during the COVID-19 pandemic and its impact in relapse or survival of leukemia patients.
Methods: We included prospectively patients aged 14 years or older with the diagnosis of acute leukemia on active treatment and treated at the National Cancer Institute (NCI) in Peru since March 8th, 2020 to June 20th, 2020. The first result was reported as part of a multicenter study in the ASH 2020 annual meeting, now we are reporting a follow-up after 8 months of the last recorded case. We compared the leukemia status between the first cohort and the last cohort using chi-square test.
Results: 126 patients were evaluated during the first 100 days of started the COVID-19 pandemic in Peru (cut point June 20th 2020), the median age was 32 (range 15-70). 52% were male. 65% of patients had high-risk factors. 53% of patients were Ph negative Acute lymphoblastic leukemia (Ph- ALL), both Ph + ALL and Acute myeloid leukemia (AML) were 18.2% each one of them. Acute promyelocytic leukemia (APL) were 10.3% (n=13). 83.3% were on complete response. 45% of patients were on consolidation, 33% on maintenance, 12.6% on reinduction and 8.7% on induction. Modification of treatment due to COVID-19 was made in 34.9%. The reasons for modification were mainly due to logistic issues (54.5%) followed by medical decision (45.5%). 3.9% of patients had COVID-19 infection, 80% of them were mild-moderate cases. Only 1 patient (25%) died from COVID-19 disease.
On June 2020, 61% of patients were alive in CR and 20.6% were alive with leukemia, (total 103 patients alive). 23 patients (18.2%) died during the study period, 14.3% had leukemia-related death, 3.2% treatment-related death (on CR), and 0.8% COVID-related death.
Up to February 28th, 2021 of the 103 patients alive in the first cohort 63 (61.1%) patients are alive in CR (previous 77 patients) being that 18% of patients relapsed. Of the 26 patients alive with leukemia (1 received intensive treatment and achieved CR). During this second cohort 9 (8.8%) patients died, 8 from leukemia-related death (7.8%) and 1 (0.9%) patient from treatment-related death. It is important to note of the 8 patients with leukemia-related death 6 (75%) were on CR. In the second cohort no COVID-19 infection was reported. From the initial 126 patients only 94 (74.5%) patients are alive. For the total cohort leukemia related death accounts for 20.6% (n=26), treatment-related death in 3.9 (n=5) and COVID-19 in one case. The difference between the leukemia status in both cohorts were compared with a statistically significant difference p<0.001.
Summary/Conclusion: The modification on the treatment due to COVID-19 was mainly because logistic issues followed by medical decision. The mortality of patients with acute leukemia has increased in a short period of time, being that a quarter of them have died mainly due to leukemia-related death, followed by treatment-related death. Both COVID-19 infection and COVID-19 death were rare in our cohort. The difference in deaths and relapsed between both cohorts was statistically significant.

PB1371 THE IMPACT OF RISK STRATIFICATION BY EARLY BONE-MARROW RESPONSE IN CHILDHOOD T- ACUTE LYMPHOBLASTIC LEUKAEMIA (A SINGLE INSTITUTION EXPERIENCE IN AZIZA OTHMANA HOSPITAL, TUNIS, TUNISIA).

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Background: T-cell acute lymphoblastic leukemia (T-ALL) represents approximately 15% of all newly diagnosed ALL cases in pediatric patients. Although historically, outcomes for T-ALL were inferior to those of B lymphoblastic leukemia (B-ALL), the prognosis of T-ALL has been steadily improving in recent years due to increased chemotherapy protocols in particular with the use of high doses of Methotrexate and Asparaginase.
Aims: This study aimed to assess the therapeutic outcomes of children and adolescents with T-ALL treated according to the EORTC 58951 protocol, patients were stratified by age, WBC at diagnosis, immunophenotype, karyotype and steroids response in peripheral smears after 7 days of corticosteroid and one IT dose of MTX. The stratification strategy was extended by additional use of early response to therapy: blast cell count in the bone marrow (BM) was examined on D19 during remission induction, and determination of MRD measured by FCM in the BM at the end of induction (D35). All patients were assigned to a DXM based induction. Patients whose blast cells were ≥ 25% in BM (M3 marrow) at D 19, or whose MRD was positive at the end of induction, had their treatment one step upgraded.
Methods: Between January 2006 and December 2017, 377 children and adolescents with previously untreated ALL were treated according to the EORTC 58951 protocol, 93 (24.6%) have T-ALL. Median age was 13 years (18months to 25 years), the ratio of male to female was 4.1: 1, 7.5% and 2.7% have initial system nervous system and testicular involvement, Median WBC was 61.5 G/l (1.5 – 960 G/l) and 40.9% with a WBC ≥ 100 Giga/l.
Results: All patients received phase IA RM2- VHR according to the EORTC58951 protocol, with a 4-drug induction containing

dexamethasone and an early introduction of Methotrexate high dose on day 8 and Cyclophosphamide on day 9. 42.4% were steroid poor responders at day 8 in in the peripheral blood (pB). On day 19, 18.4% had M3 marrow. The CR was 88,2%, induction failure and induction death rates were 6.5% and 5.3% respectively. MRD results detected by a simplified flow cytometric assay, sensitivity of 0,01%, between 0,01% and 0,1%, between 0,1% and >1% was achieved respectively in 40.3%, 34.7%, 20.8% and 4.2%.
41.4% were assigned to the average 2 risk (AR2) group, 37.9% to the very high risk (VHR) group and 20.7% had received sibling stem cell transplantation in 1st CR.
The 5-year OS, EFS and RFS were 72.9%, 66.4% and 77.7% respectively. In Univariate analyses, WBC< 100 G/l, no M3 bone marrow on day 19 and complete remission at the end of induction have a significantly better OS. The prognostic value of morphological assessment of bone marrow blasts on day 19 during remission induction and the achieving of complete remission at the end of induction were the most prognostic factors for EFS and RFS.The 5-year OS was 90% for patients assigned to AR2 group, 66.4% for VHR and 76.9% for sibling stem cell transplant in CR1 (p: 0.04).
Summary/Conclusion: Early treatment response as assessed by morphological examination has important prognostic significance, and can be performed in a resource poor patient population.

PB1372 L-ASPARAGINASE ASSOCIATED ACUTE PANCREATITIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: L-asparaginase (L-ASP) is one of the most important chemotherapy drugs in the treatment of acute lymphoblastic leukemia (ALL). This drug, which has a crucial role in the treatment of ALL induction, has many toxicities like hypersensitivity reactions, pancreatitis, hemostatic disorders, liver function test disorders, and hyperlipidemia. L-ASP-associated pancreatitis is a serious condition with a frequency of 2-10%, with significant morbidity and sometimes death.
Aims: In this study, we aimed to describe the clinical findings and complications of L-ASP-associated acute pancreatitis in children with ALL and also to examine the attitude of the centers in terms of re-administration of L- ASP after development of pancreatitis.
Methods: Patient data form sent to pediatric hematology/oncology clinics with the announcement of Turkish Pediatric Hematology Society for retrospective evaluation of ALL cases with L-ASP associated acute pancreatitis. All patients were treated with ALLIC or BFM based ALL protocols.
Results: Thirty-one ALL patients from 10 centers, who were diagnosed with L-ASP-associated acute pancreatitis between September 2008 and January 2020 were included in the study. The median follow-up time was 59 months (8-139 months). There was a total of 34 acute pancreatitis episodes due to recurrences in two patients. The median age was 70 months (21-213 months) and male to female ratio was 0.9. Twenty-four patients (77%) were newly diagnosed ALL patients and 7 patients (22%) were relapse patients. Of the 24 newly diagnosed ALL patients; 7 patients (29%) were in the standard risk group, 8 patients (33%) were in the medium-risk group, and the remaining 9 patients (38%) were in the high-risk group. Acute pancreatitis occurred during treatment phase of induction in 9 (26%) patients, consolidation in 6 (18%), re-induction in 9 (26%), maintenance in 3 (9%) and relapse in 7 (21%) patients. E. Coli L-asparaginase was the most frequently used (74%) preparation. The most common complaint was abdominal pain (96%); followed by anorexia (68%), nausea/vomiting (56%) and high fever (39%). The median time between the last dose of L-ASP and the diagnosis of acute pancreatitis was 6 days (1-18 days). The median duration of treatment interruption was 16 days (0-240 days). Complications of pancreatitis was death in 3 patients (9.6%), insulin dependent diabetes in 6 patients (19.3%), and pancreatic pseudocyst in 6 patients (19.3%). L-ASP was completely removed from the protocol in 23 patients (74%) after the incidence of acute pancreatitis while it was re-administered in 6 patients (19%). Pancreatitits recurred in 2 (33%) of those 6 patients but none of the repeated episodes resulted in death.
Summary/Conclusion: This retrospective study demonstrated a relatively high complication rate due to L-ASP associated acute pancreatitis. Most centers showed a tendency to permanently discontinue L-ASP treatment after the incidence of pancreatitis. Re-exposure to L-ASP resulted with recurrence in some of the patients. Although there are serious complications resulting in death after L-ASP-associated pancreatitis, it has already been known that event-free survival is negatively affected in patients who can not receive scheduled L-ASP doses. For this reason, large-scaled comprehensive studies are needed to determine the criteria for re-administration of the drug and also to make changes in the general protocol approach when necessary.

PB1373 ACUTE LYMPHOBLASTIC LEUKEMIA IN ADOLESCENTS AND YOUNG ADULTS HEMATOLGY DEPARTMENT EXPERIENCE OF AZIZA OTHMANA HOSPITAL

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Background: Acute lymphoblastic leukaemia (ALL) in the adolescent and young adults(AYA) population constitute a different group from acute leukaemia in children: by their incidence, which is lower, their particular epidemiological and biological profiles and finally by their prognosis which is worse.However, since the use of pediatric protocols, various studies have shown improvement in their survival.
Aims: This epidemiological study involved 79 adolescent and young adults aged between 15 and 26 years with acute lymphoblastic leukemia (ALL) and treated according to the pediatric protocol EORTC 58951. We will only report the therapeutic results of Philadelphia-negative ALL.
Methods: This is a retrospective study between January 2006 and December 2017 (12 years) at the department of Hematology at Aziza Othmana Hospital.
Results: Median age was 17 years (15-26 years). Sex ratio was 2.95 (59M / 20F).Forty patients (50%) had a tumor syndrome. Central nervous system involvement was noted in 5 patients (6%)
The mean rate of WBC was 60 G (0.8-407 G). WBC rate > 50 G was noted in 33% of patients and> 100G in 21.5%. ALL T was found in 48% of patient vs. 40% of ALL B. Karyotype was normal in 41%. 33 patients had cytogenetic abnormalities (40.5%) among them 6 (9%) had a translocation t (9, 22). Only patients who are Philadelphia negative will be analyzed.
All patients received RM2-VHR induction. Corticosensitivity was studied by a myelogram on D7 in 63 patients (M1: 6 patients, M2: 8 patients, M3: 33 patients and failure: 16 patients) and by a blood smear on D8 in all patients (17.8% of corticosteroid resistance).
Chemo sensitivity was studied by a myelogram on D19 in 71 patients: 15.5% were chemo-resistant. Three patients (4.1%) died in induction.
The remission rate was 93.1%. Minimal Residual Disease (MRD) was carried out in 65 patients: MRD 10^{-3} in 4 (6%).Thirty-four patients (47.8%) were treated according to the RM2 arm and 37 (52.2%) according to the VHR arm, among which 25 (67.5%) had an indication to transplantation. Allogeneic hematopoietic stem cell transplantation (alloHSCT)was only performed in 8 patients. - One patient died during treatment (1.4%). Fifteen patients relapsed (22%).
At 36 months: Overall Survival (OS), event-free survival (EFS) and relapse free survival (RFS)are respectively 78.4%, 81.2% and 74.1%.
At 5 years: OS, EFS and RFS are respectively 75.1%, 76.1% and 69.3%
Summary/Conclusion:: in our study, we confirm the specific aspects of ALL AYA: presence of tumor syndrome as well as the initial involvement of the central nervous system, high wbc's rate, the predominance of ALL - T, the higher frequency of Phi positive ALL and CorticO-chemoresistance. With leukemia regimens based on pediatric protocols, the survival of AYA group has clearly improved compared to patients treated with adult protocols with acceptable toxicity.

PB1374 L'ASPARAGINASE ALLERGIC REACTIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: L-asparaginase (LASPA) is an important anti-tumoral drug in the treatment of acute lymphoblastic leukemia in children, however, its toxicity, mainly due to severe allergic reactions, limits its use and even leads to its permanent discontinuation.
Aims: Describe the allergic reactions associated with the use of LASPA and their impact on overall survival (OS) and relapse-free survival (RFS).
Methods: Retrospective study conducted over 10 years (from January 2006 to December 2015) involving 316 patients treated in the clinical hematology department of Aziza Othmana Hospital according to the EORTC 58951 protocol and who received E.coli asparaginase.Allergic reactions were graded according to the Common Terminology Criteria for Adverse Events (CTAE) score
Results: All patients received intravenous LASPA.
Out of 316 patients,74 had an allergic reaction to L-asparaginase.
The median age was 6 years (18 months - 26 years) with a sex ratio of 2.36 (52 males and 22 females).
According to the CTAE score, they were grade 1 or 2 in 66% of cases, grade 3 in 24% of cases and grade 4 in 10% of cases. No deaths were noted. The occurrence of allergic reactions were noted essentially, (in 84% of cases), in post induction at the time of reintroduction of LASPA, and after having received an average of 5 doses(1-7).
The severity of the reaction was independent of age (p=0.45) and the total dose of LASPA.
Forty three patients were switched to Erwiniase. An allergic reaction was noted in 25.6% of these patients.
Of the 31 patients (42%) who were not switched to Erwiniase, 17 patients (55%) were permanently discontinued, and 14 patients (45%) were premedicated for E.coli asparaginase and have continued
their treatment with LASPA.
The 5-years OS was significantly different between patients in whom LASPA was permanently discontinued due to a severe allergic reaction and patients who continued LASPA therapy (94% versus 64% with p=0.005).
Similarly, The 5 –years RFS was 85% versus 65% with p=0.034.
Patients who received a total dose of LASPA ≥100 000 IU/m2 had better OS and RFS than those who received a lower dose with p=0.004 and p=0.01, respectively.
However, the switch to Erwiniase had no impact on OS and RFS with p=0.07 and p=0.11, respectively.
Summary/Conclusion: Discontinuation of LASPA treatment due to allergic reactions is quite frequent with important prognostic implication, which encourages to better study these allergic reactions to better manage them and to discuss new therapeutic alternatives more effective and less allergenic than LASPA to optimize the survival rates of LAL.

PB1375 ACUTE LYMPHOBLASTIC LEUKEMIA: A DECADE OF MONOCENTRIC EXPERIENCE IN MOROCCO

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Background: Several factors influence the prognosis of adult patients with novo acute lymphoblastic leukemia (ALL) including the evaluation of the therapeutic response after induction MRD1(by Flow Cytometry or molecular methods). Unfortunately, access to molecular tests in our country is limited and measurement until a few years ago was based only on measurement of cytogenetic remission.
Aims: The purpose of our study was initially describe the characteristics of adult patients treated for de Novo ALL. The secondary aim was to assess the efficacy and tolerance of the treatments received in terms of OS and PFS as well as to define the prognostic factors influencing these parameters.
Methods: We retrospectively collected data from the medical records of all young patients(age>18 years) diagnosed as having de Novo ALL between January 2010 and September 2020 at the clinical hematology service of the military hospital of Instruction Mohammed V in Rabat. All the patients were treated according to several therapeutic protocols: GRAALL-2005 and GRAALL 2014 for young patients(<60 years old) and according to the GRAALL-SA or EWALL-PH-02 protocols for the elderly(>60 years old).The FRALLE 93 and FRALLE 2000 protocols have been used in patients aged between 18 and 20 years.Allo-HCT has been indicated in eligible patients classified as high risk with an HLA-matched donor
Results: Forty-five patients were enrolled in our study.Mean age at diagnosis was 34.37± 16.42 years with a sex ratio of 1.8.13.3% of patients had lymphadenopathy,15.6% hepato-splenomegaly and 33.3% of patients had a bone pain at diagnosis.More than half(66.7%) of all patients had an ALL with B-Phenotype(ALL-B II in 66.7%) and 33.3% LAL-T.33.3% of patients had leukocytosis(WBC>100,000/mm3 in ALL-T and >30,000/mm3 in ALL-B)and 6.7% had initial central nervous system involvement.Fourteen(31.1%) patients had an unfavorable karyotype of which nine were carriers a Philadelphia chromosome.The M-BCR-Abl and m-BCR-Abl transcripts were found in 7(15.5%) and 3(8.9%)patients respectively. Almost half(47.7%) of all patients were treated according to GRAALL-2005 protocol,13.3% based on GRAAL-2014 protocol.Only 8,9% were treated according to the GRAALL-SA and EWALLPH-02 protocols.Imatinib was the most widely used TKI(17.8%).Complete hematologic remission(CR1)after induction was obtained in 84.4% of cases.Thirteen(28.28%)patients underwent an Allo-HCT among then, two were ALL Ph positive.The donors were geno-identical in 22.2% of cases and haplo-identical,-Matched unrelated Donod (MUD)or from umbilical Cord Blood(UCB) in 2.2% of cases.Haematological, infectious, thromboembolic/hemorrhagic toxicities were reported in 91.1%, 8.9% and 8.9%, respectively. Only one patient(2.2%)developed a L-Asparaginase-related toxicity and four(8.9%)patients had grade 1-3 peripheral neuropathy due to vincritine.In our series, multivariate analysis showed CR1 as being the only independent factor influencing both PFS[95% CI, 0,02-0.31](p = 0.00) and OS[95% CI, 0.06-0.58](p = 0.00).After a median follow-up of 27 months, the medians of PFS and OS were 19, 6 months and 37.3 months, respectively, with 24(53.3%) relapses and 18(40%) deaths.
Summary/Conclusion: The epidemiological and clinical profile of our patients is consistent with the findings of the studies. Our survival results are still lower than those reported in clinical trials. This may due to the limited access to Allo-HCT and the measurement of RC1 by molecular technics.It is a more precise reflection of therapeutic efficacy and allows the implementation of an optimized treatment, better adapted to the risks.

PB1376 SEVERE HAEMOPHILIA A DIAGNOSED IN A CHILD WITH ALL: FIRST REPORT IN GREECE

M. Ioannidou [1,*], M. Palabougiouki [1], E. Thomaidou [1], A. Bangeas [1], A. Tragiannidis [1], T. Papageorgiou [1], M. Economou [2], A. Teli [2], V. Tsavdaridou [3], A. Galli-Tsinopoulou [1], E. Hatzipantelis [1]

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Background: The coincidence of acute lymphoblastic leukaemia (ALL) and hemophilia is extremely rare in pediatric age group.
Aims: We report the 1st case in Greece with severe haemophilia A diagnosed in a child with ALL.
Methods: A 2,5 year old boy admitted to our Unit due to generalized weakness and episodes of severe nose bleeding for the last month. Family history revealed that boy's uncle (mother's brother) suffered from haemophilia A. From physical examination, paleness, petechiaes and ecchymoses were noticed, as well as, organomegaly. Peripheral blood count showed hemoglobin level of 5.6 g%, white cell count of 212 × 109/L (blasts 95%), and platelet count of 16 × 109/L. Activated partial thromboplastin time (APTT) found very high, but prothrombin time (PT) not.
Results: Bone marrow aspiration-immunophenotype confirmed the diagnosis of B-II (common) ALL. RT-PCR for genetic alterations BCR abl, AF-4/MLL and TEL-AML1 found negative. CSF was also negative for blastic cells. Following the placement of central venous catheter prolonged bleeding was noticed. Prolonged APTT and family history led to the possibility of hemophilia which finally diagnosed from laboratory tests (FVIII levels <1%). The patient was placed on induction therapy for ALL, according to ALLIC 2009 protocol, and FVIII replacement. On day 33 of treatment, the patient achieved complete remission. He

finished successfully the first 6 months of treatment and he will hopefully continue on maintenance phase of the protocol.
Summary/Conclusion: The most common haemorrhagic disorder in children with leukaemia is disseminated intravascular coagulation (DIC). The diagnosis of haemophilia A is very rare and there is no clear therapeutic plan in such cases, but timely diagnosis should not be delayed and proper treatment should be based on clinical findings.

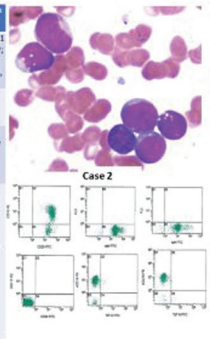
PB1377 B-ACUTE LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH ATYPICAL CLINICOPATHOLOGICAL/GENETIC FEATURES

D. S. Soliman [1,2,3,*], A. Amer [1], H. El Omri [4], S. Kohla [1], I. Bilal [5], A.-S. Ahmad [1], I. Ganwo [1], E. McBride [5], S. Elkorashi [4], F. Ibrahim [1]

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Background: B-acute lymphoblastic leukemia/lymphoblastic lymphoma is a hematologic neoplasm of precursor lymphoid B-cells. The lymphoblasts are almost always positive for the B-cell markers and TdT in most cases, whereas CD20 and CD34 expression is variable. B-ALL/LBL demarcated by expression of at least one surrogate immaturity marker and typically lack features indicating mature phenotype.
Aims: The objective of this review is to recap B-ALL/LBL with unusual clinicopathologic features diagnosed in our center.
Methods: We reviewed patients with B-ALL/LBL diagnosed in Hamad medical corporation according to WHO 2016 diagnostic criteria (2011-2019). We included B-ALL with one or more unusual features including: atypical clinical presentation, rare morphology, unusual cytogenetics, rare immunophenotype and phenotype overlapping with mature B-cell neoplasms. The relevant data correlated with the disease course, and patients' response. The relevant and most recent literature was reviewed.
Results: 15 patients with unusual challenging clinicopathologic features were detected. Rare cases showed lack of expression of immaturity markers in an otherwise typical ALL (three patients), including two patients of pediatric age group, one (# case 2) received ALL BFM 2009 protocol with good response and negative MRD. The second child (case #3), had some features overlapping with high grade B-cell lymphomas a very rare diagnosis in pediatric age group. The patients were treated according to Inter-B-NHL Ritux 2010 IGR 2009 and showed complete remission.
Few B-ALL cases showed asynchronous expression of immaturity marker (TdT) associated with markers indicating mature phenotype (mature B-ALL) (3 patients); including two patients with t(9;22)(q32;q11). Our cohort included three exceptional cases that showed loss/down regulation of pan B-markers CD19 and CD22. A single case showed rare coexistence of IGH and MYC rearrangements in de novo precursor B-ALL (double hit B-ALL). Two cases of B-ALL showed positivity for MPO by IHC in an otherwise typical B-ALL immunophenotype.
Unusual morphologic features detected in B-ALL, included increased fibrosis, BM necrosis, abnormal eosinophilia, lymphoblasts with granulation/ or pseudo Chediak-Higashi globule, Cup-like blasts or increased megakaryocytes (at presentation).

	Case No	Age/sex	Morphology	FCM features	Cytogenetics
B-ALL with negative immaturity markers	Case #1	M/26	PB: Pancytopenia, BM: 65% with stippled nuclear chromatin with vacuolation	CD45+(dim), CD19+, CD10 +(dim). CD34-, TdT-, surface IgM-, cytoplasmic IgM-, surface Kappa-, Lambda light -, CD20-	46,XY,t(8;15;17)(q13;q11.2;q23)[12] MYC-, BCL-2-, BCL-6-
	Case #2	M/9 Mon	PB: Pancytopenia BM: 40% blastoid morphology	CD45+ (negative to dim), CD19+, CD10+, CD20+, cCD79a+, HLA-DR+, cIgM+, sIgM+, TdT-, CD34 & CD117-	46,XY [30]
	Case #3	M/11	Pancytopenia, 4% blasts, stippled nuclear chromatin with vacuolation	68% B-cells with normal CD45+ (in the lymphocyte gate), CD19+, CD10+, CD20+, cBCL2+, sIgM+ with Lambda light chain restriction. CD34-, TdT-, and CD117-. MYC positive, BCL-2 pos	FISH:14q rearrangement, failed KT
B-ALL with down regulation of CD19 (Three cases)	Case #4	M/13 Mon	P.B: No circulating blasts BM: Microblasts	19% blasts (in the blast gate), CD45+(mod), CD10+, TdT+, sIgM+, CD19-, cytoplasmic CD22- and surface Kappa-, Lambda light chain-.	46,XY
	Case #5	F/41	P.B: Pancytopenia (severe anemia), no blasts. BM: Increased fibrosis (MF 2/3 score).	20% blasts, cCD79a+, CD10+, cCD22 (dim), cIgM, CD15+, CD13 (Par) and TdT. CD19 (partial on minority), PAX-5+.	Normal FISH KT:
	Case #6	M/23	Blasts morphology	91% blasts, CD34+, HLA-DR+, cCD79a+, dim CD19 (par), TdT+, CD10 (par) and cCD22 (par, dim).	46,XY



Summary/Conclusion: The complexity and variety of cases presented in this review emphasize the importance of multi-parametric approach and its value in the proper categorization of patients with B-ALL/LBL. Few cases of precursor B-ALL patients show clearly overlapping feature with mature B-cell neoplasms, however, currently no definitive WHO category that can adopt such B- neoplasms and no standard treatment protocols. In similar cases the expression of TdT was given the upper hand over other features. In pediatric age group, cases that lack expression of immaturity markers, were best classified as precursor B-ALL, being the commonest in this age group, and supported by dim CD45 expression, blastoid morphology and/or lack of surface immunoglobulin expression. Pan B-cell markers is rarely lost in denovo B-lymphoid neoplasms. Reporting B-ALL with such peculiar features would probably draw attention to B-ALL unusual/overlapping features and experiences regarding treatment and disease outcome.

PB1378 PH+ ACUTE LYMPHOBLASTIC LEUKEMIA PRESENTED AS CHOLESTATIC JAUNDICE IN A 3-YEAR- OLD BOY

E. Thomaidou [1,*], A. Bangeas [1], M. Ioannidou [1], M. Palabougiouki [1], A. Tragiannidis [1], T. Moudiou [1], T. Papageorgiou [1], V. Tsavdaridou [2], A. Athanasiadou [3], A. Papalexandri [3], A. Galli - Tsinopoulou [1], E. Hatzipantelis [1]

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Background: Acute lymphoblastic leukemia (ALL) is the most frequent malignancy in pediatric population and it can manifest with uncommon clinical features, including liver disorder.
Aims: We report an unusual case of Ph+ ALL presenting with cholestatic jaundice on initial diagnosis.
Methods: A 3-year-old boy of Asian descent, with a history of congenital hypothyroidism, presented with cholestatic jaundice and transaminasemia. Symptoms started with low grade fever for 3 days and an abdominal pain radiating to his back and he gradually developed clinical jaundice. On admission his peripheral blood count showed leukostasis, with a total white blood count of > 100 K/μl (total blast cells 80%), thrombocytopenia, with a platelet count of 19 K/μL, and anemia, with hemoglobin levels of 7,1 g/dL. Biochemical findings revealed direct hyperbilirubinemia, with total bilirubin levels of 17,3 U/L and conjugated bilirubin levels of 15,5 U/L, and remarkably elevated transaminase levels with alanine aminotransferase (ALT) 1607 U/L and aspartic aminotransferase (AST) 3246 U/L. Gamma glutamyl transferase (GGT) was 115 U/L and lactate dehydrogenase (LDH) was 1256 U/L.
Results: Serology for hepatotropic viruses was negative, as well as antinuclear antibodies and immunoglobulin levels. An abdominal ultrasound showed remarkable gallbladder wall thickening with a small amount of perihepatic free fluid. Bone marrow aspiration – immunophenotype confirmed Common ALL (B-II) diagnosis, while RT-PCR for BCR - ABL was positive. The boy started induction therapy (ALLIC 2009 chemotherapy protocol – prednisolone) with improvement of jaundice and liver function. On day 8 he started treatment with imatinib mesylate, as well as, continuation of standard chemotherapy plan. Bilirubin and transaminases levels gradually raised again. Meanwhile, after asparaginase administration he developed pancreatitis with elevated amylase and lipase levels, leading to a discontinuation of all the hepatotoxic agents and concerns regarding the course of treatment. Apart from the hematologic malignancy, viral causes, autoimmune hepatitis, Wilson's disease, and alpha-1-antitrypsin deficiency that were excluded, other causes of hepatocellular disfunction needed to be examined, such as cystic fibrosis, Dubin – Johnson, Rotor and metabolic syndromes. Up to date a liver biopsy is pending, as well as, the results of the genetic analysis with whole exome sequencing and metabolic screening.
Summary/Conclusion: Acute lymphoblastic leukemia is the most common malignancy in children and a plethora of symptoms can be manifested as a precursor of this type of blood malignancy. In most of the cases cure rate approaches 90%, but at the rare entity of Ph+ ALL prognosis is unfavorable. Challenging and unusual manifestations of ALL, such as direct hyperbilirubinemia and liver dysfunction requires great awareness at diagnosis and individualized treatment.

PB1379 BLINATUMOMAB FOR THE TREATMENT OF ADULT RELAPSED/REFRACTORY PHILADELPHIA CHROMOSOME-NEGATIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE-CENTER REAL-LIFE EXPERIENCE OVER TWO YEARS

A. Ghiaur [1,*], B. Ionescu [1], A. Tatic [1,2], M. Cirstea [1,2], A. Bardas [1,2], M. C. Stancioaica [1], R. Hirjan [1], A. M. Chirila [1], C. Constantin [1], C. Doran [1], D. Coriu [1,2]

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Background: Adults with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-cell ALL) have a dismal prognosis and a high mortality rate. The advent of new targeted therapies has led to higher rates of complete remission (CR), prolonged the overall survival (OS) and increased the likelihood of proceeding to allogeneic hematopoietic stem cell transplantation (HSCT).
Blinatumomab is a bispecific T cell-engaging antibody that binds CD3-positive T cells to CD19-positive lymphoblasts leading to the lysis of both malignant and normal B cells. The mechanisms of resistance remain unclear, but the occurence of extramedullary relapse, the loss of CD19 expression and a high disease burden are described as potential predictive factors for a poor response.
Aims: To describe patient characteristics, analyze outcomes, including the CR rate, OS and the proportion of patients who subsequently underwent allogeneic HSCT and review the tolerability of the drug.
Methods: This is a retrospective analysis of 10 patients with R/R B-cell ALL, with a median age of 29 (18-50) years, treated with blinatumomab between January 2019 and December 2020 at Fundeni Clinical Institute. Survival rates were calculated using the Kaplan-Meier method, adjusting for key patient demographic and clinical characteristics at baseline.
Results: Four patients (40%) had combined medullary and extramedullary localization – bone/lymph node/spleen. The median tumor burden before treatment was 45% blast cells (0.1 – 80%). The median number of previous salvage therapies was 1.7 (1-3).
The rate of CR was 40% (N=4) after the first cycle of blinatumomab. Among the responders, 50% (N=2) went on to receive allogeneic HSCT, and the remaining two patients relapsed before they could proceed to HSCT. All of the patients with high tumor burden received prephase therapy consisting of dexamethasone and, in selected cases, cyclophosphamide. The response rate was higher in patients with lower tumor burden compared with those with more than 50% blasts. The median OS was 5.2 months, and for those patients who achieved CR, the median RFS was 4.5 months, with a median follow-up of 9.8 months.
The treatment was generally well tolerated. All patients experienced adverse events, the most common being fever (90%, 9 patients). One of the patients developed disseminated intravascular coagulation as well as grade 3 cytokine release syndrome, leading to treatment discontinuation; one patient had grade 2 mandibular pain, which required opiod analgesia and one patient had a prolonged fever that lasted almost 3 weeks.
Summary/Conclusion: The rate of CR and the percentage of patients who underwent allogeneic HSCT following treatment with blinatumomab are similar to those reported previously. The RFS and OS rates are lower than the existing literature data. Along with previous studies, the current work highlights the existence of a subgroup of patients with poor response to blinatumomab monoterapy, which remains a major challenge in clinical practice.

Acute myeloid leukemia - Biology & Translational Research

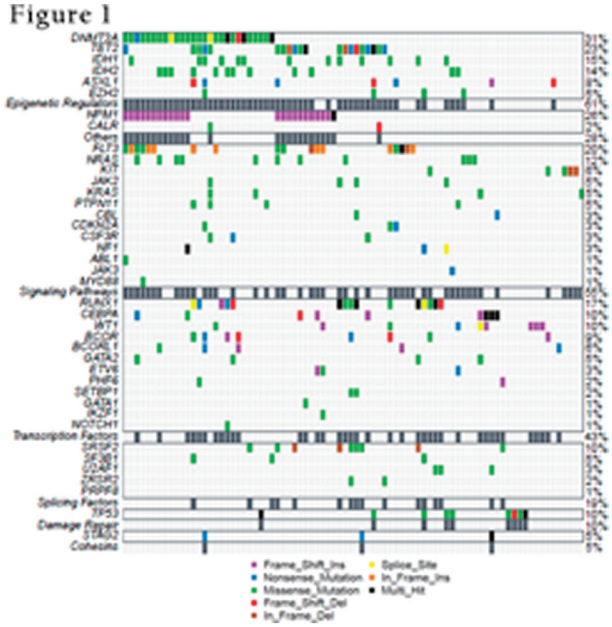
PB1380 ARGENTINE REAL WORLD DATA EXPERIENCE ON GENE MUTATION PROFILING PANELS IN ACUTE MYELOID LEUKEMIA

M. Lincango-Yupanki [1,*], M. Asinari [2], M. Zeballos [2], F. Jauk [3], M. Rahhal [4], L. Zanella [5,6], I. Giere [7], M. J. Mela Osorio [6,7], M. Zubieta [4], A. Giménez Conca [3,6], E. Agriello [5,6], A. Navickas [4,6], M. B. Castro [2], J. Arbelbide [3], A. L. Basquiera [2], C. Belli [1,6]

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Background: Sequencing data from patients with Acute Myeloid Leukemia (AML) constitute a significant guidance at prognostic and therapeutic stages to support clinical decision making. In Argentina, next generation sequencing (NGS) on hematological diseases is performed in few institutions and the experience is currently based on small cohorts of patients. We have organized a collaborative working group in an effort to interactively increase the knowledge in our media.
Aims: To evaluate NGS real-world data from AML patients in a multicenter Argentine study.
Methods: Sequencing and clinical data of 90 adult AML patients were gathered from five centers performing NGS located across Argentina. Data was analyzed by using R-bioconductor (v4.0.3) and SPSS software. Statistical analyzes included Fisher's exact /Chi2 and Kaplan Meir/Log-rank test. Median values are presented with interquartile ranges, unless otherwise specified. P values <0.05 were considered significant and, when appropriate, a false discovery rate (FDR) <0.05 was calculated.
Results: Sequencing data was obtained from eight different myeloid panels (customized or commercially available kits), targeting a median of 54 (range 30-81) complete or hot-spot gene regions. Our patients showed a median age of 58 (41-68) years and a sex ratio (M/F) of 1.36 (49/36). In this cohort, 44 genes showed at least one alteration, with a total of 291 pathogenic variants. The median of sequence variants per patient was 3 (2-5) with a median variant allele frequency of 0.4 (0.26-0.47). The most compromised genes were DNMT3A, NPM1, TET2, FLT3 and RUNX1 affecting 60% of the cohort (Figure 1). Sequence alterations in FLT3 (P<0.001) and NPM1 (P=0.008) were found differentially enriched in patients with normal karyotype. Secondary-type AML based on Lindsley's 2015 classification (sAML-L) of variants were significantly associated with secondary-type AML (P<0.001). Within this classification, the most affected genes were SRSF2, BCOR and ASXL1 in 70% of the patients, also RUNX1 sequence variants were found significantly enriched (P=0.024, FDR=0.02) and TET2 mutations showed a tendency (P=0.04, FDR=0.23). Meanwhile, non-sAML-L were distinguished by NPM1 mutations (P<0.001; FDR=0.001). In addition, the somatic interaction of mutations was analyzed and, in accordance with the literature, NPM1-FLT3 (P<0.001), RUNX1-BCOR (P=0.003), TET2-SRSF2 (P=0.003), DNMT3A-IDH2 (P=0.006) were co-occurring events, while RUNX1-NPM1 (P=0.008) were mutually exclusive.
The median follow-up of this cohort was 18 (4-19) months with 51 reported deaths. The first-line therapy was 76% standard chemotherapy, 20% hypomethylating agents and 31 patients received hematopoietic stem cell transplantation. This procedure was favorable in terms of overall survival for patients <65 years with adverse molecular findings classified according to the ELN17 (38 vs 3 months, P=0.003) and to the Eisfeld's 2020 proposal (29 vs 3 months, P<0.001), also with sAML-L or TP53 (19 vs 4 months, P=0.009) and for those with DNMT3A-TET2-ASXL1 (DTA) variants (29 vs 12 months, P=0.026).

Figure 1



Summary/Conclusion: Compilation and analysis of real-world NGS data from multiple institutions which are generated in diverse sequencing platforms represents a challenge in a collaborative setting. Nevertheless, our results are comparable to those reported in the literature and offer clinically relevant evidence that may help Argentine hematologists to make treatment decisions.

PB1381 IDENTIFICATION AND VALIDATION OF A SUBSET OF CANDIDATE FDA-APPROVED DRUGS FOR REPURPOSING IN HOXA EXPRESSING AML

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Background: Increased HOXA expression is associated with intermediate to poor prognosis in acute myeloid leukaemia (AML) and decreased expression acts as a readout for candidate experimental therapies. Underlying causes of increased HOXA expression range from gross rearrangements involving the Mixed Lineage Leukaemia (MLL) gene to mutations in single genes such as Nucleophosmin. To date, direct targeting of HOXA proteins has not been clinically feasible. In a *Hoxa* cluster-dependency model of MLL-rearranged leukaemia, we recently identified a group of FDA-approved drugs that could potentially target *HOXA* signatures indirectly by disrupting key pathways and processes.
Aims: This study aims to further identify and validate a subset of FDA-approved drugs in HOXA overexpressing AML.
Methods: RNA-sequencing was performed following conditional deletion of the *Hoxa* cluster in a mouse model of MLL-AF9 leukaemia. Bioinformatics tools including QUADrATiC, Ingenuity Pathway Analysis and the LINCS platform were used to identify candidate pathways and FDA-approved drugs. A subset of drugs were validated using cell viability assays in a panel of AML cell lines (including HL60, MOLM-13, MV4-11, OCI-AML3, THP1 and KG1a), and calculated IC50 values were obtained from dose-response curves for a subset of the candidate drugs.
Results: Connectivity mapping of the RNAseq data identified a list of candidate FDA-approved drugs with the potential to mimic *HOXA* deletion. These drugs include: Anisomycin, Butein, Calmidazolium, Digitoxigenin, Strophanthidin, Calcitriol, Emetine, Mefloquine and Trichostatin A. Cell viability assays identified measurable anti-leukaemia effects of some of these drugs at concentrations achievable clinically, most notably Anisomycin (Figure 1). Current and future work will evaluate anti-leukaemia effects of these drugs using colony forming ability, cell cycle and apoptosis analysis which will be presented during the meeting.

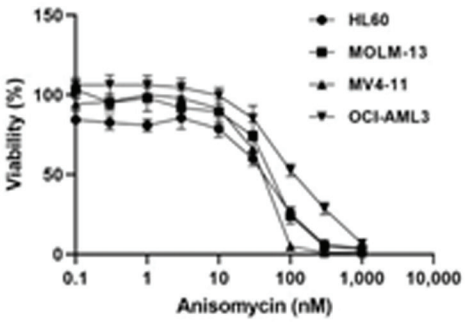


Figure 1: Effect of FDA approved drug Anisomycin on AML cell lines. Dose response of anisomycin on AML cell lines HL60, MOLM-13, MV4-11 and OCI-AML3 treated for 24 hours and subjected to RealTime-Glo™ cell viability assay (n=3).

Summary/Conclusion: Drug repurposing is an attractive and economical approach to identifying new treatment options for AML patients. This study demonstrates anti-leukaemia activity of several drugs currently used for other diseases or disorders. It is anticipated that once fully validated, some of these drugs may be accelerated to clinical application, as the toxicity profiles are already established.
In summary, this study has identified and evaluated the potential of candidate FDA-approved drugs to induce cell death in AML cell lines. Further investigation of these drugs alone and in combination with first-line therapies will provide new and safer treatment options for AML patients.

PB1383 DUAL ROLES FOR PROTEOSTATIC TARGETING IN ACUTE MYELOID LEUKAEMIA

W. Grey [1,*], A. Rio-Machin [2], P. Casado-Izquierdo [2], E. Gronroos [1], S. Ali [1], J. Miettinen [3], F. Copley [2], P. Alun [3], H. Caroline [3], S. Charles [1], C. Pedro [2], G. John [2], F. Jude [2], B. Dominique [1]

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Background: Acute myeloid leukemia (AML) is an aggressive hematological disorder comprising a hierarchy of quiescent leukemic stem cells (LSCs) and proliferating blasts with limited self-renewal ability. AML has a dismal prognosis, with extremely low two-year survival rates in the poorest cytogenetic risk patients, primarily due to the failure of intensive chemotherapy protocols to deplete LSCs, and the significant toxicity towards healthy hematopoietic cells. Whilst much work has been done to identify genetic and epigenetic vulnerabilities in AML LSCs, little is known about protein dynamics and the role of protein degradation in drug resistance and relapse.
Aims: - Delineate the roles of CKS1 in normal and malignant hematopoietic stem cells.
- Develop new strategies to specifcally target AML LSCs.
- Investigate critical roles for CKS1 in LSC intracellular signalling pathways.
Methods:.
Results: Using a highly specific inhibitor of the $SCF^{SKP2\text{-}CKS1}$complex, we present a dual role for CKS1-dependent protein degradation in reducing AML blasts *in vivo*, and importantly depleting LSCs. Whilst many AML LSC targeted therapies show significant toxicity to healthy hematopoiesis, inhibition of CKS1-dependent protein degradation has the opposite effect, protecting normal hematopoietic cells from chemotherapeutic toxicity. Together these findings demonstrate CKS1-dependent proteostasis is key for normal and malignant stem cell biology.
Summary/Conclusion: The inhibition of CKS1-dependent protein degradation holds excellent promise for AML therapy, both as a single agent towards $CKS1B^{high}$AML, and in combination with induction chemotherapy in other AML cases. Reports of *CKS1B* overexpression correlating with outcome in other solid cancer types, novel ways to modulate CKS1, and the development of more clinically ready molecules to target CKS1, indicate that proteostatic targeting, through the CKS1/CKS2 axis, holds much hope for future cancer therapy.

PB1384 MIRNA EXPRESSION IN ADULT ACUTE MYELOID LEUKAEMIA: BIOMARKERS FOR RISK SUBGROUPS?

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Background: MicroRNAs (miRNAs) are small, single strands of non-coding nucleotides that are highly conserved and endogenous. MiRNAs regulate gene transcription and translation through their targeting of specific RNAs for silencing or degradation. In recent years their importance as regulators of gene expression in health and disease has been increasingly recognised, providing a new class of readily detectable biomarkers. Acute myeloid leukaemia (AML) is a rare, heterogenous and often-times difficult to treat disease. It affects children, predominantly through single genetic changes that are impactful enough to cause AML or through the accumulation of genetic change over many years in adults. However both age groups show many similarities as well as differences, the former providing new avenues for therapy.
Aims: To better understand these two forms of AML, separated by the age of onset, we have examined the miRNAs that are differentially expressed between risk subgroups in two publicly accessible databases.
Methods: We used the (1) National Cancer Institute's Therapeutically Applicable Research to Generate Effective Treatments (NCI-TARGET) that examined paediatric patients and (2) The Cancer Genome Atlas

(TCGA) that examined adults with AML to identify miRNAs that were differentually expressed between risk subgroups.
Results: Four mIRs (mIR3186, mIR486-1, mIR1915 and mIR4740) were differentially expressed (by more than two-fold levels) when comparing intermediate vs good, and poor vs good, risk subgroups in the TCGA dataset. 21 mIRs were differentially expressed in standard versus low, while only two mIRs were differentially expressed when we compared high versus low, risk subgroups, but these were expressed in both subgroup comparisons. Analysis using the TCGA-LAML dataset showed that four differentially expressed mIRs had elevated expression in the poor risk subgroups compared to intermediate and good risk TCGA subgroups. These were mir486-1 (p=2.011 x 10-12), miR378G (p=0.01594), miR1915 (p=0.01915) and miR8086 (p=0.023). In addition, below median levels of miR486-1 and miR1915 were associated with worse outcomes in adults with AML (p=0.0062 and p=0.021, respectively).
Summary/Conclusion: Future work will include pathway and ROC analysis to determine the utility of these miRs as targets for therapy and biomarkers for survival, respectively.

PB1385 NILOTINIB INHIBITS INFLAMMATION IN ACUTE MYELOID LEUKEMIA

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Background: Inflammation may be particularly important in the context of monocyte-rich myeloid neoplasms. The discovery of drugs that prevent chronic or acute inflammation is a major goal of the pharmaceutical industry. A proof-of-concept screening showed that the BCR-ABL inhibitor nilotinib, but not the structurally similar imatinib, blocks the pro-inflammatory phenotype by MALDI-TOF.
Aims: Our main aim was to identify the off-targets proteins for nilotinib compared with imatinib in human immortalised monocytes derived from AML. And to study the differences between nilotinib and imatinib in the inflammatory response in acute myeloid leukemia and multiple myeloma cells.
Methods: In order to identify the off-targets for nilotinib, we performed a thermal proteome profiling (TPP) over a range of temperatures and compound concentrations. We validated the effects of these off-targets by western blot, RTqPCR, ELISA and flow cytometry experiments.
Results: We show that nilotinib affects MAPK signalling and, ultimately preventing the transcription of pro-inflammatory genes, cell adhesion markers and innate immunity markers.
Summary/Conclusion: In consequence, nilotinib may have therapeutic potential through the inhibition of MAPK pathway in inflammatory diseases as well as in myeloid malignancies such as myeloid leukemia and multiple myeloma.

PB1386 SYNERGISTIC EFFECTS OF A NOVEL COMBINATION OF CLADRIBINE AND CHIDAMIDE ON CELL PROLIFERATION AND APOPTOSIS OF ACUTE MYELOID LEUKEMIA

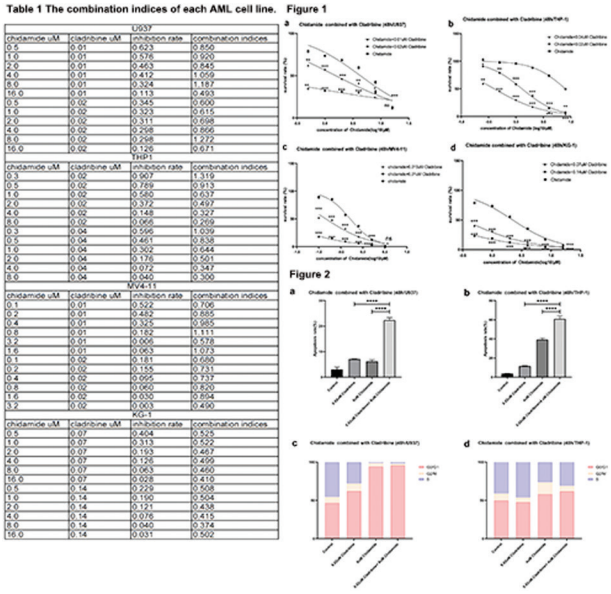
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Background: Chidamide is a histone deacetylase inhibitor (HDACi), selectively suppresses the activities of histone deacetylases 1, 2, 3, and 10. Cladribine, the deoxyadenosine analog, exerts its cytotoxic effect by being rapidly phosphorylated to the undegradable triphosphate (2-CDATP) by adenosine deaminase. The anti-leukemia effects of the two drugs have been reported. However, the synergistic therapeutic effects of the two drugs are still undetermined in acute myeloid leukemia (AML).
Aims: The relevant research that combine the cladribine with chidamide in AML has not been reported. The present resarch is aim to explore the synergistic therapeutic effects of the two drugs in AML and to provide a novel drug combination for relapse and refractory AML patients.
Methods: Cell Counting Kit-8 (CCK-8) cell proliferation assay, Annexin V apoptosis assay and Propidium Iodide cell cycle assay were performed in AML cell lines U937, THP-1, MV4-11, and KG-1 in presence of chidamide, cladribine, chidamide+ cladribine, and no-treatment control for 48h. Data were expressed as the mean ± standard deviation. T-tests statistical analysis was employed for determining the significant difference between groups. A synergistic effect was determined by the combination indices (CIs) with CompuSyn software.
Results: The 50% inhibiting concentration (IC50) of chidamide is 9.358±1.448μmol/L in U937 cells, 7.918±1.666μmol/L THP-1, 0.517±1.337μmol/L MV4-11, and 2.23±0.6885μmol/L KG-1. The IC50 of cladribine is 0.024±3.071μmol/L, 0.05±0.411μmol/L, 0.021±2.019μmol/L, and 0.14±3.13μmol/L in U937, THP-1, MV4-11, KG-1 cells, respectively. Two doses (IC50 or 1/2 IC50) of cladribine were respectively combined with various doses of chidamide for cell proliferation assay in each cell line. The survival rate decreases significantly in the combo group (chidamide plus cladribine) compared to single drug control in each cell line (Figure 1). The CI analysis showed that 7 combination doses of the two drugs have a significant synergistic effect in U937, and two in 8 in THP1, 8 in MV4-11, and all the tested combination doses (12) in KG-1 (Table 1). The combination of chidamide and cladribine significantly elevated the apoptosis rate of two cell lines, U937 and THP-1, compared with chidamide alone (p <0.0001) and cladribine alone (p <0.0001, Figure 2 a, b). The combo treatment also arrested the cell cycle at the G0/G1 phase in both THP-1 (p <0.0001) and U937 (p <0.0001, figure 2 c, d) cells.

Table 1 The combination indices of each AML cell line.

U937			
chidamide uM	cladribine uM	inhibition rate	combination indices
0.5	0.01	0.623	0.856
1.0	0.01	0.576	0.920
2.0	0.01	0.463	0.845
4.0	0.01	0.412	1.059
8.0	0.01	0.324	1.187
16.0	0.01	0.113	0.493
0.5	0.02	0.345	0.600
1.0	0.02	0.323	0.615
2.0	0.02	0.311	0.698
4.0	0.02	0.208	0.866
8.0	0.02	0.098	1.272
16.0	0.02	0.126	0.671
THP1			
chidamide uM	cladribine uM	inhibition rate	combination indices
0.3	0.02	0.907	1.319
0.5	0.02	0.789	0.913
1.0	0.02	0.582	0.637
2.0	0.02	0.372	0.497
4.0	0.02	0.148	0.327
8.0	0.02	0.066	0.269
0.3	0.04	0.596	1.039
0.5	0.04	0.461	0.838
1.0	0.04	0.302	0.644
2.0	0.04	0.176	0.501
4.0	0.04	0.072	0.347
8.0	0.04	0.040	0.300
MV4-11			
chidamide uM	cladribine uM	inhibition rate	combination indices
0.1	0.01	0.522	0.706
0.2	0.01	0.482	0.885
0.4	0.01	0.325	0.985
0.8	0.01	0.182	1.111
3.2	0.01	0.006	0.578
1.6	0.01	0.063	1.073
0.1	0.02	0.181	0.690
0.2	0.02	0.155	0.731
0.4	0.02	0.095	0.737
0.8	0.02	0.060	0.820
1.6	0.02	0.030	0.894
3.2	0.02	0.003	0.490
KG-1			
chidamide uM	cladribine uM	inhibition rate	combination indices
0.5	0.07	0.404	0.522
1.0	0.07	0.313	0.522
2.0	0.07	0.193	0.467
4.0	0.07	0.126	0.499
8.0	0.07	0.063	0.460
16.0	0.07	0.028	0.410
0.5	0.14	0.229	0.508
1.0	0.14	0.150	0.504
2.0	0.14	0.121	0.438
4.0	0.14	0.076	0.415
8.0	0.14	0.040	0.374
16.0	0.14	0.031	0.502



Summary/Conclusion: Combination of chidamide and cladribine has a synergistic effect on cell proliferation arrest, apoptosis, and cell cycle arrest in acute myeloid leukemia cells. Our data provide experimental evidence for the novel potential combination on AML therapy. The clinical study is goning on.

PB1387 A CASE OF IDH1 MUTATED AML IN AN ADULT PATIENT AFFECTED BY OLLIER DISEASE, BIOLOGICAL SPECULATIONS AND CLINICAL IMPLICATIONS

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Background: Ollier disease (OD) is a rare congenital, non hereditary disorder, characterized by early development of multiple enchondromas and genetically by mutations in isocitrate dehydrogenase (IDH) 1 and 2. Mutations are found in chondromas, but not in other tissues, suggesting that they occur during embryonic development in mesoderm, giving rise to a somatic genetic mosaicism, with the gene being mutated only in tissues of mesodermal origin. Clinically, OD is associated with an increased risk of cancer, including chondrosarcomas and gliomas. Haematopoietic cells precursors (hemangioblasts) embriologically derive from mesoderm and thus bone marrow may be involved in OD manifestations. Furthermore, IDH 1 and 2 are frequently mutated in AML. However, AML cases in OD are anecdotal and reported only in paediatric patients.

Aims: We report the case of a patient affected by OD, who at 35 years developed AML harbouring IDH1, NPM1 and FLT3 TKD mutation and speculate about etiopathogenesis.
Methods: Patient's diagnostic and therapeutic management was performed according to our centre policy as indicated in "Results".
Results: In November 2020 a 35 years old man was admitted to our unit with haemorrhagic symptoms. He had a diagnosis of OD and had underwent surgery at 14 and 22 years to remove enchondromas in the left hand. His blood counts were: WBC 85.470/mm^3, Hb 9,9 g/dl, platelets 11.000/mm^3. A bone marrow evaluation led to a diagnosis of AML, FAB M2, with normal karyotype, NPM1 exon 11 (W288Cfs*12), FLT3 TKD (D835Y and I836del) and IDH1 (R132H) mutation. An induction chemotherapy with "7+3" associated with midostaurin (days 8-21) was administered and complete remission was obtained. Subsequently the patient underwent three consolidation cycles with HD Ara-C and midostaurin (days 8-21). At a molecular level NPM1 and FLT3TKD mutations were not detectable by qualitative nested PCR after induction, while IDH1 mutation was present at all bone marrow evaluations, even after the last consolidation.
Summary/Conclusion: Mutations of the IDH 1 and/or 2 gene are found in about 16% of AMLs. IDH proteins catalyze the conversion of isocitrate to α-ketoglutarate. Mutations lead to gain of function and an enhanced production of 2-hydroxyglutarate, responsible for increased DNA methylation. According to recent AML pathogenetic models, mutations in genes encoding epigenetic modifiers, such as DNMT3A, ASXL1, TET2, IDH1,and IDH2, are acquired early in a founding clone and may be found in the context of a clonal haeatopoiesis (CHIP), even in healthy subjects. Additional mutations, such as those involving NPM1 or signalling molecules (FLT3, RAS), are secondary events occurring later during leukemogenesis. IDH 1 and 2 mutations may persist in a patient treated for AML after therapy and represent, rather than a molecular marker of MRD, a risk factor for disease relapse.
In our patient IDH1 mutation was still detectable in bone marrow after achievement of CR, indicating the persistence of a clone of haematopoietic precursors harbouring a congenital mutation, associated with OD. It is important to note that the patient had remained free from leukaemia during three decades and a half, with AML developing only after acquisition of two other gene mutations (NPM1 and FLT3 TKD). These observations shed light on the paradigm of multiple genetic hits hypothesis of leukemogenesis and, after demonstration of the same IDH1 (R132H) mutation in chondroma tissue, prompt us to monitor the patient rather than candidate him to alloHCT in I CR.

PB1389 PREDICTIVE FACTORS AFFECTING THERAPY RESPONSE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Actual prognostic factors for predicting therapy response in patients with acute myeloid leukemia (AML) are formed on the basis of detected cytogenetic and molecular genetic abnormalities, as well as initial clinical data, including the patient's age, the number of leukocytes in peripheral blood, and the level of blasts in the bone marrow. However, the therapy response is often influenced by the presence of primary resistance of tumor cells to cytotoxic drugs. Assessment of the combined impact of these factors on the therapy response of leukemia patients can be done by the forming of the multivariate predictive models.
Aims: The aim of this work was to assess the risk of development and progression of drugresistance in patientswith acute myeloidleukemia based on thepatients' age, MDR1 gene expression, sensitivity of tumor cells to cytostatic drugs, cytogenetic and molecular genetic abnormalities detected initially at diagnosis before treatment start.
Methods: The study included 53 patients withAML.Leukemic cells were collected from peripheral blood and bone marrow of patients. Assessment of multidrug resistance in tumor cells of leukemia patients was performed using real-time RT-qPCR) and WST1-test. RT-qPCR was used to evaluate the expression of the MDR1 gene. WST1-test was used to evaluate the sensitivity of tumor cells to chemotherapeutic drugs *in vitro*. The correlation analysis was performed using Spearmen's correlation coefficient (r).All statistical analyses were done with software MS Excel, OriginPro 7.5, Statistica 10.0.
Results: The average age of the patients was 51.2±14.5 years.In the group of AML patients who receivedanthracycline-based therapy, reliable correlations for response to therapy ($p < 0.05$) with the following indicatorswere obtained: age ($r = 0.55$), sensitivity to daunorubicin ($r = 0.72$), karyotype of tumor cells ($r = 0.6$), standard risk stratification by genetics ($r = 0.7$), total sensitivity to cytotoxic drugs ($r = 0.61$), standard prognosis stratification by cytogenetic/molecular markers and clinical characteristics($r = 0.55$). There was also direct correlation between response to therapy and the level of MDR1 gene expression ($r = 1.0$), however, due to the small sample size the differences were statistically insignificant, $p > 0.05$. Based on this data, a new prognostic scale was developed –all patients were divided into 3 prognostic groups: low risk group, intermediate risk group and high risk group.
Summary/Conclusion: Thus, the prognostic factors influencing the therapy response of AML patients were analyzed. The most prognostic values were detected for the following variables: the sensitivity of tumor cells to cytostatic drugs, the level of MDR1 gene expression, the karyotype of tumor cells, the age of patients, and the presence of cytogenetic abnormalities in tumor cells. Our prognostic scale allows to predictthe patient's response to the planned treatment protocol before the therapystart, which enables a personalized approach to the selection of patient management strategy.

Acute myeloid leukemia - Clinical

PB1390 RETROSPECTIVE ASSESSMENT OF TREATMENT PATTERNS AND RESOURCE UTILIZATION FOR PATIENTS NEWLY DIAGNOSED WITH ACUTE MYELOID LEUKEMIA IN CANADA, UK, FRANCE, GERMANY, ITALY, AND SPAIN

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Background: Few studies have assessed treatment patterns and healthcare resource utilization (HRU) in patients with acute myeloid leukemia (AML) by *FMS*-like tyrosine kinase 3 (*FLT3*) mutation status (ie, *FLT3* gene mutation [*FLT3*$^{mut+}$] vs *FLT3* wild-type [*FLT3*^{wt}]), the most frequently identified molecular mutation in AML. The rapidly evolving treatment landscape and high cost of care in AML widen the persistent gap in detailed real-world evidence for this population.
Aims: To describe and compare baseline characteristics, real-world treatment patterns, and AML-related HRU by *FLT3* mutation status in patients newly diagnosed with AML.
Methods: Retrospective chart-level data were abstracted by hematology/oncology physicians that participate in the IQVIA Oncology Panel Survey in Canada, the UK, France, Germany, Italy, and Spain. Patients newly diagnosed with *FLT3*$^{mut+}$ or *FLT3*^{wt} AML from 01/09/2017-30/06/2019 were selected for inclusion (study period: 01/01/2017-31/03/2020). The index date was defined as the date of first treatment after initial AML diagnosis; follow-up ended at death, end of available data, or end of study. Treatment patterns were assessed from the index date until the end of follow-up; HRU was assessed from the diagnosis date through the end of follow-up.
Results: Data from 525 patients were included (*FLT3*$^{mut+}$, 41.5%; *FLT3*^{wt}, 58.5%; **Table**). In both cohorts, >80% of patients started AML treatment in 2019 and had a median follow-up of 4.4 months. Patients with *FLT3*$^{mut+}$ vs *FLT3*^{wt} AML were significantly younger and more likely to be in the adverse molecular/genetic risk group at diagnosis (both $P<0.0001$). Most patients received only one line of therapy during the follow-up period (*FLT3*$^{mut+}$, 89.4%; *FLT3*^{wt}, 90.6%). A higher proportion of patients with *FLT3*$^{mut+}$ (84.9%, n=185) than *FLT3*^{wt} AML (58.6%, n=180) received first-line high-intensity chemotherapy (HIC). The predominant HIC regimen was 7+3 (7 days cytarabine + 3 days anthracycline) (*FLT3*$^{mut+}$, 89.2%; *FLT3*^{wt}, 81.1%)—most commonly 7+3 with FLT3 inhibitor (predominantly midostaurin) (43.8%) in *FLT3*$^{mut+}$ patients and 7+3 alone (72.0%) in *FLT3*^{wt} patients. Nearly all patients who received low-intensity chemotherapy (LIC) had *FLT3*^{wt} AML; the predominant LIC regimen was a hypomethylating agent with or without venetoclax (*FLT3*$^{mut+}$, 51.5%; *FLT3*^{wt}, 67.7%). Most patients received supportive care during treatment, and transfusion of blood products was common (**Table**). HRU was assessed in 424 patients (80.8%). Patients with *FLT3*$^{mut+}$ vs *FLT3*^{wt} AML had ≥4 times more inpatient admissions

(*P*=0.0045) and higher proportions of intensive care unit admissions (*P*=0.0003) and emergency department visits (*P*=0.0005).

Table. Patient Characteristics, Treatment Patterns, and HRU in Patients Newly Diagnosed With AML by *FLT3* Mutation Status

Variable	*FLT3*$^{mut+}$ AML N=218	*FLT3*^{wt} AML N=307	*P*-value[a]
Baseline demographic and clinical characteristics			
Age, years (categorical), n (%)			
<60	120 (55.0)	105 (34.2)	<0.0001
60-74	65 (29.8)	110 (35.8)	
75+	33 (15.1)	92 (30.0)	
Male, n (%)	124 (56.9)	182 (59.3)	0.5555
Country, n (%)			
Germany	48 (22.0)	53 (17.3)	0.2539
Spain	46 (21.1)	48 (15.6)	
Italy	43 (19.7)	63 (20.5)	
United Kingdom	41 (18.8)	77 (25.1)	
France	38 (17.4)	54 (17.6)	
Canada	2 (0.9)	12 (3.9)	
Molecular/genetic risk stratification at diagnosis, n (%)[b]			
Favorable	19 (8.7)	105 (34.2)	<0.0001
Intermediate	101 (46.3)	123 (40.1)	
Adverse	96 (44.0)	69 (22.5)	
Unknown/Not tested	2 (0.9)	10 (3.3)	
First-line treatment patterns			
High-intensity chemotherapy, n (%)	185 (84.9)	180 (58.6)	<0.0001
Low-intensity chemotherapy, n (%)	33 (15.0)	127 (41.4)	<0.0001
Use of supportive care, n (%)			
High-intensity chemotherapy			
Any supportive care	180 (97.3)	175 (97.2)	0.1212
Red blood cell transfusion	159 (85.9)	165 (91.7)	**0.0189**
Platelet transfusion	141 (76.2)	154 (85.6)	**0.0037**
Low-intensity chemotherapy			
Any supportive care	30 (90.9)	116 (91.3)	0.9864
Red blood cell transfusion	29 (87.9)	102 (80.3)	0.3216
Platelet transfusion	15 (45.5)	59 (46.5)	0.9182
Healthcare resource utilization (N=424)			
Patients with HRU data available, n (%)	169 (75.1)	255 (78.0)	0.0809
Follow-up time from AML diagnosis, mean (SD), days	200.5 (150.6)	221.7 (182.0)	0.1361
Inpatient admission, n (%)	166 (98.2)	232 (90.98)	**0.0065**
Number of visits PPPM, mean (SD)	4.1 (39.8)	0.7 (0.7)	**0.0045**
Total LOS, mean (SD), days	13.1 (12.9)	9.6 (11.2)	0.8133
ICU stay, n (%)	47 (27.8)	35 (13.7)	**0.0003**
Number of visits PPPM, mean (SD)	0.3 (2.3)	0.0 (0.1)	0.2025
Total LOS, mean (SD), days	2.4 (5.4)	1.6 (5.9)	0.2372
Emergency department, n (%)	95 (56.2)	96 (37.6)	**0.0006**
Number of visits PPPM, mean (SD)	0.2 (0.4)	0.2 (0.3)	0.9403
Outpatient visits, n (%)	150 (88.8)	208 (81.6)	0.0693
Number of visits PPPM, mean (SD)	3.0 (14.2)	1.4 (1.8)	0.0675

[a] Bold formatting indicates values that are statistically significant (*P*<0.05).

[b] Molecular/genetic risk stratification at diagnosis were provider-reported and captured from patients' medical charts.

Abbreviations: AML, acute myeloid leukemia; *FLT3*$^{mut+}$, *FMS*-like tyrosine kinase 3 mutation; *FLT3*^{wt}, *FMS*-like tyrosine kinase 3 wild-type; HRU, healthcare resource utilization; ICU, intensive care unit; LOS, length of stay; PPPM, per patient per month; SD, standard deviation.

Summary/Conclusion: These real-world data illustrate the differences in demographic and clinical characteristics, first-line treatment patterns, and HRU between *FLT3*$^{mut+}$ and *FLT3*^{wt} AML patient populations in Canada, the UK, France, Germany, Italy, and Spain. Age and *FLT3* mutation status appeared to influence the type of induction regimen used; although most patients received HIC, *FLT3*$^{mut+}$ vs *FLT3*^{wt} patients were significantly younger and a higher percentage received HIC. Nearly half of *FLT3*$^{mut+}$ patients receiving HIC also received a FLT3 inhibitor. The high use of supportive care and inpatient and outpatient HRU highlight the significant morbidity and economic burden associated with managing AML, the importance of knowing patients' *FLT3* mutation status, and the need to further understand how patients with *FLT3*$^{mut+}$ AML may differ from other patients with AML.

PB1391 A PHASE 1A/B DOSE ESCALATION STUDY OF THE MUTATION AGNOSTIC FLT3/BTK INHIBITOR LUXEPTINIB (CG-806) IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

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Background: Luxeptinib (CG-806) is a potent oral small molecule inhibitor of the wild type and all mutant forms of the FLT3 kinase, including ITD, D835Y, and F691L. Luxeptinib simultaneously suppresses additional signaling pathways in AML cells (CSF1R, PDGFRα, TRK, SYK, BTK, LYN, AKT, ERK, MAPK), kills primary AML cells insensitive to other FLT3 inhibitors at pM and low nM concentrations, and shows enhanced activity in combination with venetoclax. Patient-derived AML cells retain sensitivity to luxeptinib even when harboring mutations of *NPM1*, *IDH1*, *ASXL1*, or *TP53*. Luxeptinib is being evaluated in a Phase 1a/b trial in patients with relapsed or refractory (R/R) AML (NCT04477291).
Aims: The primary objectives are to assess the safety and tolerability of luxeptinib and to determine the recommended Phase 2 dose for future clinical trials in patients with R/R AML. Key secondary objectives include elucidation of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, and evidence of antitumor activity.
Methods: The study is enrolling patients with relapsed or refractory *de novo* AML, secondary AML, or therapy-related AML. Luxeptinib is administered continuously as oral capsules BID in 28-day cycles, in ascending cohorts of 3 or 4 patients. Treatment emergent adverse events (TEAEs) and tumor responses are evaluated using CTCEA and International Working Group criteria respectively.
Results: As of December 10, 2020, a total of 4 patients (mean age 67.0 ± 20.9 years, 2 FLT3-ITD, 1 FLT3-ITD/TKD, and 1 FLT3-WT) with a median of 3 prior treatments (range, 2 - 8) have been treated with luxeptinib at the starting dose level of 450 mg BID. Observed possibly drug related TEAEs included nausea in 2 (50%; Gr 1), prolonged activated partial thromboplastin time in 1 (25%; Gr 1), increased blood alkaline phosphatase in 1 (25%; Gr 1), headache in 1 (25%; Gr 1), pericardial effusion in 1 (25%; Gr 3), photophobia in 1 (25%; Gr 1), and pleural effusion in 1 (25%; Gr 2). The steady-state (C_{min}) plasma levels of luxeptinib in AML patients treated with 450 mg Q12 hours were generally in the 1μM range by the end of Cycle 1. PD analysis demonstrated luxeptinib in the plasma of patients significantly reduced phosphorylated FLT3, ERK, SYK and PDGFRα in EOL-1 reporter cells in a plasma inhibitor activity (PIA) assay. One heavily pretreated patient with relapsed AML with mutated *NPM1*, *DNMT3A*, and *FLT3*-ITD who had previously progressed after chemotherapy, alloSCT, and two FLT3 inhibitors (gilteritinib, crenolanib) demonstrated clinical anti-leukemic activity with a decrease in peripheral blood blasts from 93% to 10% during Cycle 1.
Summary/Conclusion: Luxeptinib has been well tolerated at the starting dose level of 450mg Q12 hours. Pharmacodynamic studies documented inhibition of FLT3 signaling pathway, and anti-leukemic activity has been observed in the setting of AML relapsed following therapy with multiple prior FLT3 inhibitors. Enrollment of patients with R/R AML continues and updated clinical data from this dose escalation study will be presented at the meeting.

PB1392 PROGNOSTIC IMPACT OF MOLECULAR MARKERS IN ELDERLY PATIENTS AFFECTED BY NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: MONOCENTRIC EXPERIENCE

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Background: Acute Myeloid Leukemia (AML) is a bone marrow clonal disorder characterized by the proliferation of myeloid blasts. The European LeukemiaNet (ELN) 2017 risk stratification is a consolidated prognostic system focused on AML genetic features which is able to predict the probability of AML response and relapse following an intensive chemotherapeutic approach.
However, chemosensitivity and risk of disease relapse is age-dependent and limited for patient aged up to 60 years.
Aims: We investigated the predictability of this risk stratification in AML patients aged ≥ 60 years who underwent intensive chemotherapy.
Methods: We retrospectively revised data of 79 patients with new diagnosis of AML since 01/01/2015, followed at AORN Cardarelli Hospital, Naples. The inclusion criteria were age ≥60 years, Eastern Cooperative Oncology Group (ECOG) score ≤2, intensive chemotherapy as frontline approach. Patients were risk stratified according to ELN 2017 recommendations.
Results: Patients and disease characteristics are summarized in Table1. The median age of the entire population was 66 years (60-77). Mutations in NPM1 and FLT3-ITD were detected in 24/75 (32%) and 19/75 (25%) cases. Patients were classified, according to ELN 2017 stratification, as follows: 17/75 (23%) favourable, 40/75 (53%) intermediate and 18/75 (24%) adverse risk. A hematologic al complete response (CR) after induction treatment was achieved by 32/75 (43%) patients and was significantly associated with favourable ELN 2017 risk (p=0.03).The median Overall Survival (mOS) of the entire population was 6 months (0-59)(CI:4.82-7.10). The ELN2017 stratified mOS was 9 (0-59) for favourable, 5 (0-56) for intermediate and 4 months (0-43) for adverse risk AML (p=0.1).

Particularly, the difference in mOS resulted significant in comparing the favourable to intermediate+adverse risk AML (9 vs 5 months; p=0.038). No significant differences in terms of mOS were observed between NPM1 mutated vs unmutated (7 vs 6 months; p=0.806) or FLT3-ITD mutated vs unmutated AML (2 vs 6 months; p=0.119), respectively.
In multivariate analysis, the only conditions significantly related to longer OS were the allogenic hematopoietic stem cell transplantation (HSCT)(median OS not reached;HR:15.19;CI:3.34-69.05;p<0.005) and a CR after induction therapy (median OS 11months;HR:2.55;CI:1.30-5.00;p=0.006), while belonging to ELN 2017 favourable risk compared to intermediate+adverse risk AML was not significant (median OS 9 months; HR:0.58;CI:0.25-1.35; p=0.201).
The median Disease-Free Survival (mDFS) of the entire population was 8 months (1-58)(CI:3,92-12,07). No significant differences were found among the ELN2017 groups in mDFS. In multivariate analysis no variables resulted significantly associated with longer DSF.

	Global population	Favorable risk	Intermediate risk	Adverse risk
Patients (n)	75	17	40	18
Median age (range), years	66 (60-77)	64 (60-73)	65 (60-73)	69 (60-77)
ECOG score n (%)				
0	64 (85)	16 (94)	36 (90)	12 (66)
1	7 (9)	1 (6)	3 (7)	3 (17)
2	4 (6)	0	1 (3)	3 (17)
Gender n (%)				
M	50 (67)	15 (88)	26 (65)	9 (50)
F	25 (33)	2 (12)	14 (35)	9 (50)
Mutations or karyotype abnormalities n (%)				
NPM1	24 (32)	14 (82)	10 (25)	0
FLT3-ITD	19 (25)	3* (18)	9 (22)	7 (39)
FLT3-TKD	5 (7)	3 (18)	2 (5)	0
T(8;21)	0	0	0	0
INV(16) o t(16;16)	3 (4)	3 (18)	0	0
INV (3)	1 (1)	0	0	1 (6)
1st line chemotherapy n (%)				
FLA	51 (68)	8 (47)	28 (70)	15 (82)
FLAI	8 (11)	3 (18)	5 (13)	0
3+7	4 (5)	1 (6)	2 (5)	1 (6)
3+7 + Midostaurin	8 (11)	4 (24)	3 (7)	1 (6)
CPX 351	3 (4)	0	2 (5)	1 (6)
ICE	1 (1)	1 (6)	0	0
Hematological CR n (%)	32 (43)	13 (77)	10 (25)	9 (50)
Relapse n (%)	18 (56)	8 (61)	5 (50)	5 (56)
Allogenic HSCT n (%)	11 (15)	2 (12)	7 [18)	2 (11)
Median OS (range),months	6 (0-59)	9 (0-59)	5 (0-56)	4 (0-43)
Median DFS (range),months	8 (1-58)	8 (1-58)	5 (2-55)	11 (2-27)

Summary/Conclusion: Our study demonstrated only the ELN2017 favourable risk had a significant benefit in terms of CR rate and mOS but not mDFS in patients aged ≥60 years with AML diagnosis who underwent intensive chemotherapy as frontline approach. The outcome of ELN2017 intermediate and adverse risk AML was very poor, without any difference between the two risk classes. Interestingly, NPM1 or FLT3-ITD mutations added no significant variation in terms of mOS or mDFS, while a significant impact of HSCT still remained.
Our results finally showed how prognostic significance of genetic abnormalities in AML might be influenced by age, and that a new risk stratification integrating performance status, age, presence of targetable mutations by tyrosine kinase inhibitors and transplant eligibility should be considered in setting of elderly patients.

PB1393 FAVOURABLE OUTCOMES WITH ATRA AND ARSENIC VERSUS ATRA AND CHEMOTHERAPY IN NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA IN WESTERN AUSTRALIA-A POPULATION-BASED STUDY.

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Background: Outcomes of Acute Promyelocytic Leukemia (APML) have improved considerably with the use of targeted therapies in trials.
Aims: We aimed to study the outcomes of APML in real-word WA patients.
Methods: Retrospective, multicentre analysis of survival outcomes of patients with APML presenting to public tertiary hospitals from 2005-2019 was undertaken, median follow-up of 46months (mo). Kaplan Meir survival analysis with log-rank Mantel Cox test, Cox proportional hazard was used, p<0.05 was considered significant.
Results: De-novo APML (n=89) patients had overall survival (OS) of 110.25 mo (95% CI 97.8-122.5) and early mortality rate of 10.1%. Of the treated patients (n=88), patients received ATRA-IDA (n=21), ATRA-IDA-ATO (n=30), ATRA-ATO (n=35), 7+3 Idarubicin/Cytarabine/ATRA (n=2). Event free survival, OS of patients on ATRA-IDA, ATRA-IDA-ATO, ATRA-ATO was 57.2%, 86.6 % and 88.5 % (p=0.0154); 80.3 (95% CI 55.5-105.1), 123 (95%CI 107-138.9) and 80.6 (95% CI 71.3-89.9) mo (p=0.041) respectively. Secondary malignancy occurred in 4.7%, 10%, 0% patients on ATRA-IDA, ATRA-IDA-ATO, ATRA-ATO respectively. Using Cox regression, age at diagnosis significantly influenced overall survival outcomes (p=0.01, HR 1.051 (95% CI 1.011-1.093).
Summary/Conclusion: Population-based outcomes of APML have shown an improvement in EFS and OS with ATRA-ATO which may be attributed to reduction in relapse-related mortality and secondary malignancies.

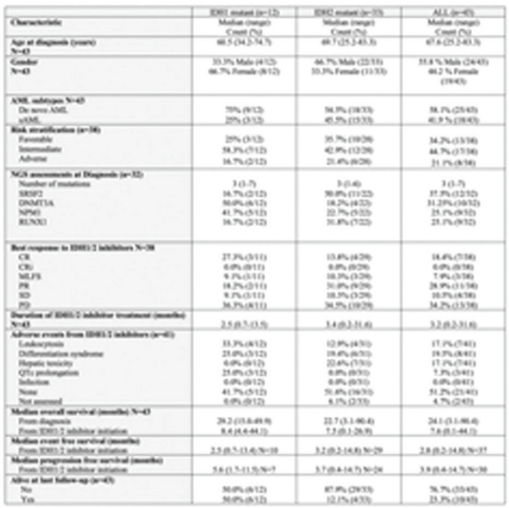
PB1394 SURVIVAL OUTCOMES AND ADVERSE EVENTS OF IDH1/2 MUTANT AML PATIENTS TREATED WITH IDH1/2 INHIBITORS: A SINGLE INSTITUTIONAL EXPERIENCE

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Background: Recent genomic studies showed that IDH1/2 are frequently mutated in AML at about 20% and pre-clinical studies demonstrated that aberrant 2-HG elevation driven by the mutant IDH1/2 proteins plays a pivotal role in AML development by suppressing 5mC-to-5hmC conversion. Subsequent clinical trials of IDH1/2 inhibitors demonstrated promising outcomes in *IDH1/2*^{mut} AML patients.
Aims: In this single institutional retrospective study, we explored the efficacy and safety outcomes of *IDH1/2*^{mut} AML patients treated with Ivosidenib or Enasidenib.
Methods: We retrospectively identified AML patients who had *IDH1/2* somatic mutations based on NGS assessments. Clinical and demographic data were extracted from the medical records. Statistical analyses were performed using GraphPad Prism (v.7.03) and SPSS (v.24.0).
Results: A total of 43 (*IDH1*^{mut}, n=12; *IDH2*^{mut}, n=33; both *IDH1/2*^{mut}, n=2) patients were included in the study. Median age at AML diagnosis was 67.6 (24.2-83.3) years and 24 (55.8%) patients were male. Eighteen (42%) patients had secondary AML and 13 (34.2%), 17 (44.7%), and 8 (21.1%) patients had favorable, intermediate, and adverse risk, respectively. A total of 23 (53.5%) and 9 (20.9%) patients received intensive chemotherapy and hypomethylating agents as their 1st line therapy. One patient received Enasidenib as the 1st line therapy and the rest of the patients had relapsed/refractory disease prior to IDH1/2 inhibitor therapy. Median number of treatment prior to IDH1/2 inhibitors was 4 (0-8). The median duration of IDH1/2 inhibitor treatment was 3.2 (0.2-31.6) months (*IDH1*^{mut}, 2.5 [0.7-13.5]; *IDH2*^{mut}, 3.4 [0.2-31.6]). Treatment response was assessed in 38 patients and 18 had overall response (CR, n=7 [18.4%]; PR, n=11 [28.9%]). Of note, among 33 (76.7%) patients who had NGS assessments prior to IDH1/2 inhibitor initiation, a total of 13 patients had concurrent somatic mutations in the survival pathway that include *FLT3, KRAS, NRAS,* and *PTPN11*. The overall response rate in these patients was not statistically different compared to patients who did not have survival pathway mutations (38.5% vs. 40%, p>0.05). The median PFS was 3.9 (0.4-14.7) months (*IDH1*^{mut}, 5.6 [1.7-11.5] vs. *IDH2*^{mut}, 3.7 [0.4-14.7], p>0.05) and median OS was 7.6 (0.4-44.1) months. The most common reason for IDH1/2 inhibitor discontinuation was disease progression (n=21) followed by adverse events (n=3) and allogeneic transplant (n=2). The adverse events were assessed in 41 patients and the most common adverse events were differentiation syndrome (*IDH1*^{mut}, n=3; *IDH2*^{mut}, n=5) and leukocytosis (*IDH1*^{mut}, n=4; *IDH2*^{mut}, n=4) followed by hepatic toxicity (*IDH2*^{mut} n=7), and QTc prolongation (*IDH1*^{mut}, n=3).

Table 1. Characteristics of the study cohort



Summary/Conclusion: Our study indicates that IDH1/2 inhibitors remain a viable option for the refractory/relapsed *IDH1/2*^{mut} AML. However, significant number of patients failed to show any response and many of the patients who showed initial response had short response duration. These findings warrant further studies to identify underlying resistance mechanisms of IDH1/2 inhibitors and the optimal combination therapeutic strategies.

PB1395 SYSTEMATIC LITERATURE REVIEW OF THE EFFICACY AND SAFETY OF MAINTENANCE THERAPIES FOR ADULTS WITH ACUTE MYELOID LEUKEMIA IN COMPLETE REMISSION WHO ARE INELIGIBLE FOR HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Intensive induction therapy in patients (pts) with acute myeloid leukemia (AML) can induce complete remission (CR) and is often followed by consolidation chemotherapy and/or allogeneic hematopoietic stem cell transplant (HSCT) in eligible patients. However, in elderly pts with AML who are HSCT-ineligible, relapse rates are relatively high, overall survival (OS) rates are low, and pts have limited treatment options. Maintenance/post-remission therapy intends to prolong the duration of remission and survival in pts with AML; however, additional studies are required to evaluate maintenance options for HSCT-ineligible pts.
Aims: Identify clinical studies from a systematic literature review (SLR) of randomized controlled trials (RCTs) to assess the efficacy and safety of maintenance therapy in HSCT-ineligible adult pts ≥18 y with newly diagnosed AML who have achieved CR or CR with incomplete platelet recovery (CRi) after intensive chemotherapy induction, with or without consolidation.
Methods: An SLR of RCTs reporting efficacy (OS, relapse/disease/event-free survival [RFS/DFS/EFS], and time to relapse), time to discontinuation, and safety of maintenance therapy was performed to identify relevant studies from 2005–2020 indexed in MEDLINE®, Embase, and EBM Reviews databases (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment Database) using controlled vocabulary and keywords. A supplementary search of clinicaltrials.gov, the FDA database, and abstracts from selected hematology conferences (2018–2019) was also conducted. Two independent reviewers determined eligibility and quality of all studies for inclusion using the Population, Intervention, Comparator, Outcomes, Study Design, and Time framework.
Results: The SLR identified 6701 citations through database searches and 1 from a supplementary search; of these, 25 publications were included in the review representing 22 distinct RCTs. All 22 studies included a maintenance phase with treatments across 3 broad classes of drugs (hypomethylating agents [n=8], immunotherapies [n=7], and anthracyclines [n=4]) and 3 other therapies, although variability in study design was significant. Of the 16 trials with pts randomized to maintenance therapy, 13 trials were designed to assess the efficacy of different maintenance therapies with the baseline population comprising pts randomized to maintenance therapy and outcomes reported by maintenance arm. The remaining trials were designed to assess the efficacy of induction (n=7) and consolidation therapies (n=2). All 13 trials with the primary analysis of maintenance therapy reported RFS/DFS/EFS by maintenance treatment arm, and 11 studies reported OS. Although time zero definitions for RFS/DFS/EFS and OS differed across trials, median RFS/DFS/EFS and median OS ranged from 5–16 and 10–39 mo, respectively. Only the QUAZAR trial of oral azacitidine demonstrated significant improvements in both RFS and OS with maintenance therapy (**Table**). A total of 17 studies reported safety outcomes related to maintenance therapy, with infection being the most commonly reported adverse event (n=10).

Median RFS and OS with oral azacitidine maintenance in the QUAZAR trial

	Median RFS, months (95% CI)	Median OS, months (95% CI)
Oral azacitidine maintenance	10 (8–13)	25 (19–31)
No maintenance	5 (5–6)	15 (12–18)

CI, confidence interval; OS, overall survival; RFS, relapse-free survival

Wei AH et al. *Blood* 2019;134(suppl 2):LBA-3

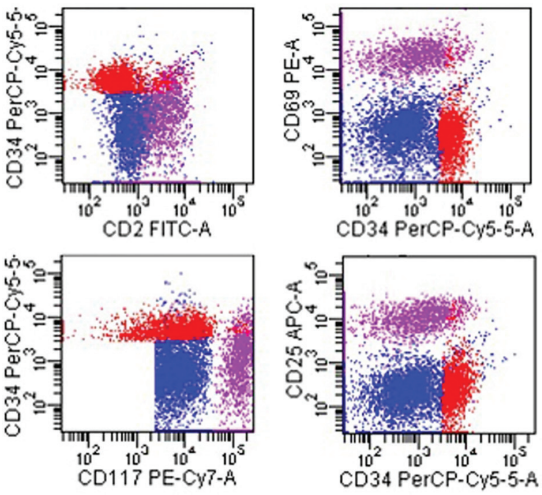
Summary/Conclusion: This SLR identified 22 RCTs reporting efficacy and safety data on maintenance therapies in the treatment of AML in adult pts who achieved CR/CRi and were ineligible for HSCT. Study design varied significantly. Few RCTs eligible for review were adequately designed to assess the efficacy of maintenance therapies and only 1 study demonstrated a significant survival benefit with maintenance therapy.

PB1396 KIT D816 MUTATED T(8;21)(Q22;Q22.1) ACUTE MYELOID LEUKEMIA WITH CONCURRENT SYSTEMIC MASTOCYTOSIS SHOWS POOR RESPONSE TO COMMON CHEMOTHERAPY AND TRANSPLANTATION

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Background: Acute myeloid leukemia with t(8;21)(q22;q22.1) translocation was classified as favorable risk group in NCCN guidelines, whereas KIT D816mutations is a poor prognostic factor. Such patients with concurrent systemic mastocytosis are extremely rare, their clinical features and prognosis are still unclear.
Aims: To explore the clinical features and prognosis of t(8;21)AML bearing KIT D816 mutation associated with SM.
Methods: The clinical data, outcomes of chemotherapy and allo-HSCT of 5 patients with t(8;21) AML bearing KIT D816 mutation associated with SM admitted to Hebei Yanda Ludaopei Hospital from July 3, 2019 to February 1, 2021 were retrospectively analyzed. The median follow-up time was 323 (112-580) days.
Results: Among the 5 patients, 4 were males and 1 female, with a median age of 9 (3-16) years old. The median ratio of bone marrow blasts at onset was 64 (46-78.5)%; the chromosome was t(8;21)(q22;q22.1), and the RUNX1-RUNX1T1 fusion gene was positive. After 2 courses of chemotherapy, 3 patients achieved complete morphological remission, and 2 patients were in NR status. Flow cytometry shows malignant myeloblasts in 3 patients, in addition abnormal mast cells were found in 4 patients. A less than 3log reduction of RUNX1/RUNX1T1 transcript in bone marrow was seen in all of 5 patients. The flow sorting of 2 patients showed that the RUNX1-RUNX1T1 fusion gene mainly been expressed by abnormal mast cell. 4 patients underwent allo-HSCT, all haplotype 5/10 compatible, adopting Bu/Cy-based myeloablative intensified conditioning regimen. After transplantation, all 4 patients had hematopoietic engraftment. The bone marrow findings at +30 days all showed CR status, no malignant myeloblasts were found in bone marrow flow cytometry, yet abnormal phenotypic mast cells were found. RUNX1-RUNX1T1 transcripts did not turn negative. All 5 patients met the diagnostic criteria for SM: ① KIT D816 mutation was detected (3 cases of D816V mutation, 3 cases of D816Y mutation, 1 case of D816F mutation; 1 patient had the above 3 mutations); ②>25% of mast cells found in bone marrow cytology of all patients were immature or atypical mast cells; ③mast cells all expressed CD25, with or without CD2. Subsequently 1 patients was treated with midostaurin, RUNX1-RUNX1T1 and mast cells became negative after 63 days of treatment. The other 3 patients were treated with dasatinib and/or interferon. The fusion genes and abnormal mast cells did not turn negative. Patient who did not undergo transplantation continued to detect abnormal mast cells and transcripts of RUNX1-RUNX1T1.



Summary/Conclusion: t(8;21)AML bearing KIT D816 mutation associated with SM shows poor response to common chemotherapy and allo-HSCT, neither can eliminate clonal mast cells, hence this type of disease requires targeted therapy intervention.

PB1397 COVID-19 IN PATIENTS WITH ACUTE LEUKEMIA: THE EXPERIENCE OF A HEMATOLOGICAL CENTER

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Background: Patients with hematologic malignancies appear to have a greater risk of SARS-CoV-2 infection and severe disease due to myelosuppression; furthermore, delays in treatment of patients with hematologic malignancies, especially those with acute leukemia planned for chemotherapy or transplantation, are associated with a risk of disease progression. To date, some societies recommend that chemotherapy should generally not be started until COVID-19 symptoms have completely resolved and viral testing becomes negative. However, implications of the aforementioned recommendations remain uncertain in routine clinical practice, and data on COVID-19 in patients with hematologic malignancies are still limited.
Aims: We carried out a single-center analysis of acute leukemia inpatients who developed COVID-19 during the last year.
Methods: Since February 2020 to February 2021, a total of 310 Hospitalizations, 163 adult patients were admitted in our Center for treatment of hematologic malignancies. The indication for admission was acute myeloid leukemia (AML) in 50 (30%) patients, acute lymphoblastic leukemia (ALL) in 14 (8%), lymphoma in 54 (33%), myeloma in 14 (8%), other 31 (19%). Diagnosis of SARS-CoV-2 infection was based on virus detection by real-time polymerase chain reaction (SARS-CoV-2 E-gene RT-PCR) in respiratory tract specimens. Standard preventive measures for SARS-CoV-2 infection control were applied to all patients care, accordance with National disease control and prevention guidelines.
Results: Ten (6%) patients tested positive for SARS-CoV-2 via PCR in a unique Covid-19 outbreak during hospitalization stay, and they were immediately transferred to Covid Infectious Unit. All these patients, were affected by Acute Leukemia (8 pts AML, 2 pts ALL ph negative), the majority of them was in peak of cytopenia at the Covid-19 infection time. Nine patients had been treated with intensive chemotherapy before SARS-CoV-2 confirmation. At SARS-CoV-2 diagnosis, only one patient had untreated, newly diagnosed AML; 3 patients had refractory/relapsed AML. One patient was in complete remission with incomplete hematologic recovery (CRi). Deep vein thrombosis complicated by pulmonary embolism and interstitial pneumonia was observed in a patients despite anticoagulation and in thrombocytopenia. After SARS-CoV-2 infection, no leukemia-specific treatment was adjusted. Three patients (30%) died due to severe acute respiratory distress syndrome (ARDS) despite extracorporeal membrane oxygenation (ECMO) in deep aplasia, all of them was in refractory disease. Seven patients delayed in chemotherapy treatment for a media of 34 days; chemotherapy started until COVID-19 symptoms have completely resolved and two viral testing becomes negative. However, these patients are still alive and maintained their complete remission, remaining for long-time negative for SARS-CoV-2. One patient underwent to bone marrow transplantation

ID	Age	Sex	Diagnosis	Time of Covid-19 infection	Covid-19 complications	Change or delay in the Hematological Treatment	Days delay	Deaths owing to Covid-19	Remission status after current therapy
1	82	M	AML	No yet treated	progressive respiratory failure	No treatment	Na	died owing to progressive respiratory failure before treatment could be started	Na
2	56	F	AML	in peak cytopenia post I consolidation	None	delay	60	no	RC
3	62	M	AML	Relapsed post I induction	progressive respiratory failure	Na	Na	died owing to progressive respiratory failure	Na
4	64	M	AML	in peak cytopenia post	Interstitial pneumonia	delay	30	no	RC
5	53	M	AML	in peak cytopenia post I induction	None	delay	10	no	In peak cytopenia after allo-BMT
6	67	F	AML	Relapsed post I induction	DVT-EP; Interstitial pneumonia	delay	30	no	RC;scheduled to allo-BMT
7	62	F	AML	in peak cytopenia post I consolidation	Interstitial pneumonia	delay	40	No	RC
8	66	M	ALL Ph-	in peak cytopenia post I consolidation	Interstitial pneumonia	delay	50	No	RC
9	21	M	ALL Ph-	RC post II consolidation	None	delay	20	No	RC
10	59	M	AML	Refractory to I induction	progressive respiratory failure	Na	Na	died owing to progressive respiratory failure	Na

AML: Acute myeloid Leukemia; ALL Ph-: acute lymphoblastic Leukemia Philadelphia negative. RC: Complete Remission, allo-BMT: allogeneic bone marrow transplant. DVT-EP: Deep vein Thrombosis-Embolism Pulmonary; Na: not applicable

Summary/Conclusion: Our findings support the vulnerability of patients with hematologic malignancies in the COVID-19 pandemic, and we reported a high COVID-19 infection mortality of 30%, in accordance with other hematological case series. However, deaths owing to Covid-19 were observed in patients in disease leukemia progression; furthermore, our recovered COVID-19 leukemia patients remained negative for SARS-CoV-2 after delivery of chemotherapy, and underwent to their following chemotherapy and allo-BMT program without any other complications.

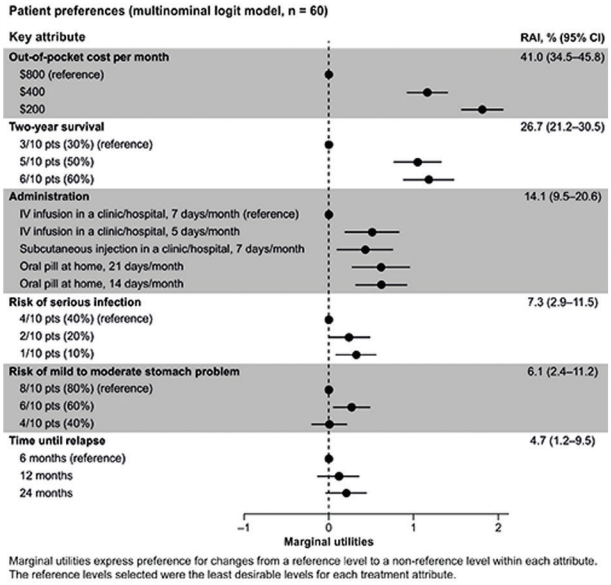
PB1398 PATIENT PREFERENCES FOR MAINTENANCE THERAPY OF ACUTE MYELOID LEUKEMIA: A DISCRETE CHOICE EXPERIMENT SUBANALYSIS OF PATIENTS IN GERMANY AND ITALY

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Background: In older patients (pts) with acute myeloid leukemia (AML), intensive chemotherapy can induce complete remission, but responses are often short and overall survival (OS) is poor after relapse. Azacitadine (AZA) maintenance therapies (MT) may improve disease-free survival in pts aged ≥60 years, but have not been shown to improve OS (Oliva EN, et al. ASH 2019; Huls G, et al. *Blood* 2019). In addition, AZA is given subcutaneously or intravenously (IV), resulting in a high administration burden and potential for infusion reactions. In the phase 3 QUAZAR AML-001 study, a novel oral formulation of AZA was the first MT to show a significant and clinically meaningful improvement in both OS and relapse-free survival (Wei AH, et al. *N Engl J Med* 2020). While oral AZA offers an effective MT option, little is known about the treatment preferences of pts with AML. We conducted a discrete choice experiment (DCE) survey of pts aged ≥55 years with AML in the USA, Canada, Germany, and Italy to assess the relative importance of key attributes of MT options (Tervonen T, et al. ASH 2020). Globally, pts placed the highest importance on survival probability at 2 years and were willing to accept reduced efficacy for the convenience of oral administration; this subgroup analysis explored the importance that pts in Germany and Italy placed on key factors.
Aims: To examine the relative importance of key attributes of MT among a subgroup of pts aged ≥55 years with AML from Germany and Italy.
Methods: An online DCE was conducted in the USA, Canada, Germany, and Italy between November 2019 and April 2020 to identify preferences for MT attributes among pts aged ≥55 years with AML. DCE data were analyzed using a multinomial logit (MNL) model. The MNL model estimated marginal utilities, which describe the relative value of changing from a reference to a non-reference level. The derived marginal utilities were used to calculate relative attribute importance (RAI), where higher values indicated larger effects on preferences. The 95% confidence intervals (CI) were estimated using a bootstrap algorithm over one thousand iterations.
Results: The survey was completed by 170 pts, including 30 from Germany and 30 from Italy. Among pts from Germany and Italy, mean age was 62.9 years and 67% were male. In all, 67% of pts had achieved remission at some point, 70% were diagnosed with AML >6 months

before survey completion, and 75% experienced ≥1 relapse event. The estimated MNL models revealed that pts most valued decreasing out-of-pocket cost from $800 to $400 or $200 (RAI = 41.0%, 95% CI 34.5–45.8) and increasing 2-year survival from 30% to 50% or 60% (RAI = 26.7%, 95% CI 21.2–30.5; Figure). Pts preferred therapies with oral administration once daily for 14 or 21 days per month, followed by IV administration 5 days per month, and subcutaneous injection 7 days per month, compared with IV administration in a hospital or clinic 7 days per month (RAI = 14.1%, 95% CI 9.5–20.6). Pt were least concerned about the treatment risks of serious infection, mild-to-moderate stomach problems, and unlike in the global population, time until relapse.



Marginal utilities express preference for changes from a reference level to a non-reference level within each attribute. The reference levels selected were the least desirable levels for each treatment attribute.

Summary/Conclusion: Consistent with findings from the global population, results from this subanalysis of pts from Germany and Italy aged ≥55 years with AML indicated that the most important clinical attribute of MT is improved 2-year survival. Lower out-of-pocket costs and the convenience of an oral pill were also valued. As there is no standard approach to treating AML after intensive chemotherapy, pt preferences should inform decision-making when selecting an MT.

PB1399 ACUTE PROMYELOCYTIC LEUKEMIA WITH PML-RARA: 10 YEARS EXPERIENCE OF A PORTUGUESE SINGLE CENTER.

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Background: Acute promyelocytic leukemia with PML-RARa (APL) is a subgroup of acute myeloid leukemia with a favorable prognosis after the advent of differentiation agents. The present standard of care for non-high risk APL is the chemo-free combination therapy of trans retinoic acid (ATRA) plus arsenic trioxide (ATO). These therapies comprise a specific toxicity profile.
Aims: Description of one center therapy experience. Comparison of outcomes and toxicities between two different treatment regimens.
Methods: A retrospective single-center study including all patients (pts) diagnosed with de novo APL between June/2010 and June/2020. Low and intermediate risk groups (low/int), according to the Sanz Risk Score, were analyzed together. Prior to 2017, the PETHEMA APL 2005 protocol (and 2012 update) was in use to all patients; from 2017 onwards, pts were progressively switched to the AML17 protocol. Early and late death refer to events occurring during the 30 days after diagnosis or later, respectively.
Results: We identified 32 pts with a median age at diagnosis of 46y (range 22-80y) and female predominance (n=20, 62.5%). The majority presented with bleeding (n=26, 81.3%) and had low/int risk criteria (n= 26, 81.2%).
High-risk group: 5 pts completed induction with ATRA+Idarrubicin (AIDA), 1 pt with ATRA in monotherapy. Low/int-risk group: until 2017, 11 pts (42.3%) completed induction with AIDA; after 2017, 10 pts (38.5%) were treated with ATRA+ATO; the remaining 5 pts (received only ATRA or ATO in monotherapy (and 1 pt wasn't treated) due to early complications.
All pts evaluated at the end of the induction cycle (n=27) met complete hematologic response criteria (CHR). Pts received consolidation and maintenance therapy according to the established protocols with the exception of 7 pts due to complications during treatment (n=5 AIDA, n=2 ATRA+ATO).
The main toxicities observed in our sample and their management are reported in Table 1.
With a median follow-up time of 35 months (52.4 and 19.8 months in AIDA and ATRA+ATO, respectively), the median overall survival was 32 months (51.5 and 22 months in AIDA and ATRA+ATO, respectively) and the overall mortality rate was 25% (n=8). Four of the above pts were undertreated (3 early deaths and 1 late death) and the remaining 4 pts were treated according to the AIDA protocol (1 early death and 3 late deaths; n=3 int/low and n=1 high risk). Five pts relapsed (4 in the AIDA group and 1 in the ATRA+ATO), with a median time to relapse of 13 months. Four of these pts were rescued (n=2 ATRA+ATO; n=1 ATO monotherapy; n=1 AIDA) and consolidated with autologous stem cell transplantation and remain in molecular response.

Table 1: Treatment Related Toxicities

	Total	AIDA	ATRA+ATO	ATO	ATRA
Number	31	16 (51,6%)	10 (32,3%)	2 (6,4%)	3 (9,7%)
Treatment related toxicities - Description and Management					
Infections	18 (58,1%)	14 (87,5%)	0	1 (50%)	3 (100%)
Transitory Withdrawal	2/18 (11,1%)	2/14 (14,3%)		0	0
Permanent Withdrawal	4/18 (22,2%)	4/14 (28,6%)		0	0
Death	5/18 (27,7%)	2/14 (14,3%)		0	3/3 (100%)
Differentiation Syndrome	13 (41,9%)	8 (50%)	2 (20%)	1 (50%)	2 (66,7%)
Transitory Withdrawal	5/13 (38,5%)	2/8 (25%)	0	1/1 (100%)	2/2 (100%)
Hepatotoxicity	5 (16,1%)	0	3 (30%)	1 (50%)	0
Transitory Withdrawal	2/5 (40%)		1/3 (33,3%)	1/1 (100%)	
QTc interval extension	2 (6,4%)	0	2 (20%)	0	0
Transitory Withdrawal	1/2 (50%)		1/2 (50%)		
Permanent Withdrawal	1/2 (50%)		1/2 (50%)		
Pericarditis	1 (3,2%)	0	1 (10%)	0	0
Permanent Withdrawal	1/1 (100%)		1/1 (100%)		
Dermatotoxicity	3 (9,6%)	1 (6,3%)	1 (10%)	1 (50%)	0
Transitory Withdrawal	2/3 (67,7%)	1/1 (100%)		1/1 (100%)	

ATRA: All-Trans Retinoic Acid; ATO: Arsenic Trioxide; AIDA: ATRA + Idarrubicin

Summary/Conclusion: We present the real-life experience of one small center in the management of APL across a long and changing period. We underline the inclusion of undertreated pts due to comorbidities and early life-threatening complications. We confirmed the differences in toxicity profiles of chemotherapy-based and -free regimens, with infections in almost all pts in the AIDA group and hepatotoxicity and cardiac complications in a substantial part of the ATRA+ATO treated pts. Both regimens induced CHR in all pts post-induction, but we observed a trend for higher relapse risk in the AIDA group, at least partially explained by the short follow-up and low number of pts in the ATRA+ATO group.

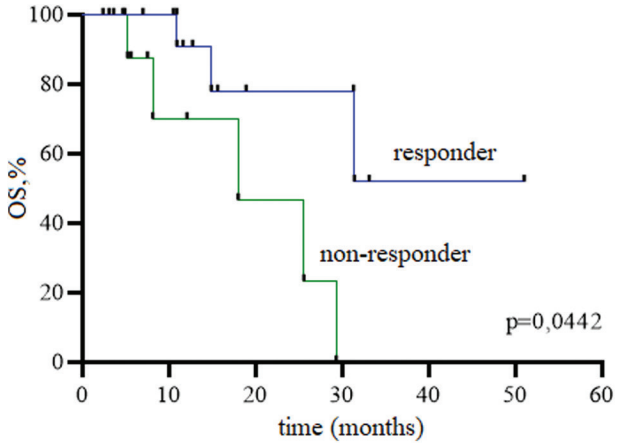
PB1402 EFFICACY AND SAFETY OF GEMTUZUMAB IN RELAPSED AND REFRACTORY AML IN REAL WORLD PRACTICE

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Background: ALFA group and some others have shown gemtuzumab (GO) to be effective in low risk acute myeloid leukemia (AML). However, limited data on GO efficacy are available in relapse/refractory (R/R) setting outside clinical trials.
Aims: To assess the efficacy and safety of GO in combination with chemotherapy "FLAG+/-Ida" and azacitidine in patients with R/R AML in real clinical practice.
Methods: The study included 32 patients (16 male, 16 female patients, median age–44 years (23-83 y.o.)). 46,8% (15/32) with refractory and 53,2% (17/32) with relapsed AML. 46,8% (15/32) patients received "GO-FLAG+/-Ida", 53,2% patients (17/32) received "GO-azacitidine". "GO-azacitidine" was given to patients unfit for intensive chemotherapy (advanced age, low somatic status, relapse or refractoriness to high-dose chemotherapy). 19 (59,3%) patients underwent the BMT subsequently.
Results: ORR (CR, CR_{MRD-}; CRi, MFLS) was 59,4% (19/32). Early mortality was 9,4 % (3/32). OR rate was not associated with expression of CD33 (p=0,452), gender (p=0,6), age (p=0,145), prognostic risk group (p=0,646), number of previous lines (p=0,482), number of relapses

(p=0,489). 80% patients, refractory to FLAG, achieved a response after "GO-azacitidine" with subsequent BMT. Non-eligible for high-dose chemotherapy patients obtained "GO-azacitidine" regimen. 66,6% of them improved their somatic status and subsequently undergone BMT. 1 of 2 patients with a relapse after high-dose chemotherapy achieved a response, BMT was performed in 2 patients. The rate of toxicity was not significantly different between the groups. No cases of VOD were reported. The rate of infusion-related complications was 46,7% (7/15) (40%>grade 1-2, 6,7%>grade 3) in the "GO-FLAG+/-Ida" group and 35,3% patients (6/17) (29,4%>grade 1-2, 5,9%>grade 4) in the "GO-azacitidine" group. SAEs were reported in 33,3% patients in the "GO- FLAG+/-Ida" group, with 100% having sepsis, and 35,3% in the "GO-azacitidine" group (66,6%>sepsis, 16,7%>acute cardiovascular failure, 16,7%>acute respiratory). No significant difference was observed in grade 3-4 neutropenia between the groups. The duration of thrombocytopenia was higher in patients who received GO in combination with "FLAG+/-Ida", however, no significant differences were observed. The median of OS was 31,4 months, the median of RFS was 13,3 months. The median of OS was 31,4 months, the median of RFS was 13,3 months. OS was higher in the group of patients responded to therapy than in non-responder to therapy (median not achieved versus 17,97 months, respectively, p=0,044) (Fig. 1).



Summary/Conclusion: The combinations GO with FLAG/FLAG-Ida and azacitidine have shown to be effective regimen in patients with relapsed and refractory AML. The remission rate did not depend on the risk group, gender, age, CD33 expression, number of previous lines of therapy, number of relapses. "GO-azacitidine" demonstrated efficacy and tolerability in patients, refractory to high dose chemotherapy and in patients with poor performance status, enabling some patients to proceed to the BMT. The rate of toxicity, the duration of blood levels recovery was not statistically different between the groups, however, there was a higher duration of thrombocytopenia in "GO-FLAG+/-Ida" group. There was a higher OS in the GO responders in contrast to non-responders.

PB1403 EVALUATION OF MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA PATIENTS TREATED WITH HYPOMETHYLATING AGENTS: A REAL WORLD EXPERIENCE

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Background: Hypomethylating agents (HMAs), azacitidine and decitabine, are a standard of care in high risk myelodysplastic syndromes (MDS) and in acute myeloid leukemia (AML) patients ineligible for intensive therapy. The clinical activity of HMAs in myeloid neoplasms has been firmly established now, but still remains limited in the real world especially in terms of using after failure of the first HMA.
Aims: In this study, it was aimed to evaluate the clinical and laboratory characteristics of patients with MDS and AML who were treated with HMAs, as well as their treatment responses and factors affecting prognosis.
Methods: A hundred and twenty patients, over the age of 18 who were diagnosed AML or MDS according to WHO 2008 diagnostic criteria between August 2010 and February 2020 and received at least 4 cycles of HMA were included in the study. The data was collected retrospectively.
Results: Seventy four (61.7%) of patients were male and 46 (38.3%) were female. The diagnosis was MDS in 63 (52.5%) and AML in 57 (47.5%) of patients. The mean age at the time of diagnosis was 69.9 ± 12 years. Sixty four (53.3%) of the patients received only azacitidine, 8 (6.7%) only decitabine, and 48 (40%) azacitidine and decitabine consecutively. When we compared the laboratory findings before and after HMA treatment, there was an improvement in hemoglobin level, white blood cell, neutrophil, platelet and blast counts (p<0.05). The need for red blood cell and platelet suspensions during HMA treatment was significantly higher than the pre-treatment period (p <0.001). While febrile neutropenia (FN) developed in 96 (80%) of the patients totally, FN developed in 75 (66.9%) of 112 patients who received azacitidine and in 49 (87.5%) of 56 patients who received decitabine. Complete response, partial response or hematological recovery was detected in 63 (52.5%) of the patients. Relapse or progression developed in 81 (67.5%) patients. Response rates were similar in patients with AML and MDS (p=0.48). FN and relapse or progression were significantly higher in AML patients (p = 0.007 and p = 0.03). Survival in MDS was longer than AML patients (17.2±9 vs 12±6.7 months, p = 0.003).
Single cox-regression analysis revealed that mortality risk was 2.2 times higher in AML patients compared to MDS (HR=0.45, p=0.01, 95% CI 0.28–0.73). High blast ratio in flow cytometry before treatment, presence of poor risk cytogenetic before treatment, high blast ratio in flow cytometry after treatment, high blast ratio in post-treatment bone marrow biopsy, poor risk cytogenetic after treatment, increased number of platelet suspensions before treatment, presence of FN, length of hospitalization, no response to treatment and presence of relapse / progression were poor prognostic in terms of survival.
Multiple cox-regression analysis revealed that the mortality risk in AML patients was 2.39 times higher than MDS patients (p = 0.03, 95% CI 1.04--5.5). Those with a higher pre-treatment platelet suspension replacement and those who had FN had a higher risk. The mortality decreased as the number of azacitidine cycles increased (HR = 0.9, p = 0.002 (95% CR 0.84-0.96).
Summary/Conclusion: In conclusion, response rates are similar in AML and MDS treated with HMAs. Although FN and relapse/progression are higher, and survival is shorter in AML, HMAs are effective in MDS and AML patients witha response rate of 52.5%.

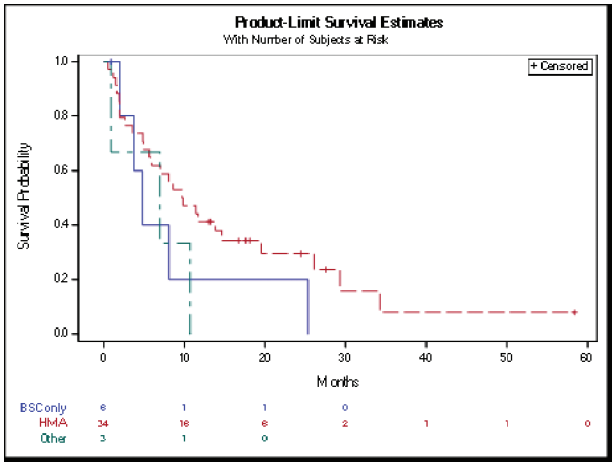
PB1404 REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES IN UNFIT PATIENTS WITH AML RECEIVING FIRST LINE SYSTEMIC TREATMENT OR BEST SUPPORTIVE CARE (CURRENT): A BELGIAN SUBANALYSIS

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Background: Acute myeloid leukemia (AML) is a disease affecting older patients with a median age of 67 years. Because of age, comorbidities and unfavorable cytogenetics, older patients are frequently not eligible to the standard 7+3 induction chemotherapy combining aracytine and an anthracycline. Their survival remains poor.There is a growing need to better understand the current treatment patterns and their associated outcomes since the field of AML is evolving with the emergence of newer agents.
Aims: To describe treatment patterns and clinical outcomes including survival and remission rates, clinic-pathological characteristics and healthcare resource utilization of AML patients who are unfit to receive intensive chemotherapy in the Belgian real world clinical practice.
Methods: This retrospective chart review was conducted in 6 centers across Belgium. Adult patients who were deemed ineligible for intensive chemotherapy and that have started a systemic treatment or best supportive care between 1st of January 2015 and 31th of December 2018 in the first line setting were included. Patients were followed until death or last recorded contact, whichever came first at time of data collection. Primary objective was to evaluate the overall survival of these patients in the real-world setting. Secondary objectives included but were not limited to progression free survival, time to treatment failure and healthcare resource utilization.
Results: In this Belgian sub analysis, 43 patients were included (65% male, 35% female and 65% >75 years old) of whom 37 (86%) received systemic treatments (29,7% azacitidine, 62,2% decitabine and 8,1% other systemic treatment) and 6 (14%) received Best supportive care including transfusions, pain relief and infection management. Median OS in the overall population was 8,5 months (respectively 9,76 months, 6,74 months and 4,77 months in patients who were treated with hypomethylating agents, other systemic treatment, or best supportive care). A CR/CRI was achieved in 29% of the patients who received systemic treatment, median time to best response was 129,5 days, median duration of the complete response was 458,5 days. During the first

course of systemic treatment 34/37 patients were hospitalized due to treatment administration-related (45,5%) and infections (38,1%).



Summary/Conclusion: This Belgian sub analysis of the real-world study shows that OS and CR/CRi rates reported are consistent with previous clinical trials but that outcomes for this patient population remain poor. Future combination therapies with HMA or new agents will hopefully improve their outcome.

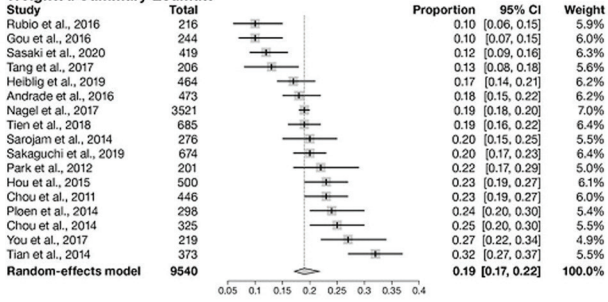
PB1405 FREQUENCY OF FLT3-ITD AND FLT3-TKD MUTATIONS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Background: There is a range of estimates for the frequency of *FMS*-like tyrosine kinase 3 (*FLT3*) mutations in patients with acute myeloid leukemia (AML) in the literature, but no available systematic review on this topic.
Aims: To provide a comprehensive review of the *FLT3* mutation frequency in unselected populations of patients with AML.
Methods: We conducted systematic literature searches of the Medline/PubMed and Embase databases through 31/08/2020. Search terms were "acute myeloid leukemia," "AML," "fms like tyrosine kinase 3," and "FLT3" combined with "epidemiology," "incidence," "prevalence," "frequency," "presentation," and "occurrence." There were no limits on publication year. Full-text English-language papers of studies with ≥200 total patients were selected. Only studies reporting data for both the *FLT3*–internal tandem duplication (*FLT3*-ITD) mutation and *FLT3*–tyrosine kinase domain *(FLT3*-TKD) point mutation, study location (country), population source (eg, hospital or medical center), data collection dates, age range, sex distribution, and a description of *FLT3* mutation test methodology were included. Animal studies, in vitro studies, case reports, commentaries, reviews, and clinical trials were excluded. Using meta-analysis methods, weighted summary estimates and confidence intervals (CIs) were generated for each *FLT3* mutation from untransformed data.
Results: Of 1,618 records identified, 17 studies were included (16 hospital or medical center cohort studies, one cross-sectional study). Studies were conducted in Asia, Europe, South America, or North America with data collection dates ranging from 1994 through 2018. Sample sizes for the 16 cohort studies ranged from 201 to 685 total patients; the cross-sectional study included 3,521 patients. Across studies, 46.8% to 60.0% of participants were male. One study included only children (aged 0-17.9 years [Rubio 2016]), two studies included children and adults (aged 1-84 years [You 2017]; 0-21 years [median: 7 years] [Andrade 2016]), and 14 studies included patients aged ≥15 years. All studies reported using a polymerase chain reaction (PCR)–based test to identify the mutations; some studies reported also using additional methods (gene sequencing, fluorescence fragment analysis). Across the 17 studies, the frequency of FLT3-ITD mutation ranged from 10.2% to 31.6% (Figure), and the frequency of FLT3-TKD mutation ranged from 1.9% to 8.8% (not shown). These ranges were unchanged when the three studies with patients aged

Figure. Proportion of AML Patients With the *FLT3*-ITD Mutation Across 17 Studies, Weighted Summary Estimate



Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; *FLT3*-ITD, *FMS*-like tyrosine kinase 3 gene internal tandem duplication.

Summary/Conclusion: We conducted a comprehensive systematic review of the frequency of the *FLT3* mutation in unselected populations of patients with AML. The results suggest a population frequency of around 19% for a *FLT3*-ITD mutation and 5% for a *FLT3*-TKD mutation. Further research is needed to help explain the heterogeneity in the frequency of the *FLT3* mutation across populations, and to put these results into context (including comparison with selected populations, such as in clinical trials).

PB1406 EUROPEAN GUIDELINES AND REAL-WORLD EVIDENCE OF MAINTENANCE TREATMENTS FOR ADULTS WITH ACUTE MYELOID LEUKEMIA IN FIRST COMPLETE REMISSION

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Background: Standard treatment with chemotherapy of patients with acute myeloid leukemia (AML) can induce remission; however, despite previous evaluation in clinical trials, maintenance/post-remission therapy is currently not a standard approach in the treatment of AML. Variation in therapy approval, reimbursement, and clinical practice may influence regional differences across Europe. Currently, recommendations from European organizations on maintenance therapy lack consistency, and the use of maintenance in the real-world setting in Europe is poorly understood.
Aims: Identify European guideline recommendations and real-world evidence on the use of maintenance/post-remission therapy for adult patients with AML who had achieved complete remission after intensive chemotherapy induction.
Methods: Two targeted literature reviews were conducted by an information specialist via database searches of MEDLINE® and EMBASE using controlled vocabulary (eg, "leukemia, myeloid, acute") and keywords (eg, "observational study" and "retrospective"); search results were not limited by language, region, or publication year. Additionally, literature searches of region-specific hematology conferences were conducted to identify unpublished treatment guidelines and real-world studies. Webpages of European health ministries were also searched for treatment guidelines. Identified records were reviewed at the title/abstract and full-text levels, with relevant information from included studies extracted.
Results: In total, for treatment guidelines, 116 records were identified from database searches and 13 from supplementary searches. For real-world studies, 482 records were identified from database searches. After screening, 14 records were included in the review of guidelines (3 pan-European, 11 region-specific) and 5 studies were included in the review of real-world studies (all limited to conference abstracts in 2010–2019, with no full publications identified; locations: 2 in Spain, 1 each in Russia, the UK, and Italy). Guidelines regarding induction and consolidation with chemotherapy were consistent, but recommendations for maintenance therapy varied (recommended [n = 7], not recommended [n = 5], and no guidance [n = 2]). In the guidelines that recommended maintenance therapy, the most common therapy was midostaurin (n = 4). Other therapies included azacitidine (n = 1) and histamine dihydrochloride (n = 1); notably, 2 guidelines recommended use of post-remission maintenance therapy, but the therapy was not specified. For the real-world studies, all 5 studies evaluated the efficacy of maintenance with injectable azacitidine (**Table**). Overall, the design of studies was heterogenous with limited sample size (range: n = 3–24), with only one study providing a direct comparison of treatment effects between maintenance options (injectable azacitidine maintenance vs no maintenance). Reported outcomes varied across studies, with survival at study follow-up and relapse rates being the most frequently reported. In the largest study (n = 24), the

relapse rate (at 10 months) with azacitidine maintenance was 17% (n = 2/12) vs 67% (n = 8/12) with no maintenance.

Summary of real-world studies evaluating maintenance with injectable azacitidine

Patient population (N)	Maintenance therapy details	Outcomes
Girshova L, et al. *Clin Lymphoma Myeloma Leuk* 2019;19(suppl 1):S204		
• AZA maintenance (n = 12) or no maintenance (n = 12)	• AZA, subcutaneous, 75 mg/m^2	• Median RFS (AZA vs non-AZA): NR vs 8.7 mo • Relapse rate (at 10 mo; AZA vs non-AZA): 2/12 vs 8/12
Shah V, et al. *Haematologica* 2014;99:619		
• AZA maintenance (n = 2)	• "5-day AZA regimen", RoA unspecified	• Discontinuation from maintenance: 100%
De La Fuente A, et al. *Haematologica* 2011;96:479		
• AZA maintenance (n = 5)	• AZA, RoA and dose unspecified	• Mean OS of 2 patients that died: 22.9 mo
Loseto G, et al. *Haematologica* 2011;96:195		
• AZA maintenance (n = 3)	• AZA, 75 mg/m^2/d, RoA unspecified	• CR maintained for all 3 patients (4–12 cycles) • AEs: Gr 3 hematologic toxicity (n = 2); gr 4 neutropenia (n = 1)
Hernandez Vazquez H, et al. *Haematologica* 2010;95:564-565		
• AZA maintenance (n = 6)	• AZA, 75 mg/m^2/d, RoA unspecified	• Alive and transfusion-independent at 9 mo: 66%

AE, adverse event; AZA, azacitidine; CR, complete remission; d, day; mo, month; gr, grade; NR, not reported; RFS, relapse-free survival; RoA, route of administration

Summary/Conclusion: There is a lack of consistency in recommendations for maintenance therapy across European guidelines, and very limited evidence exists in the published literature on the use of maintenance after first complete remission in the real-world setting, thereby highlighting an unmet need in the treatment of AML.

PB1407 PEVOLAM: TRIAL DESIGN FOR A RANDOMIZED PHASE 3 MULTICENTER STUDY COMPARING AZACITIDINE PLUS PEVONEDISTAT VS AZACITIDINE IN OLDER OR UNFIT PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

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Background: Despite recently approved treatment options, outcomes remain poor in patients (pts) with acute myeloid leukemia (AML) who are older or unfit for intensive chemotherapy. Pevonedistat (PEVO) is a first-in-class small-molecule inhibitor of the neural-precursor-cell-expressed developmentally down-regulated protein 8 (NEDD8)-activating enzyme (NAE), an enzyme that targets critical regulatory proteins for degradation. NAE inhibition interferes with protein homeostasis, leading to cancer-cell death. The combination of PEVO+AZA has shown synergistic antitumor activity in some AML cell lines *in vitro*. PEVO has also shown encouraging clinical efficacy in combination with AZA with a similar safety profile to that of AZA alone with no added myelosuppression. In a randomized, phase 2 trial (NCT02610777), median OS trended longer with PEVO+AZA compared with AZA alone (23.6 versus 16.0 months, respectively; P = 0.081) in pts with low-blast AML (N = 36).
Aims: The primary objective of this trial (NCT04090736) will be to evaluate if PEVO+AZA improves OS compared with AZA alone in treatment-naive pts with AML who are ineligible for standard induction chemotherapy. Key secondary objectives will be event-free survival (EFS) and the proportion of pts achieving composite complete remission when treated with PEVO+AZA (arm A) versus AZA alone (arm B). Pt reported outcomes and centralized minimal residual disease will be analyzed.
Methods: This phase 3, prospective, randomized (1:1), open-label study conducted at 62 sites in Spain will compare PEVO+AZA versus AZA alone. The planned sample size of 466 pts (233 pts in each treatment arm) is estimated to be enrolled within 24 months. An additional follow-up of 22 months after the accrual will be needed to obtain a total of 386 OS events. This will provide 80% power to detect a statistically significant difference in OS between the two treatment arms under the assumption of a hazard ratio of 0.75. An interim analysis of OS will be performed after 75% of death events have occurred. Pts in arm A will receive PEVO 20 mg/m^2 intravenously on days 1, 3 and 5 plus AZA 75 mg/m^2 subcutaneously on the 5-on/2-off (weekend)/2-on schedule in a 28-day cycle. Pts in Arm B will receive AZA 75 mg/m^2 on the 5-on/2-off (weekend)/2-on schedule in a 28-day cycle. Eligible pts include adults with newly diagnosed AML who have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≤ 3 and are not eligible for intensive chemotherapy (≥ 75 years of age, or ≥ 18 years of age with comorbidities that preclude intensive chemotherapy [e.g., renal, cardiac, or hepatic dysfunction, or ECOG PS of 2 or 3]). Pts with secondary AML are also eligible for inclusion. Exclusion criteria include white blood cell count ≥ 25 × 10^9/L, previous treatment for myelodysplastic syndrome or chronic myelomonocytic leukemia or myeloproliferative neoplasm, with chemotherapy or other antineoplastic agents including up to two cycles of hypomethylating agents. An independent data monitoring committee will review safety and efficacy data.
Results: N/A
Summary/Conclusion: Since September 2019 and throughout the coronavirus pandemic, 187 pts were recruited; recruitment is ongoing. Given its novel mechanism of action and non-myelosuppressive safety profile, data from this trial may support the use of PEVO as an additional combination therapy partner for pts with AML to improve survival outcomes while preserving QoL.

PB1408 PHASE 1/2 FIRST IN HUMAN STUDY OF THE MENIN-KMT2A (MLL) INHIBITOR KO-539 IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

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Background: The histone-lysine-*N*-methyltransferase 2A (*KMT2A*) gene (formerly known as mixed-lineage leukemia (*MLL*)) plays an essential role in regulating gene expression including that of *MEIS1* and the homeobox gene family, which are known to be important for maintenance of leukemia when dysregulated. In 5-10% of acute myeloid leukemia (AML) cases, specific *KMT2A* gene perturbations can occur which result in an aggressive and poor prognosis. The Menin-KMT2A complex also appears to play a central role in the epigenetic dysregulation in AMLs with co-mutations in genes such as *NPM1*, *IDH1/2*, *FLT3*, *EZH2*, and *DNMT3A*, with *NPM1* mutation accounting for 25-30%. Therefore, there is strong rationale for targeting these AML subsets, which may be exquisitely sensitive to the menin-KMT2A complex inhibition.
Aims: The objectives of the Phase (Ph) 1 dose escalation are to assess safety and tolerability, characterize the pharmacokinetics (PK), determine a recommended Ph2 dose (RP2D), and investigate early signs of anti-leukemic activity. The Ph1 expansion cohorts will assess anti-leukemic activity, PK, safety and tolerability in AML pts with *NPM1* mutation or *KMT2A* rearrangement at doses that have already met the safety threshold to help determine a minimally safe and biologically effective dose. Once a RP2D has been determined, Ph2 expansion cohorts including AML pts with *NPM1* mutation or *KMT2A* rearrangements will be conducted to assess safety, tolerability and efficacy at the RP2D.
Methods: KO-539 is a novel, once daily, oral investigational drug candidate targeting the menin-KMT2A protein-protein interaction.

KOMET-001 (NCT04067336) is an ongoing Ph1/2 open-label study evaluating KO-539 in adult patients (pts) with relapsed or refractory (R/R) AML. Key inclusion criteria include: R/R AML defined as the appearance of > 5% blasts in the bone marrow and who have failed or are ineligible for any approved standard of care therapies, including transplant, ECOG performance status of 0 to 2, and adequate organ function. Key exclusion criteria include: pts with acute promyelocytic leukemia or chronic myelogenous leukemia in blast crisis, clinically active central nervous system leukemia, pts who have undergone transplant and have not had adequate hematologic recovery or with Grade >2 active graft-versus-host disease issues, or pts on concomitant drugs that are strong inhibitors or inducers of CYP3A4 except for antibiotics, antifungals, and antivirals. All pts are being followed for safety during treatment and up to approximately 28 days after treatment discontinuation, or until immediately before the initiation of another anticancer therapy, whichever occurs first. Anticipated efficacy assessment will include assessment of: complete remission (CR) plus complete remission with partial hematologic recovery (CRh) composite; CR with and without minimal residual disease (MRD), and duration of remission (DOR) as key secondary endpoints. Additional anticipated assessments in the expansion cohorts will include transfusion independence, relapse-free survival (RFS), and overall survival.
Exploratory biomarkers will be examined in bone marrow biopsies/aspirate as well as peripheral blood collected serially from all pts pre- and post-treatment.
KOMET-001 is continuing to enroll pts in dose escalation and, in parallel, will be enrolling Ph1 expansion cohorts in genetically defined populations to better inform the RP2D. This will be followed by the Ph2 expansion portion in genetically defined populations once a RP2D is determined.
Results: N/A (trial in progress)
Summary/Conclusion: N/A (trial in progress)

PB1409 CPX-351 IN THERAPHY RELATED ACUTE MYELOID LEUKEMIA AND ACUTE MYELOID LEUKEMIA WITH MYELODYSPLASIA-RELATED CHANGES: A MULTICENTER REAL-LIFE EXPERIENCE IN YOUNG PATIENTS (<60 YEARS OLD)

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Background: Therapy-related acute myeloid leukemia (t-AML) and AML with myelodysplasia-related changes (AML-MRC) are two AML subtypes with very poor prognosis. The CLTR0310-301 study showed survival advantages in favour of CPX-351 compared to "7+3" in newly diagnosed t-AML or AML-MRC, 60-75 years old.
Aims: To explore the efficacy of CPX-351 in younger patients in a real-life setting.
Methods: Since September 2019 we treated 9 patients with CPX-351, with a median age of 51 (range 32-59) and ECOG range 0-2. Our cohort consisted in 6 patients with MRC-AML, 2 patients with t-AML and 1 patient with t-AML after a therapy-related myelodysplastic syndrome (t-MDS). 2 patients (both with AML-MRC) harboured *FLT3*-ITD (Allelic Ratio 0.1), 1 patient *IDH1* and 1 patient *TP53* mutation. 4 patients had a complex karyotype and 2 patients had received prior treatment with hypomethylating agents (HMA).
Results: All patients underwent induction therapy with intravenous administration of CPX-351 at day 1, 3 and 5 except 1 patient who received just two doses due to pneumonia outbreak. One patient developed a right upper limb lesion, initially with phlebitic appearance and then with necrotic evolution. He eventually died due to severe pneumonia. Eight out of 9 patients were evaluable at the end of treatment. Disease re-evaluation was performed on average 42 days since induction therapy start. Four patients reached a complete remission (CR) and 1 patient a CR with incomplete haematological recovery (CRi), with 63% overall response rate (ORR). One patient showed a partial remission (PR), while 2 patients were refractory. Median days of severe neutropenia (defined as neutrophils lower than 500/uL) were 31. Median days of severe thrombocytopenia (defined as platelets lower than 20.000/uL) were 25. The patient in PR, who was *FLT3* mutated, underwent reinduction, with administration of CPX-351 in day 1 and 3, obtaining a CR. Three patients completed both consolidation cycles and underwent bone marrow transplantation. One patient, who was *IDH1* mutated, received just one consolidation cycle before transplant and 1 patient was transplanted immediately after induction. A 46 years old patient in CR after induction relapsed after 5 months being off therapy due to a fungal infection whose treatment required a long period of hospitalization to carry out targeted antifungal therapy. Given the CR achieved and the high infectious risk highlighted during induction, the patient did not carry out any consolidation cycle while waiting for transplant. The 2 refractory patients, who both showed complex karyotype and one of them was *TP53* mutated, were switched to other regimens.
Summary/Conclusion: We found that CPX-351 is active in young patients with t-AML and AML-MRC with a rate of ORR higher than that reported in the pivotal study (63% vs 47%). This improvement be explained by the fact that younger patients better tolerate chemotherapy and its complications. Complex karyotype and *TP53* mutation confirmed their role as negative prognostic factors, while better prognosis was observed for *FLT3* and *IDHs* mutated patients although numbers are too small to drive full conclusions. With this therapy we were able to bridge 5 out of 8 (62%) evaluable candidate patients to HSCT. Regarding the safety profile, the most frequent complication was febrile neutropenia (60%), successfully managed with supportive therapy. In conclusion, our results are in line with those reported by other institution real-life data in patients <60 years.

PB1410 IDENTIFYING LEUKEMIA-ASSOCIATED IMMUNOPHENOTYPES IN ACUTE MYELOID LEUKEMIA PATIENTS USING MULTIPARAMETER FLOW CYTOMETRY

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Background: Acute myeloid leukemia is nowadays considered the most common acute leukemia in adults and the most common cause of leukemia-associated mortality in adults. Being a heterogeneous disease, patients can achieve complete hematological remission with bone marrow blasts <5% by intensive chemotherapy, but will eventually relapse due to the persistence of leukemic cells after chemotherapy unidentified by routine morphologic evaluation which is known as minimal residual disease.
Aims: To identify leukemia-associated immunophenotypes in sixty acute myeloid leukemia patients at diagnosis using an eight color multiparameter flow cytometry panel and to detect if they showed any alteration in relapse/refractory cases.
Methods: Eight color multiparameter flow cytometry panel with CD45/SSC log gating strategy was used for analysis of leukemia-associated immunophenotypes in bone marrow samples obtained from sixty consecutive, unselected acute myeloid leukemia patients presenting to Alexandria University Hospitals at diagnosis, relapse and refractory cases. Twenty bone marrow samples from patients performing bone marrow aspirate for non-malignant hematological indications and twenty regenerative bone marrow samples from acute lymphoblastic leukemia patients on chemotherapy in follow up of matched age and sex were included as controls.
Results: Leukemia-associated immunophenotypes were observed in 53 cases (88.3%). Only one aberrant immunophenotype was identified in five cases (8.3%), while two to twelve aberrant immunophenotypes were found in the other 48 cases (80%). *Strong leukemia-associated immunophenotypes* were obtained by the combination of CD2, CD4, CD56 with either CD34 or CD117, in contrast to CD19 which has to be combined with CD117. Refractory cases showed the presence of same leukemia-associated immunophenotypes at both initial diagnosis and persistent disease, while one of the relapsed cases showed acquisition of new leukemia-associated immunophenotypes after relapse.
Summary/Conclusion: The good choice of leukemia-associated immunophenotypes depends on their specificity rather than their frequency. The results of this study can help in increasing the sensitivity of leukemia-associated immunophenotypes strategy in minimal residual disease using multiparameter flowcytometry in acute myeloid leukemia patients which is considered an important post-diagnosis parameter associated with prognosis and clinical outcome.

PB1411 JUVENILE MYELOMONOCYTIC LEUKEMIA IN A PATIENT WITH NOONAN SYNDROME AND FAMILIAL MEDITERRANEAN SYNDROME

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Background: We report a female patient of Armenian origin initially suspected with myelodysplastic syndrome of unknown origin at the age of 8 y.o based on initial analysis of the bone marrow described also with abnormal hemoglobin, anemia and neutropenia. However, the clinical picture was also characterized with periodic fevers accompanied with joint and thoracic pains starting from the age 5 y.o. Later, the patient was described with splenomegaly and hepatomegaly. No familial case was reported. Further, she developed a swelling of the feet with pain, exudative pneumonia, general weakness and loss of weight.
Aims: The lack of clinical diagnosis for treatment required performance of the differential complex examinations, including the cellular immunophenotyping, cytogenetic, and whole genome analyses.
Methods: The analysis of human cluster of differentiation (CD) antigens the patient's bone marrow was analyzed by flow cytometry analysis capturing 30 human CDs. Molecular cytogenetic analysis was performed by FISH method on the patient's bone marrow cells for the detection of the major seven cytogenetic aberrations related to leukemias. Whole Exome Sequencing (WES) of the patient's DNA extracted from the peripheric leukocytes on a MiSeq platform.
Results: Immunophenotyping analysis detected less than 7% of blast cells in the bone marrow which antigen spectrum (CD7, CD11a, CD11c, CD13, CD33, CD34, CD45, CD64, CD117, CD123, and HLA-DR) confirmed its relation to acute myeloid leukemia. Molecular cytogenetic analysis did not find any cytogenetic aberration in the bone marrow. However, the WES detected two pathogenic variants in two genes: a heterozygous variant c.214G>A (p.Ala-72Thr) in the PTPN11 gene which is associated with developmental and lymphatic dysplasia and a heterozygous variant c.2080A>G (p.Met694Val) in the MEFV gene which is associated to hereditary autoinflammatory syndromes. De novo status of the detected PTPN11 variant was confirmed by parental testing. Detection of the heterozygous state of the PTPN11 variant with frequency of 40% is compatible with both germline and mosaic states.
Summary/Conclusion: The WES result was compatible with a genetic diagnosis of the autosomal-dominant Noonan syndrome type 1 and/or the predisposition to juvenile myelomonocytic leukemia caused by somatic PTPN11 variants. Further physical examination of the patient did describe several features characteristic to the Noonan syndrome, including the short stature, chest abnormality, hypertelorism, as well as facial and developmental features of variable degree. Pathogenic somatic variants in the PTPN11 gene are associated with juvenile myelomonocytic leukemia. Leukemias occurring in the absence of any other finding of Noonan syndrome could harbor somatic PTPN11 variants, particularly in children with myelodysplastic syndrome. The latter is indeed more specific in case of excess of blast cells in acute myeloid leukemia with poor prognosis. Therefore, more detailed physical and phenotypic characterization of the patient at the initial state of the disease could support to the suspicion of the rare genetic syndrome of DNA reparation system associated with oncological features. The heterozygous MEFV pathogenic variant common in the Armenian population is the strongest pathogenic variant in patients with Familial Mediterranean Fever (FMF). Despite FMF is an autosomal recessive disorder, less than 10% of cases are described with only one MEFV mutation. Thus, several clinical features of the patient not specific to the myelomonocytic leukemia are explained with accompanied autoinflammatory condition.

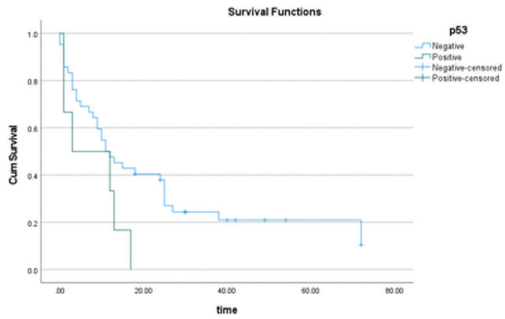
PB1412 IMPACT OF P53 AND BCL2 EXPRESSION ON PROGNOSIS IN PATIENTS WITH ACUTE MYELOID LEUKAEMIA: A TEN YEAR SINGLE CENTRE STUDY

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Background: Acute myeloid leukaemia (AML) is a heterogenous disorder that arises from clonal expansion of malignant haematopoetic precursor cells. Somatic mutations of the tumour suppressor p53 gene have been reported in 5-10% of all patients with AML, although the incidence is higher in therapy-related disease and elderly patients. Alteration or loss of the p53 gene is one of the most powerful independent indicators of poor outcome. Overexpression of the *BCL2* proto-oncogene in AML is less well described in the literature and its impact on prognosis is uncertain.
Aims: This is a single-centre, retrospective analysis of AML patients treated over a ten year period (2006-2016).
Methods: Patients were identified through our pathology database. p53 expression was analysed as a surrogate marker for TP53 mutation, as was BCL2 expression, by immunohistochemical analysis of marrow trephine biopsies. We analysed presentation, management and overall survival (OS) of AML patients, and correlated these with p53 mutational status and with BCL2 expression.
Results: We identified 48 patients with AML; the majority were male (60%) and the median age at diagnosis was 68.5 years (range 37-85). Thirty-four patients (71%) had *denovo* presentation of AML. p53 overexpression was identified in 6 patients (12.5%), of whom 3 had secondary AML, and 3 had *denovo* presentations. *BCL2*expression analysis showed a median value of 60% (range 5-100%). *BCL2* positivity was seen in 39 patients (81.2%).

Figure 1: Overall survival comparison of patients with *TP53* positive disease vs *TP53* negative disease



Thirty-nine patients (83%) received active treatment; the remainder received only supportive care due either to frailty or patient choice. Nineteen patients (49%) of patients subsequently had relapsed/refractory disease. Five patients (13.5%) with *BCL2* overexpression at diagnosis received Venetoclax as single agent, either as 2nd or 3rd line therapy. Median OS was 11.5 months (range 0-72); at time of follow-up, 39 patients (81%) had died. Twenty-six patients died from disease progression (79%) and 7 (19%) of sepsis; in 2% the cause of death was unknown. OS in those with wild-type p53 was 11.5 months, which compared favourably to 7.5 months in those with p53 overexpression. *BCL2* overexpression also conferred a poorer prognosis; median OS was 10 months compared to 17 months in *BCL2* negative disease.
Summary/Conclusion: This study reflects real-life practice in treating AML patients outside of a clinical trial context. It demonstrates a slightly higher prevalence of p53 mutation in the elderly, and confirmed the previously reported poor prognosis of p53 alterations in AML (OS 7.5 months). It also demonstrates poorer OS in disease with *BCL2*overexpression. Further studies are needed to identify treatment strategies to overcome both p53 and *BCL2* disruption in AML.

PB1413 REAL WORLD DATA ON THE USE OF BCL2 INHIBITION IN ACUTE MYELOID LEUKAEMIA; THE IRISH EXPERIENCE

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Background: The BCL2 gene is a regulator of apoptosis, playing a key role in leukaemogenesis. BCL2 positivity in Acute Myeloid Leukaemia (AML) and its impact on prognosis is unclear. Recently, BCL2 inhibitors (Venetoclax) have shown promise in AML when used in combination with other agents. Treatment of relapsed/refractory AML is an unmet need and often has a dismal prognosis, especially in patients unsuitable for intensive chemotherapy.
Aims: Venetoclax was, until recently, made available in Ireland on a named-patient basis for use in AML. The aim of this multicentre, retrospective study was to analyse its use in this context.
Methods: Data was collected from 9 centers in Ireland. Patient and disease characteristics, prior treatment and outcomes were analysed. Real world data was also gathered regarding tolerability of Venetoclax and adverse events.
Results: Data were collected for 26 AML patients treated with Venetoclax. Most had *de novo* AML (n=19; 73%). Cytogenetic and molecular analyses are outlined in Table 1. Indications for initiating Venetoclax therapy were refractory disease (n=15, 58%) and relapsed disease (35%). One patient had not tolerated Azacitadine. Venetoclax was used as a single agent in 13 patients (50%) and in combination in 11 patients (42%). Other agents used were Azacitadine (n=8, 61.5%), Decitabine (n=2, 15%), and induction chemotherapy (n=1).
When initially investigated for treatment of CLL, the main risk with initiating Venetoclax was Tumour Lysis Syndrome (TLS). This is less well characterised for patients with AML, and therefore a more rapid dose escalation regimen has been advocated. The majority (n=18, 72%) were admitted to hospital for initiation of therapy. Most patients (69%) received TLS prophylaxis with Allopurinol alone. Seven patients (27%) received Rasburicase, and one patient received intravenous fluid alone. TLS was reported in only one patient who had received Rasburicase.
Venetoclax was mostly well-tolerated. Ten patients (40%) had adverse events or side effects. Myelosuppression was the most commonly reported adverse event (n=9, 36%) and treatment was temporarily interrupted due to cytopenia in 4 of these. GCSF support was commonly used. Infections were reported in 5 patients (20%), and recurrent febrile neutropenia led to treatment discontinuation in one. Overall, seven patients required hospital admission due to Venetoclax toxicity (28%).
The median duration of treatment was 2 months (range 0.5-12). Treatment response was assessed clinically (peripheral blood counts) in 17 patients (71%) and by bone marrow aspirate and trephine biopsies in seven patients (29%). Response to treatment was variable; the majority (n=11, 46%) had progressive disease, 8 patients (33%) had stable disease, 4 patients achieved Partial Response (17%) and only one patient had a Complete Response. There was no significant difference between response rates and survival in patients treated with Venetoclax as a single agent compared to in combination (median survival from commencing Venetoclax was 2 months vs. 3 months respectively). At time of data collection, 19 patients had died (76%).
Summary/Conclusion: Venetoclax is not yet a standardised treatment for AML, and in Ireland was available only on a Compassionate Access Scheme and this has now closed. This study of real-world data indicates that Venetoclax is well-tolerated with a low risk of serious adverse events. However, OS was not as prolonged as has been reported in the literature. Based on our experience, Venetoclax may be more effective when commenced earlier in patients with relapsed/refractory disease.

PB1414 FREQUENCY OF AN HP196–197 INSERTION (6BP) IN C/EBPA TAD2 REGION IN RUSSIAN POPULATION OF AML PATIENTS COMPARING TO CONTROL COHORTS.

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Background: CCAAT/enhancer-binding protein-α (C/EBPα) is a transcription factor encoded by the CEBPA gene and involved in the control of proliferation and differentiation of myeloid progenitors. C/EBPα consists of C-terminal DNA-binding basic leucine zipper (bZIP) domain and two transactivation domains TAD 1 and TAD 2 in the NH2 terminus. Mutations in CEBPA are found in 5% to 14% of acute myeloid leukemia (AML). AML patients with biallelic mutations of CEBPA are included in "favorable" group, which determines treatment strategy. It has been shown that HP196–197 insertion (6bp) in TAD2 domain is a common inherited mutation spread in normal population; however, there has been no studies on the occurrence of this insertion in the Russian population.
Aims: To compare the frequency of 6bp insertion in TAD2 domain of CEBPA gene in AML patients with healthy and no-myeloid leukemia (CLL) control cohorts.

Table 1: Disease Cytogenetic and Molecular characteristics

	n=26 (%)
Cytogenetic analysis	
Normal	14 (58)
Complex	4 (17)
CEPBA mutation	2 (9)
16q deletion	1 (4)
Trisomy 11	1 (4)
17p deletion	1 (4)
t(10;11)	1 (4)
Not available	2
NPM1 Mutation analysis	
Positive	6 (43)
Negative	8 (57)
Not available	12
FLT3-ITD Mutation analysis	
Positive	3 (18)
Negative	14 (82)
Not available	9

Methods: The study included 120 healthy controls, 117 de-novo AML patients, and 100 chronic lymphocytic leukemia (CLL) patients undergoing treatment at the National Research Center for Hematology (Moscow, Russia). Genomic DNA was isolated from bone marrow/peripheral blood samples taken at the time of diagnosis. For AML patients we also analyzed bone marrow/peripheral blood samples taken after treatment. Detection of 6bp insertion was performed on genomic DNA by PCR and fragment analysis. To amplify the region, we used a fluorescently labeled forward (F) primer FAM-5′-CCGGCTACCTGGACGGCAGG-3′ and a reverse (R1) primer 5′-CGTTGCTGTTCTTGTCCACCGACTTCTT-3′ [T Benthaus et al, 2008]. The fragment analysis was performed on ABI3130 Genetic Analyzer (Thermofisher Scientific, USA). Comparisons between patient characteristics were performed using the Pearson χ^2 test for binary variables.
Samples with detected 6bp insertion in TAD2 domain were further analyzed to confirm that 6bp insertion was located in a region that accounts for a His–Pro duplication (HP196–197ins). Samples were amplified using fluorescently labeled forward (F) primer FAM-5′-CCGGCTACCTGGACGGCAGG-3′ [T Benthaus et al, 2008] and reversed (R) primer 5′-TGCGGGTGCGGGTGCGGGT-3′ [in house design] with subsequent fragment analysis (see figure 1).
Results: 6bp insertion in TAD2 domain of CEBPA gene was detected in 7 of 117 (6%) AML patients, in 9 of 120 (7,5%) healthy controls, and in 10 of 100 (10%) CLL patients; differences between these groups were not statistically significant (χ^2=1.234, df=2, p=0.540). It was confirmed that 6bp insertion was HP196–197ins in all cases. In all AML patients with 6bp insertion in TAD2 domain in samples taken before treatment, this insertion was also detected after treatment as well.
Summary/Conclusion: Expected occurrence of 6bp insertion in TAD2 domain of CEBPA gene (HP196–197ins) is equal in AML patients, healthy controls, and patients with non-myeloid leukemia. Moreover, this insertion in AML patients persists after treatment, which suggests its hereditary nature. Therefore, this insertion should not be taken into account when determining the risk group and treatment strategy.

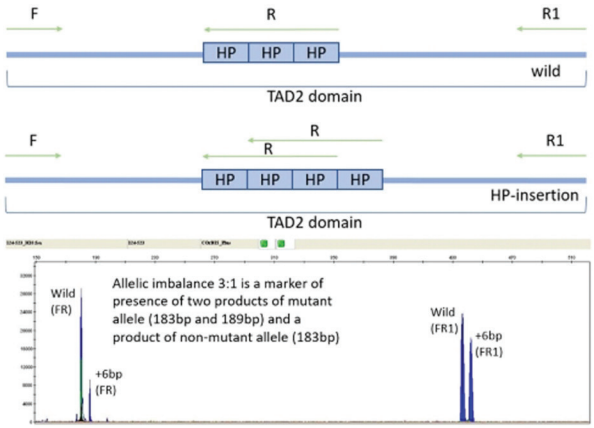
PB1415 A PHASE 1 STUDY OF NKX101, AN ALLOGENEIC CAR NATURAL KILLER (NK) CELL THERAPY, IN SUBJECTS WITH RELAPSED/REFRACTORY (R/R) ACUTE MYELOID LEUKEMIA (AML) OR HIGHER RISK MYELODYSPLASTIC SYNDROME (MDS)

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Background: Patients with R/R AML, or R/R higher risk MDS have a poor prognosis with a 5-year survival of <10%, or median overall survival of 0.8-3.0 years, respectively. Novel chimeric antigen receptor (CAR) T cell products

have had limited clinical success in patients with myeloid disorders due to absence of clear targets and a hostile microenvironment. Complete remission with or without hematologic recovery was achieved in 20%>50% of patients treated with non-engineered, allogeneic, haplo-matched NK cells after lymphodepletion; and minimal cytokine release syndrome and neurotoxicity were observed. The cytolytic activity of NK cells is due to the balance of activating and inhibitory signaling; key among the activating receptors is NKG2D, which recognizes multiple ligands upregulated in tumor tissues. NKX101 is composed of CAR NK cells engineered to express a chimeric receptor that fuses the extracellular ligand-binding domain of NKG2D to co-stimulatory (OX40) and signaling (CD3ζ) domains, to enhance its intrinsic antitumor activity. NKX101 also expresses a membrane-bound form of interleukin-15 that serves as an autocrine growth factor to increase NK cell persistence. Preclinical characterization has demonstrated that NKX101 achieves a 4- to 8-fold greater cytotoxicity, superior intrinsic longevity, and enhanced antitumor activity in AML xenograft models relative to nonengineered NK cells.
Aims: A Phase 1 study to investigate NKX101 in subjects with R/R AML or higher risk MDS.



Methods: This multicenter, open-label, Phase 1 study of NKX101 will be conducted in 2 parts: Part 1 to determine the recommended Phase 2 dose (RP2D) of NKX101 utilizing a modified "3+3" enrollment schema. The study will enroll subjects with either R/R primary or secondary AML or R/R higher risk (intermediate-, high-, and very high-risk) MDS. Building on existing clinical data with nonengineered haplomatched NK cells (referenced above), NKX101 manufactured from NK cells obtained from haplomatched, related donors (H) will be used in Part 1. Part 2 (dose expansion) will evaluate safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics (PDn), and antitumor activity of NKX101 from unrelated, HLA-mismatched donors with separate expansion cohorts for patients with AML or MDS. The starting dose of NKX101 is 1×10^8 CAR NK cells where NKX101 will be administered on Days 0, 7, and 14 of a 28-day cycle following standard fludarabine/cyclophosphamide lymphodepletion. Three dose levels are planned. Additional dosing schedules may be considered in the future. The primary endpoint is incidence of adverse events, dose-limiting toxicities, clinically significant laboratory abnormalities, and determination of the RP2D. Secondary endpoints include evaluation of standard cellular PK parameters, PDn, immunogenicity, and antitumor responses. AML patients will be assessed for efficacy using updated ELN criteria including measurable residual disease assessment, and MDS using modified IWG criteria. Exploratory endpoints are correlation of various degrees of HLA and KIR ligand match/mismatch between donor and recipient with primary and secondary safety, PK, and efficacy measures.
Results: The trial is in progress.
Summary/Conclusion: NKX101 is a novel fourth generation allogeneic CAR NK being evaluated in a Phase 1 trial with R/R AML or higher risk MDS patients at multiple centers (NCT04623944).

PB1416 MUTATION SPECTRUM OF FLT3-ITD POSITIVE ACUTE MYELOID LEUKEMIA AND ITS PROGNOSTIC INDICATIONS IN A CHINESE PATIENT COHORT

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Background: FMS-like tyrosine kinase 3 gene (FLT3) internal tandem duplication (ITD) mutation is one of the most frequent genetic mutations in patients with acute myeloid leukemia (AML). Although patients with FLT3-ITD mutations have an unfavorable outcome, variant allelic frequency (VAF), insertion site (IS), insertion length all may potentially impact the prognostic significance of FLT3-ITD mutations.
Aims: The aim of this study is to explore the mutation spectrum of FLT3-ITD positive AML and potential markers, including VAF, IS, insertion length, co-occurring mutations, which may influence the prognoses of this subset of patients.
Methods: Illumina MiSeq™Dx next generation sequencing (NGS) was performed to screen genetic mutations in 145 *de novo* patients with FLT3-ITD positive AML (excluding acute promyelocytic leukemia). VAF was defined as the fraction of mutant alleles as a percentage of all FLT3 alleles (FLT3-ITD/FLT3-WT + FLT3-ITD).
Results: The median VAF was 36.4% (range 1-81.8%), and median insert length was 45 bp (range 7-186 bp). Patients with FLT3-ITD VAF ≥33% was associated with a higher percentage of bone marrow blasts (0.7959±0.17333 versus 0.7306±0.20225, P=0.038) compared with those with VAF <33%. Forty-one types of other molecular mutations were detected in these patients, and the top three mutated genes were NPM1 (n = 79) (54.5%), DNMT3A (n = 62) (42.8%), and WT1 (n = 25) (17.2%). FLT3-ITD VAF ≥33% was associated with a higher NPM1 mutation ratio (P < 0.05) as compared to the VAF <33%. Based on Cancer Genome Atlas Research Network, the distributions of patient subsets consist of DNA-methylation-related genes (63.4%), the gene encoding nucleophosmin (NPM1) (54.5%), signaling genes (28.3%), myeloid transcription-factor genes (23.4%), tumor suppressor genes (22.8%), cohesin-complex genes (6.2%), and spliceosome-complex genes (6.2%), and chromatin-modifying genes (5.5%).
The CR, ORR, and early mortality rates were 65.3% (64/98), 79.6% (78/98), and 2.7% (3/113), respectively. Finally, 63 cases who achieved CR entered long-term follow-up (including 20 cases who received allo-HSCT). The follow-up time ranged from 3.17 to 60.1 months (median 15.97 months). In total, 42 patients relapsed, and 35 patients died. Our studies showed that longer insertion length (≥45bp) indicated a better RFS (P=0.02) and OS (P=0.016) compared with shorter insert length (<45bp) in patients with normal karyotype who consolidated with chemotherapy only. DNMT3A mutant patients had an inferior RFS and OS (p=0.003 and p=0.011), while NPM1, WT1 mutations had no significant influence on outcomes of patients in this study.
Summary/Conclusion: High FLT3-ITD VAF was associated with high levels of blasts in the bone marrow and NPM1 mutations. DNMT3A might be a poor prognostic factor in FLT3-ITD positive AML patients. The impact of insertion length is still unclear, and further investigation is needed to verify this conclusion.

PB1417 A PROSPECTIVE RANDOMIZED COMPARISON OF HIGH-DOSE CYTARABINE AND HIGH-DOSE DAUNORUBICIN IN THE INDUCTION CHEMOTHERAPY FOR ACUTE MYELOID LEUKEMIA

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Background: Over the past four decades, induction chemotherapy for acute myeloid leukemia (AML) has been standardized as so-called 7+3 regimen comprising 7 days of cytarabine and 3 days of anthracycline. To improve the treatment outcomes of AML patients, several prospective trials had been conducted with regards to the dosing schedule of induction chemotherapies. The E1900 trial showed improved complete remission (CR) rate and survival with high-dose daunorubicin (90 mg/m^2/d for 3 days) than standard-dose daunorubicin (45 mg/m^2/d for 3 days). During the similar period, our group also conducted a randomized study comparing high-dose and standard-dose daunorubicin (90 vs. 45 mg/m^2/d for 3 days) and confirmed superior CR rate and survival of high-dose daunorubicin. A randomized trial of Australian group comparing standard dose cytarabine (100 mg/m^2/d for 7 days) and high-dose cytarabine (3 g/m^2 q12hr for 4 days) showed improved duration of response, disease-free survival and overall survival (OS) after CR of high-dose cytarabine. Later, another randomized trial also revealed that high-dose cytarabine was associated with higher CR rate and longer survival than standard-dose cytarabine.
Aims: To optimize the induction treatment of AML, we designed a randomized study comparing high-dose cytarabine and high-dose daunorubicin for newly diagnosed AML patients.

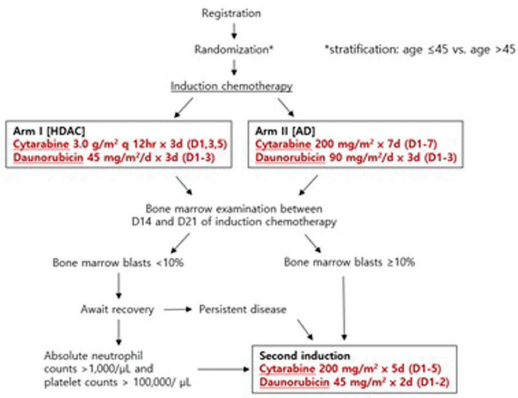
Methods: The patients with previously untreated AML who are ≤60 years old and eligible for intensive induction chemotherapy have been recruited in the study. Patients are randomized to one of the two induction treatment arms; high-dose cytarabine plus daunorubicin ([HDAC], cytarabine 3.0 g/m^2 q12hr on days 1, 3, 5 plus daunorubicin 45 mg/m^2/day on day 1-3) or cytarabine plus high-dose daunorubicin arm ([AD], cytarabine 200 mg/m^2/day on day 1-7 plus daunorubicin 90 mg/m^2/day on day 1-3). Patients who achieve CR receive consolidation chemotherapy or can proceed with hematopoietic cell transplantation (HCT) based on their genetic risk. The study was designed as a single-center, non-blind, two-arm randomized prospective controlled trial and plans to expand into a multicenter study. The primary endpoint is event-free survival, and the secondary endpoints include CR rate, cumulative incidence of relapse, regimen-related toxicities, and OS.
Results: Between March 2018 and December 2020, 103 patients were enrolled in the study; 48 in HDAC and 46 in AD arm. The median age was 49 (range, 16-60) and 61 patients were male (59.2%). Of 103 patients, 51 (49.5%) were classified into favorable genetic risk, 19 (18.4%) into intermediate risk, and 32 (31.1%) into adverse risk according to the European Leukemia Net risk stratification. *FMS-like tyrosine kinase 3*-internal tandem duplication and nucleophosmin mutations were detected in 18 and 29 patients, respectively. Overall, 75 and 2 patients achieved CR and CR with incomplete hematologic recovery, and 47 and 2 patients proceeded with allogeneic and autologous HCT, respectively. Eighteen patients died, and 2 died within 30 days from randomization.
Summary/Conclusion: We are currently conducting a randomized controlled trial for newly diagnosed AML patients comparing two induction chemotherapeutic regimens; high-dose cytarabine and high-dose daunorubicin. We expect to get insights from this study into optimal induction chemotherapy for AML patients and to reveal the relationship between genetic risk based on the mutational study and the benefits of each induction regimen.

PB1418 LIPOSOMAL ANNAMYCIN FOR R/R AML

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Background: Despite progress in the treatment of AML, most patients will relapse and die from refractory disease (R/R AML). De novo and acquired MDR is a critical mechanism of resistance and limits the efficacy of anthracyclines. Liposomal Annamycin is a novel anthracycline that has been shown to overcome MDR in vitro and in vivo. In addition it has been shown both preclinically and clinically to have no cardiotoxicity.
Aims: The aims this phase I/II trial is to determine the MTD or RP2D for the phase II component to evaluate efficacy. In addition, confirmation of no cardiotoxicity is an aim.
Methods: The clinical trial is a standard 3 + 3 first proving safety with an expansion phase at the MTD to determine efficacy. The cohorts started at a dose of 120 mg/m2 and is now up to 240 mg/m2 with no significant toxicity. All patients have very sensitive testing for any cardiotoxocity including strain echocardiography performed in the Duke cardio-oncology lab with review in cardio-oncology at the Cleveland Clinic. Sensitive biomarkers are also done for all patients.
Results: To date, no significant toxicity has been seen. All cardiotoxicity testing including strain echocardiography and biomarkers have remained completely normal.



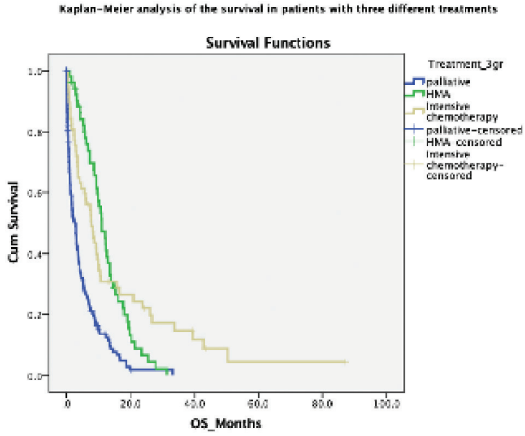
Summary/Conclusion: This ongoing phase I/II clinical trial is being done in Europe to confirm the previous clinical trials done in the US showing no cardiotoxicity and the ability to overcome MDR. From the previous studies, Liposomal Annamycin was shown to overcome MDR and have no cardiotoxicity.

PB1419 REAL-LIFE EFFICACY OF FIXED-DOSE HYPOMETHYLATING AGENTS IN OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Background: Prognosis of elderly patients with acute myeloid leukemia (AML) is dismal. Hypomethylating agents(HMAs) are recommended treatments for these patients due to their acceptable toxicity profiles and favorable efficacy. However, their high cost precludes their general use, especially in developing countries. Therefore, the fixed-dose HMAs approach was adopted in Thailand in order to reduce the expense.
Aims: This study aimed to investigate the clinical outcome of various treatment protocols including intensive chemotherapy, fixed-dose HMAs, and palliative treatment in Thai AML patients aged over 60 years. Fixed-dose HMAs included 5-azacitidine given at 100 mg per day for 7 days and decitabine given at 20 mg per day for 5 days.
Methods: We conducted a 10-year retrospective, single-center study in elderly AML patients diagnosed between January 1, 2010, and December 31, 2020. The inclusion criteria were (1) patients aged above 60 years; and (2) patients with newly diagnosed AML. The exclusion criteria were acute promyelocytic leukemia with *PML-RARA*.
Results: A total of 243 elderly AML patients were enrolled, with a mean age of 71± 8 years. Most of which (70%) had de novo AML. Poor risk cytogenetics was observed in the majority of cases (32.9%). The overall mortality rate was 90.9%. Median overall survival (OS) was 5 months (95% CI 3.6-6.4). Comparing a 3-group of treatment regimens (intensive chemotherapies fixed-dose HMAs and palliative treatment), the proportions of patients in each category accounted for 23.5%, 21.3%, and 55.1%, respectively. Median OS in each therapeutic option was 7.7, 11, and 2.5 months, respectively. From a multivariate analysis, palliative treatment had significantly inferior OS when compared to intensive treatment and fixed-dose HMAs (HR 0.41: 95% CI 0.28-0.61 and HR 0.42: 95% CI 0.29-0.60, respectively). Nevertheless, the OS outcome in patients with fixed-dose HMAs was comparable to those with intensive treatment (HR 0.89: 95% CI 0.57-1.38).



Summary/Conclusion: Our study confirms the poor outcome of AML in elderly patients, especially in patients receiving palliative strategy. The fixed-dose regimen of HMAs is the treatment of choice for these patients which is non-inferiority to intensive therapy.

PB1420 CORE-BINDING FACTOR ACUTE MYELOID LEUKEMIA: RESULTS OF A TUNISIAN EXPERIENCE

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Background: Core-binding factor acute myeloid leukemia (CBF-AML) belong to the cytogenetic favourable risk group. Although the prognosis of CBF-AML is better than other cytogenetic groups, 30 to 40% of patients will experience relapse and require stem cell transplantation.
Aims: In this study we aimed to assess treatment outcome of CBF- AML treated in in our hospital.
Methods: We retrospectively evaluated outcomes of CBF-AML treated at the hematology department of Aziza Othmana hospital between 2010 and 2019. All patients had cytogenetic at diagnosis. Only few patients had fusion genes study.
For all patients, induction consisted of idarubicine 12mg/m^2 per day on days 1 to 3 and cytarabine 200mg/m^2 per day over 7 days. Patients in complete remission had 3 consolidations consisting of high dose cytarabine.
Results: Five hundred and twenty-one AML adult patients were treated during the period of study. 32 patients had CBF-AML (6.1%). Median age was 34.5 years (range 20 to 56 y). Median WBC at diagnosis was 16.9 G/L (range 0.3 to 86.4 G/L). 78.1% of patients had inv 16 (p13;q22) and 21.9% had t(8;21) (q22;q22). 11 patients had additional cytogenetic abnormalities.
One patient died during induction. Complete remission was achieved in 90% of CBF-AML. Relapse occurred in 9 patients (31%) at a median of 12.9 months (range 5.4 to 48.5 months). A second remission was obtained in 77.7% of patients. Allogeneic stem cell transplantation was performed in only 3 patients. Median overall survival (OS) and relapse free survival (RFS) at 5 years were 60%.
Summary/Conclusion: In our study, Complete remission was achieved in 90 % of the CBF-AML patients. It is consistent with published results. Long term survival in our series compared favourably with results reported by cooperative groups.
In our study very few CBF-AML patients in relapse had stem cell transplantation. In fact, in our country allogeneic stem cell transplantation is performed in only one center receiving patients from all the country and is limited to young patients having an HLA-matched sibling donor. Our results could be improved using autologous system cell transplantation which can be considered as a part of post remission therapy in CBF-AML offering superior RFS an OS in favourable risk AML in first remission compared to chemotherapy.

PB1421 T(6;9)(P22;Q34)/DEK-NUP214-POSITIVE ACUTE MYELOID LEUKEMIA IN ADULTS IS A RARE POOR PROGNOSIS SUBTYPE AFFECTING YOUNGER PATIENTS: THE BULGARIAN EXPERIENCE

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Background: Translocation t(6;9)(p22;q34) is a recurrent rare genetic abnormality which defines an unique acute myeloid leukemia (AML) subtype characterized by poor prognosis. At molecular level, t(6;9) results in *DEK-NUP214* fusion gene formation which has a key role in the pathogenesis of the disease. The translocation accounts for only 0.5-2% of AML cases and therefore information concerning the clinical and laboratory features of t(6;9)/*DEK-NUP214*-positive patients (pts) is relatively limited. No data concerning the incidence and characteristics of AML with this abnormality in Bulgarian patients have been published so far.
Aims: To determine the incidence and the main characteristics of Bulgarian patients with t(6;9)/*DEK-NUP214*-positive AML.
Methods: Bone marrow aspirates of 945 consecutive adult pts with confirmed diagnosis AML were tested centrally in the Laboratory of Cytogenetics and Molecular Biology of the National Specialized Hospital for Active Treatment of Hematological Diseases – Sofia. Successful karyotypes were obtained in 812 of the cases. In all pts with cytogenetically detected t(6;9), the presence of the *DEK-NUP214* fusion transcripts was confirmed by reverse transcription polymerase chain reaction (RT-PCR). AML diagnosis and subclassification were performed according to the WHO Classification criteria (2016).
Results: Overall, t(6;9)/*DEK-NUP214* was detected in 6 (0.74%) pts, including 4 males and 2 females, with a mean age of 40±7.4 years (range 33 – 53 years). The median white blood cell (WBC) count in positive pts was 86x10^9/L (range 21-106x10^9/L), the median platelet count - 29x10^9/L (range 14-97x10^9/L), and the median hemoglobin level - 78.5 g/L (range 55-96 g/L). All pts were with de novo AML. The average bone marrow blast cell infiltration was 62.7%±29.5%. In 5/6 pts morphology revealed a monocytic component and AML was classified as AML-M4 according to FAB criteria. However, basophilia wasn't encountered in any of the cases. In 5 patients, t(6;9) was the sole chromosome abnormality, while in 1 patient, in addition, trisomy 13 was observed in all metaphases. *FLT3*-ITD was found in 3/6 of the *DEK-NUP214*-positive pts, and interestingly, a certain number of "cup-like" blasts was seen in all of them. Immunophenotyping revealed CD34 and/or CD117 positivity and aberrant myelomonocytic phenotypes in all pts, with an aberrant expression of CD56 in 2 of them. In two pts early dead occurred. In the remaining 4 pts, a standard 7+3 induction protocol ± midostaurin was initiated, but without significant reduction of blast population. Complete remission (CR) was achieved in 2 pts after a second high-dose induction course, followed by allogenic stem cell transplantation in 1 of them who is still alive 30 months after the diagnosis. The other was lost of follow up. The remaining patients were refractory and died within 2-13 months.
Summary/Conclusion: The present study confirmed the low incidence of t(6;9)/*DEK-NUP214* in Bulgarian pts with AML. Despite of the heterogeneous clinical and laboratory features, our series was characterized by relatively younger age, high WBC counts, myelomonocytic morphology, absence of additional chromosomal aberrations in most of the cases, presence of *FLT3-ITD* in half of the pts and poor outcome with conventional chemotherapy.

PB1422 OUTCOME OF TREATING PEDIATRIC LANGERHANS HISTIOCYTOSIS WITH LCH III IN TERTIARY CENTER, SAUDI ARABIA.

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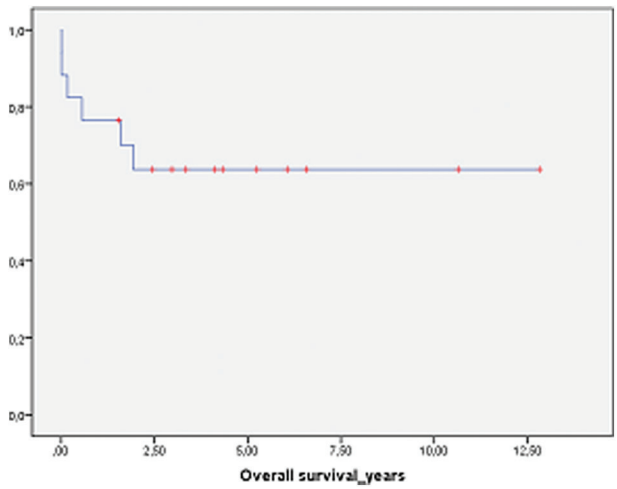
Background: *Background:* Langerhans cell histiocytosis (LCH) is a rare disease affects any age and any organ; its presentations and outcome vary from self-healing lesions to life-threatening disseminated disease.
Aims: This study evaluated the outcome of treating children diagnosed with Langerhans cell histiocytosis (LCH) at Oncology Center, Saudi Arabia.
Methods: Through a retrospective study design, the researchers reviewed the medical records and electronic files of all children (aged from 0-≤ 14 years) who had been diagnosed and treated for LCH at Princess Norah Oncology Center (PNOC), King Abdelaziz Medical City, Saudi Arabia, in the period from January 2000 to December 2019 (n=33).
Results: Males constituted (66.7%), with remarkable dominance of Saudis (93.9%). The median age at diagnosis was 28 months (IQR=49 months); (42.4%) were diagnosed before reaching their second birthday. Fourteen patients (42.4%) had multisystem (MS-LCH) involvement, of which 13 patients with risk organ (RO) (+) and one patient without risk organ (RO) (-). Most of the patients received LCH III protocols. Reactivation occurred in 11 patients (33.3%), and two deaths (6.1%) occurred in cases with MS (RO) (+) progressive disease. The overall survival was 93.9%; with no statistically significant difference in event free survival observed between patients with multisystem compared to single system involvement.
Summary/Conclusion: Excellent outcome of LCH is associated with single system involvement and worse outcome (reactivations, or morality) is determined by multi-organ involvement especially at younger age less than 24 months. Better understanding of pathophysiology and genetic molecular background could lead to a striking transformation to novel therapy that warrants a prospective clinical trial.[u1] A high mortality in patients with progressive disease demands an earlier aggressive salvage in such group. Prospective clinical trials are required for improved treatment strategies in these subgroups.

PB1423 CHILDREN ACUTE PROMYELOCYTIC LEUKEMIA: HEMATOLOGY DEPARTMENT EXPERIENCE AT AZIZA OTHMANA HOSPITAL

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Background: Acute promyelocytic leukemia (APL) is a rare subtype of AML which represents < or = 10% of childhood acute myelogenous leukemia.
Aims: We conducted a retrospective analysis diagnosed between January 2008 to December 2016 and actively followed. The hematologic complete remission (CR) rate and overall survival (OS) rate were evaluated. Prognostic factors and complications were investigated
Methods: We studied the outcomes of children, up to 18 years of age, with APL treated by acute promyelocytic leukemia (APL) 2005 protocol, in Hematology Departement of Aziza Othmana Hospital.
We conducted a retrospective analysis diagnosed between January 2008 to December 2016 and actively followed. The hematologic complete remission (CR) rate and overall survival (OS) rate were evaluated. Prognostic factors and complications were investigated
Results: A total of 13 patients with a median age of 9 years (range, 2-18 years) were included. We had 9 boys vs 8 girls, sex ratio 1.1.
76.5 % patients had hemorrhagic findings at admission. Severe bleeding manifested as intracranial haemorrhage was present in one patient. Disseminated intravascular coagulation (DIC) was diagnosted in 11 patients (65%). We stratified APL patients into three risk subgroups using Sanz score: low risk (1 patient), intermediate risk (6 patients) and high risk (10 patients).
All patients were treated with AIDA 2005 protocol. Induction death rate was 6%. Nine patients showed side effects of ATRA such as differentiation syndrome (7 patients), pseudotumor cerebri (one patient) and Sweet syndrome (one patient).
The median overall survival of the live patients was 8.4 years. The 5-year overall survival was estimated at 64%. On univariate analysis of overall survival, age, number of leukocytes, Prothrombin Time, risk classification and blast marrow infiltration were associated with overall survival. Sex, and DIC were not significant predictors of overall survival.



Summary/Conclusion: Life-threatening bleeding was the primary problem in APL. Urgent treatment with ATRA is a critical factor to reduce early losses.

PB1424 ALL-TRANS RETINOIC ACID INDUCED MYOCARDITIS AS PART OF DIFFERENTIATION SYNDROME: A CASE REPORT AND LITERATURE REVIEW

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Background: Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia defined by the translocation t(15;17)(q22;21). All-trans retinoic acid (ATRA) is a cornerstone of treatment for APL. However, ATRA use is associated with a spectrum of severe complications known as differentiation syndrome (DS). With the exception of pericardial effusion, cardiac involvement is extremely rare after ATRA exposure.
Aims: We present a patient who developed myocarditis as an unusual complication after ATRA treatment.
Methods: A 23-year-old female presented with one week history of generalized headache, emesis, and ecchymosis. Lab findings revealed leukocytosis (44.5 x 109/mm^3), normocytic anemia (11.3 g/dL), thrombocytopenia (38 000/mm^3), hypofibrinogenemia (fibrinogen 64 mg/dL), elevated d-dimer (48 293 ng/mL), and coagulopathy (prothrombin time international normalized ratio 2.0) consistent with disseminated intravascular coagulation. Peripheral blood smear demonstrated 82% blasts with Auer rods, consistent with acute promyelocytic anemia (APL) and later confirmed on bone marrow aspirate and biopsy. PCR for PML-RARA fusion gene was positive. Karyotype was 46,XX,del(9)(q13q22),t(15;17)(q24;q21). On confirmation of the diagnosis, the patient was initiated on ATRA and idarubicin. One day following the first administration of ATRA, the patient began to complain of dyspnea on exertion and chest pain. She developed transient hypoxia (SpO2 90%) and sinus tachycardia.
Results: Troponin I was elevated to 2849 pg/mL, but there were no electrocardiographic changes suggestive of ischemia. Computerized tomography of the chest demonstrated new bilateral interstitial infiltrates and small pleural effusions. Blood and bronchoalveolar lavage microbiology cultures were negative. Echocardiogram was negative for any valvular dysfunction, systolic dysfunction, or wall motion abnormalities. However, cardiac magnetic resonance imaging (MRI) demonstrated delayed focal subepicardial enhancement suggestive of myocarditis. The patient was immediately started on intravenous dexamethasone 10 mg every 12 hours for treatment of both DS and myocarditis, and demonstrated resolution of symptoms as well as normalization of cardiac enzymes. She was advised to continue a prolonged prednisone tapering regimen after completion of dexamethasone for 14 days. Three months after her diagnosis, follow-up echocardiogram demonstrated normal function with a complete resolution of symptoms.
Summary/Conclusion: DS is a heterogeneous condition whose pathogenesis and diagnostic criteria remain yet to be clearly defined. This patient meets criteria for possible differentiation syndrome given the presence of dyspnea with interstitial pulmonary infiltrates, as well as a small pericardial effusion, after ATRA induction. Review of existing literature identified 11 other cases of ATRA-induced myocarditis, of which only 2 reported concurrent DS-defining symptoms. All cases demonstrated onset of symptoms within 1 month of ATRA induction. Due to the scarcity of available reports, cardiac complications are an under-recognized sequelae of ATRA use. We postulate that myocarditis although rare, is likely to be a constituent of the amalgam of pathologies involved in DS. Cardiac MRI may be a more accurate non-invasive diagnostic test to confirm myopericarditis after ATRA induction.

PB1425 THERAPY-RELATED MYELOID NEOPLASMS: A DESCRIPTIVE ANALYSIS AT A SINGLE INSTITUTION

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Background: Over the years, the incidence of therapy-related myeloid neoplasm (t-MN) has increased as a consequence of the increased survival rate of cancer due to constant improvement of treatments. t-MN represents 10-20% of all myeloid neoplasms and its prognosis is relatively poor.
Aims: The aim of this study was to analyze the characteristics and the outcome of patients with t-MN.
Methods: The present retrospective study comprises a series of 23 patients with t-MN diagnosed at Hospital Universitario Guadalajara between 2009 and 2020. Electronic medical records from the database were reviewed in order to identify all cases of t-MN. The data collected included: age, sex, cytogenetics, primary malignancy type or autoimmune disease and treatment received.
Results: The median age of the patients was 72 years (range, 56 to 85 years) and 52% of them were male. Fourteen patients (61%) had preceding solid tumors (the most frequent was lung cancer), 3 patients (13%) had hematologic malignancies and 6 patients (26%) had autoimmune conditions. The median interval between primary malignant disease and t-MN diagnosis was 6.9 years (range, 0.3 to 22.5). Immunosuppressant drugs were administered to 6 patients (26%), 7 patients (30%) were treated with chemotherapy alone and 10 patients (43%) received radiation associated with chemotherapy. The type of chemotherapy received was alkylating agents alone or different

combinations of alkylating, targeting topoisomerase II, alkaloids and antimetabolites agents. Patients treated with immunosuppressant drugs took longer to develop t-MN (median 10 years) and they had a better survival rate.
Unbalanced aberrations of chromosomes 5 and 7 and/or a complex karyotype were described in 7 patients (30%); all these patients had received alkylating agents and/or radiotherapy. Six (26%) patients exhibited TP53 mutation, 5 of them (83%) developed t-AML and all these 5 patients deceased due to progression of the condition, despite the treatment received (intensive anthracycline and cytarabine based chemotherapy, daunorubicin and cytarabine liposome or hypomethylating agents). The median overall survival after t-AML diagnosis was 8 months.
Summary/Conclusion: Development of t-MN is a serious complication with poor prognosis. Predictive markers should be identified in patients with cancer in order to prevent the risk of developing t-MN.

PB1426 TAGRAXOFUSP AS FIRST-LINE TREATMENT OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN). A CASE REPORT

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Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare myeloid malignancy, for which conventional chemotherapy has poor outcomes. Tagraxofusp (SL-401) is a CD123-directed cytotoxin consisting of human interleukin-3 fused to truncated diphtheria toxin which has recently been approved by EMA.
Aims: To describe our positive experience with Tagraxofusp and to present our diagnosis process and observed adverse events.
Methods: We present the case of a 38-year-old female, who presented with pancytopenia, polyadenopathy and skin lesions and was diagnosed with blastic plasmacytoid dendritic cell neoplasia with complex karyotype, PTPN11 mutation by NGS Expression. Infiltration of bone marrow, skin, lymph nodes and CNS was noted.
We administered Tagroxofusp according to the dose of the technical data with 12 mcg/kg by intravenous infusion over 15 minutes, once a day, on days 1-5 of a 21-day cycle considering that this administration could be extended with delays until day 10 of the cycle. Prior to preparing each dose vital signs, albumin, transaminases, creatinine, body weight, sistolic blood pressure and heart rate was made.Treatment was administered as a bridge therapy to allogeneic hematopoietic stem cell transplantation (HSCT)
Results: Until the availability of the drug; 4 doses of intrathecal treatment were administered. Two weeks after diagnosis, treatment with tagraxofusp was started. During this time the patient maintained a good general condition. After the second dose of tagraxofusp a grade 2 capillary release syndrome (CLS) emerged. Other adverse events were shaking chills, rash, weight gain, and hepatotoxicity. After resolution of these problems, the next dose of treatment was administered after 21 days with a total of 3 cycles with excellent tolerance in a total of 5 days and without observing adverse events. Evaluation of the disease showed complete remission (medullary, skin, peripheral, CNS, and lymph node) with positive MRD (0.09). The 4th cycle remains pending prior to HSCT.
Summary/Conclusion: The use of tagraxofusp specially as a front-line therapy has shown in this patient promising clinical activity, with a high overall response rate and prolonged responses and acceptable toxicity. CLS grade 2 was observed only in cycle 1, therefore can be good therapeutic option for this hematological disease. Nevertheless future work will define its place in treating relapse or refractory disease as well as its role as a first line therapy or bridge to transplantation.

PB1427 TWO CASE REPORT: CONCURRENT CROHN'S DISEASE AND MYELODYSPLASTIC SYNDROME OR ACUTE LEUKEMIA

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Background: Many cases of simultaneous development of inflammatory bowl diseases and myelodysplastic syndrome or acute myeloid leukemia have been reported since 1980. Until today there are 70 cases including ours published in reference sites in the majority of these cases the acute leukemia was associated with the ulcerative colitis while the Crohn's disease was associated with the myelodysplastic syndrome (MDS).
Aims: The objective is to insist on the association between inflammatory bowel disease and myelodysplasia or acute leukemia and to analyze the propses explanations for the mechanism leading to this association
Methods: We report two cases,followed up in our clinical hematology service in Monastir-TUNISIA,of crohn's disease associated with hematological malignancies: the first is about a patient who had myelodysplasia progressed to an acute myeloid leukemia (AML) in whom Crohn's disease was diagnosed few months later. The second is a about a simultaneous discovery of crohn's disease and acute myeloid Leukemia: this patient was followed up by gastrologists for crohn's disease and some months later (before the onset of the treatment) a myeloid leukemia was diagnosed.
Results: Many studies reported patients with myelodysplastic syndrome or myeloid leukemia associated with Crohn's disease have received treatment for crohn's disease or radiological examinations before the onset of the hematologic malignancy. However other studies have found that there's no connection between radiation, Crohn's disease treatment and the onset of MDS or leukemia. Our cases confirmed these studies because the MDS or the AML were discovered before the onset of the Crohn's disease treatment.
The other propositions include a common chromosome abnormality. However, many cases have been reported to have normal karyotype. In our cases the karyotype was abnormal witch can support this suggestion but the fact that many cases present a normal karyotype still against.
The most attractive proposition still: a common immune dysfunction: admitting that inflammatory bowel disease and MDS are autoimmune diseases. In the MDS there is T-cell clonal proliferation, tumor necrosis factor secretion and excessive interleukin 1 and 6 which can lead to the development of the IBD.
Summary/Conclusion: Crohn's disease can precede the MDS or acute leukemia or inversely, so a patient followed up by hematologists for a hematological malignancy can develop an inflammatory bowel disease and a patient followed up by gastrologists for IBD can develop a MDS or AML.
Many explanations were supposed to the possible common mechanism leading to this association but the causal relationship has yet to be determined.

Aggressive Non-Hodgkin lymphoma - Clinical

PB1428 THE CORRELATION BETWEEN SKIN RESPONSE AND BLOOD INVOLVEMENT WITH MOGAMULIZUMAB

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Background: Cutaneous T-cell lymphomas (CTCL) are non-Hodgkin lymphomas with a variety of subtypes. Mycosis fungoides (MF) and Sézary syndrome (SS) together account for up to two-thirds of CTCL cases. Disease staging in CTCL was first comprised of tumour, lymph node and metastasis (TNM) assessments, with blood being added in 2007 due to establishment of blood tumour burden as a negative prognostic factor. Overall survival (OS) and disease-specific survival (DSS) are negatively impacted by increased blood tumour burden and risk of disease progression (RDP) is increased (Agar 2010, Am Soc J Clin Oncol). However, there is still further validation to be done for confirmation.
Aims: This post hoc analysis of MAVORIC trial data looked at the correlation between patients' levels of blood involvement and response in the skin following treatment with either mogamulizumab or vorinostat.
Methods: MAVORIC (NCT01728805) was an open-label, phase 3 study comparing mogamulizumab and vorinostat. Patients were randomised 1:1 to each treatment arm and received either intravenous mogamulizumab 1.0 mg/kg weekly for the first 28-day cycle, then on days 1 and 15 of subsequent cycles, or oral vorinostat 400 mg once daily. Vorinostat treated patients who experienced disease toxicity or intolerable toxicity following at least one cycle could cross over to the mogamulizumab treatment arm. The Modified Severity Weighted Assessment Tool (mSWAT), was used to measure skin response in both mogamulizumab and vorinostat patients and data was stratified by blood classification. The median mSWAT percentage change per treatment cycle and best overall response by percentage change in mSWAT were examined.

Results: Mogamulizumab patients with B1 and B2 blood classifications experienced a greater median percentage change in mSWAT compared to patients with B0, and B2 patients experienced the greatest improvement of -86.0% by Cycle 12 (Figure 1**a**). The majority of patients experienced improvement in mSWAT, with the greatest degree of responses generally experienced by B1 and B2 patients.
Vorinostat patients saw an improvement in median percentage change in mSWAT, although to a lesser degree compared to mogamulizumab patients, with B2 patients showing the lowest response in skin, -22.1% by Cycle 12, compared to other blood classes (Figure 1**b**). Best overall mSWAT response by patient show that vorinostat patients overall experienced less improvement compared to mogamulizumab patients, with little-to-no correlation with blood class.
Summary/Conclusion: MOGA is effective in patients with blood involvement (B1 and B2), including patients with MF. Drug safety is similar between patients irrespective of level of blood involvement.

PB1430 CAR-T CELL THERAPY FOR PEOPLE WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A COCHRANE SYSTEMATIC REVIEW

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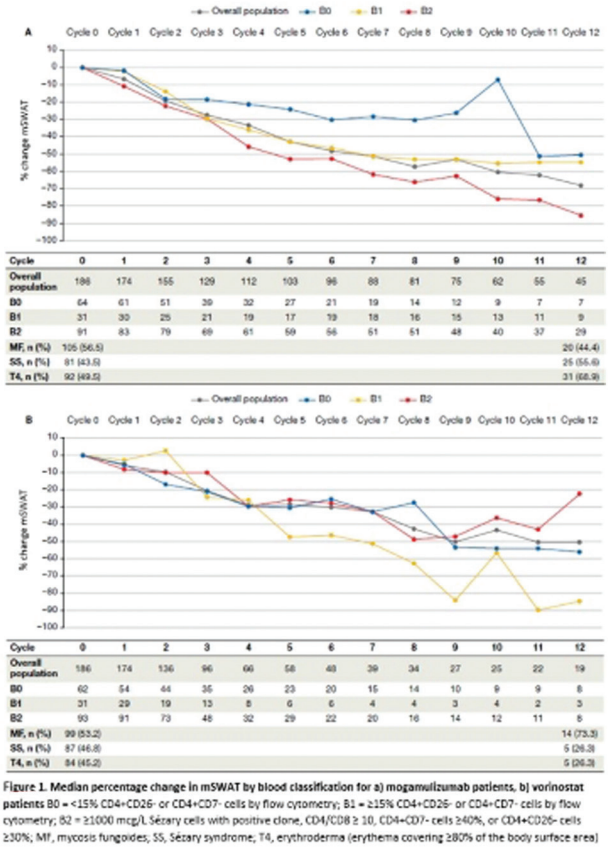


Figure 1. Median percentage change in mSWAT by blood classification for a) mogamulizumab patients, b) vorinostat patients B0 = <15% CD4+CD26- or CD4+CD7- cells by flow cytometry; B1 = ≥15% CD4+CD26- or CD4+CD7- cells by flow cytometry; B2 = ≥1000 mcg/L Sézary cells with positive clone, CD4/CD8 ≥ 10, CD4+CD7- cells ≥40%, or CD4+CD26- cells ≥30%; MF, mycosis fungoides; SS, Sézary syndrome; T4, erythroderma (erythema covering ≥80% of the body surface area)

Background: A substantial proportion of people with diffuse large B-cell lymphoma (DLBCL) experience relapse or are refractory to therapy (r/r). With a median overall survival below 6-12 months, the prognosis of those who relapse or are refractory to advanced lines of treatment or those who are ineligible for autologous stem cell transplantation is very poor. For these individuals, chimeric antigen receptor (CAR)-T cell therapy provides a promising treatment option.
Aims: To assess the benefits and harms of CAR-T cell therapy for people with r/r DLBCL.
Methods: In accordance with a published Cochrane protocol, we systematically searched CENTRAL, MEDLINE, Embase, conference proceedings, trial registries and databases for prospectively planned trials – beginning with randomised controlled trials (RCTs) – evaluating CAR-T cells for people with r/r DLBCL until September 2020. We excluded trials with less than 10 participants with r/r DLBCL and trials with less than 70% of participants with r/r DLBCL, unless respective data were reported separately. Two review authors extracted data and assessed potential risk of bias independently. As we did not identify any controlled trials, we did not meta-analyse data. We used the GRADE approach to assess the certainty of the evidence for prioritised outcomes.
Results: We included 13 uncontrolled trials and identified 38 ongoing trials, three of which are RCTs to be completed between 2022 and 2025. We judged all included trials to be at high risk of bias. Primarily due to the lack of a control group, study limitations and restricted applicability, our certainty in the evidence was very low for all outcomes.
Overall survival (OS) was reported by eight studies with substantial variation in sample size, duration of follow-up and proportion of people with DLBCL. Four studies reported 12-month survival rates of 48-59%, and one study reported an OS rate of 50.5% at 24 months (very low-certainty evidence). Two studies described improvements of **quality of life** over time (very low-certainty evidence). Five studies reported that a vast majority of participants experienced **adverse events** (AEs) (99-100% any grade, 68-98% grade ≥3; very low-certainty evidence). According to three studies, 56-68% of participants had **serious AEs**, while in one study, no serious AEs occurred (very low-certainty evidence). Various criteria were used by 11 studies to report **Cytokine release syndrome** (CRS). In five studies, 42-100% of participants had CRS according to criteria described by Lee 2014 (very low-certainty evidence). Nine studies reported **progression-free survival** (PFS), disease-free survival or relapse-free survival at any time of follow-up. Twelve-month PFS rates between 44-75% were reported by four studies. In one study, relapse-free survival rates remained at 64% at both 12, and 18 months (very low-certainty evidence). All 13 studies provided data on **complete response** (CR). Three studies reported 6-month CR rates between 40-45% (very low-certainty evidence).
Summary/Conclusion: The available evidence on the benefits and harms of CAR-T cell therapy for people with r/r DLBCL is limited, especially due to the absence of comparative clinical trials. Given the uncertainty in the current evidence, the risk of substantial and potentially life-threatening complications that require supplementary treatment and the large number of ongoing investigations, it is critical to continue evaluating how the evidence on this novel therapy will evolve.

PB1431 RELATIONSHIP BETWEEN GENETIC ABERRATIONS IN THE 17P13/TP53 LOCUS AND IMMUNOHISTOCHEMICAL PROTEIN P53 EXPRESSION IN TUMOR CELLS OF DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is one of the most common, aggressive, clinically and biologically heterogeneous B-cell neoplasms. Impaired cell differentiation, maturation, and proliferation of B lymphoid elements are the main components of the disease pathogenesis. Protein p53 encoded by the *TP53* gene is the key tumor suppressor that holds the cell cycle, enables DNA reparation and apoptosis. Disruption of the structure and functions of this transcription factor in DLBCL patients is caused by various mechanisms, including mutations in *TP53* exons, deletions of chromosome 17p13 locus, abnormal p53 promoter methylation, etc. Inactivation of certain pro-apoptotic genes or hyperactivation of anti-apoptotic mechanisms can also affect p53 functions. Many researchers agree that *TP53* mutations and immunohistochemical (IHC) protein p53 expression in tumor cells are important factors that have an impact on the prognosis of DLBCL. However, studies investigating their relationship are few and contradicting, which confirms the relevance of this study.

Aims: To evaluate the relationship between genetic aberrations in the 17p13/*TP53* locus and IHC protein p53 expression in tumor cells in patients with DLBCL.
Methods: The study included a total of 75 patients aged from 30 to 82 years (median age: 58 years) with newly diagnosed DLBCL who received treatment at the clinic of the Institute. All patients received R-CHOP as a first-line treatment. The deletion of the 17p13/*TP53* locus was determined by fluorescence *in situ* hybridization (FISH) in biopsy specimens of tumor tissue using the Kreatech *TP53* (17p13) / SE 17 FISH probes. The relative number of p53-expressing tumor cells was calculated by IHC and morphometry. The threshold value of IHC p53 expression was evaluated by ROC analysis. The association between 17p13/*TP53* deletion and protein p53 expression in tumor cells was evaluated using Fisher's exact test (F). The correlation was evaluated using Cramer's rule (V).
Results: Deletions of the 17p13/*TP53* locus were detected in 8 (11%) of 75 DLBCL patients. ROC analysis showed that the threshold value of IHC expression of p53-positive cells was 43%. This value was used to determine marker hyperexpression (≥ 43% of tumor cells) in 33 (44%) of subjects. The percentage of expressive cells in the remaining patients was lower than the threshold value. The incidence of 17p13 deletions was significantly higher in patients with p53 hyperexpression than in patients with protein p53 levels below the threshold value: 87.5% vs. 12.5%, respectively (p=0.018; OR=11.04). A correlation between 17p13/*TP53* deletion and protein p53 expression in tumor cells (p=0.018; V=0.3) was established.
Summary/Conclusion: 17p13/*TP53* deletions in DLBCL patients are associated with suprathreshold IHC protein p53 expression in tumor cells. A direct moderate correlation has been established between these laboratory values.

PB1432 RELATIONSHIP BETWEEN PAKT1, PSYK PROTEINS CO-EXPRESSION AND SURVIVAL IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. Currently, a number of clinical stratification systems (international prognostic indexes, staging, and others) are used to determine the prognosis of the disease. However, they do not accurately assess the individual risk of therapy failure. In this regard, it is of interest to search for additional biological criteria that determine the prognosis of the disease.
Dysregulation of key molecules (pAKT1, pSyk) of the PI3K / AKT / mTOR and BCR signaling pathways affects the biological characteristic of tumor cells and may determine the prognosis of DLBCL. It is known that monotypic overexpression of pAKT1 and pSyk is associated with low overall (OS) and progression-free survival (PFS) in DLBCL patients; however, the combined expression of these proteins in this pathology has not been studied, which emphasizes the relevance of the study.
Aims: To assess the association of the co-expression of the pAKT1 and pSyk proteins in tumor cells with OS and PFS in DLBCL patients.
Methods: As a material for the study, FFPE samples of lymph nodes and other organs and tissues were used, obtained from 100 patients with a newly diagnosed DLBCL who were treated at the clinic of the KRIHBT in the period from 2012 to 2018. All patients received standard first-line immunochemotherapy according to the R-CHOP regimen. The determination of the relative number of tumor cells expressing pAKT1, pSyk was carried out using immunohistochemical and morphometric methods. OS and PFS were calculated by the Kaplan-Meier method using the log-rank test. The cutoff for expression of these proteins was calculated using the ROC analysis: for pAKT1 was set at 70% of positive tumor cells, for pSyk - 28%. According to the established thresholds, all subjects were divided into groups with high [≥70% (+) for pAKT1; ≥28% (+) for pSyk] and low [<70% (-) for pAKT1; <28% (-) for pSyk] by expression of the indicated proteins. The interrelation between different variants of pAKT1 and pSyk co-expression with the course of DLBCL was analyzed.
Results: The highest OS (90.2%) was recorded in the group of patients (n=41) with low coexpression of markers (pAKT1-/pSyk -). In the presence of coexpressions of pAKT1+/pSyk- and pAKT1-/pSyk+, it was 52% (n=29) and 60% (n=15), respectively. The lowest values of OS (26.7%) were observed in patients (n=15) with the combination of pAKT1+/pSyk+, which significantly differed from other variants of co-expression of markers (p<0.001; HR=5.2; 95% CI=2.49-10.9).
A similar pattern was established in the analysis of PFS. The proportion of patients without disease progression with the variant of co-expression of pAKT1 - / pSyk- was 78.1% (n=41), and in the presence of combinations of rACT1+/pSyk - and rACT1-/pSyk+ - 55% (n=29) and 53% (n=15), respectively. The lowest level of PFS (40%) was registered in patients with simultaneous overexpression of markers (n=15; p=0.002; HR=3.3; 95% CI=1.54-7.30).
Summary/Conclusion: Conclusion. Combined overexpression of the pAKT1 and pSyk biomarkers is associated with a more unfavorable prognosis of DLBCL compared to other variants of their coexpression.

PB1433 ABNORMAL AND COMPLEX KARYOTYPE IS FREQUENT ON ROUTINE KARYOTYPING ON PRIMARY TISSUE IN PATIENTS WITH DIFFUSE LARGE B-CELL AND TRANSFORMED LYMPHOMA BUT DOES NOT INFLUENCE CLINICAL OUTCOMES

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Background: Diffuse large B-cell lymphoma (DLBCL) has significant clinico-histological and molecular heterogeneity but the frequency and prognostic significance of cytogenetic abnormalities on primary tissue has not been fully established.
Aims: To describe the the cytogenic and clinical data of DLBCL patients with nodal tissue subjected to conventional karyotyping and describe the effects of chromosomal abnormalities on survival outcomes.
Methods: All cases with cytogenetic studies performed on extramedullary tissue with a histopathological diagnosis of DLBCL made between 2003 and 2017 at ACT Pathology, Australian Capital Territory were included in this study. Histological diagnosis was made in accordance with the World Health Organisation classification criteria, and the lymphoma subtype and cell of origin using Han's algorithm was recorded. Relevant clinical data was extracted from electronical medical records. Chromosome analysis was performed on fresh extramedullary tissue, whereby G-banding metaphases were analysed after a minimum of 24 hours of unstimulated culture. The karyotype was reported in accordance with the International System for Cytogenetic Nomenclature.
Results: In 78 patients identified, an abnormal karyotype (AK) was identified in 50 (64.1%) patients [39 patients (50%) with complex karyotype (CK) and 11 patients (14.1%) with 1-2 chromosomal abnormalities] and more frequent in transformed lymphoma (77.8%, with 55.6% having CK). AK was not associated with an inferior overall survival (OS) and progression-free survival (PFS) when compared to normal karyotype (5-year OS 78% vs 78.2%, p = 0.854 and 5-year PFS 72% vs 71.4%, p = 0.840). In univariate and multivariate analysis, AK, CK and frequent cytogenetic abnormalities were not found to be significant predictors of survival.
Summary/Conclusion: Chromosomal abnormalities in DLBCL detected on routine karyotyping are frequent but do not improve risk-stratification or alter treatment outcomes.

PB1434 ESCALADE: ACALABRUTINIB + RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (R-CHOP) IN UNTREATED NON-GERMINAL CENTER B-CELL–LIKE (NON-GCB) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: R-CHOP remains the standard of care for DLBCL. Although most patients can be cured, 35–40% will experience relapsed/refractory disease, leading to poor outcomes in the majority of patients. Covalent irreversible Bruton tyrosine kinase inhibitors (BTKi) have shown higher responses in patients with non-GCB DLBCL than with GCB DLBCL. In untreated non-GCB DLBCL patients, the phase 3 PHOENIX study (Younes et al. *J Clin Oncol*. 2019;37:1285-95) showed that addition of the BTKi ibrutinib to R-CHOP (R-CHOP-I) did not improve outcomes in the intent-to-treat population. However, patients age <60y treated with R-CHOP-I had significantly improved progression-free survival (PFS) and overall survival (OS) compared with those receiving R-CHOP alone. Acalabrutinib is a second-generation BTKi with enhanced kinase selectivity and potential for better efficacy and tolerability than first-generation BTKis. There is a strong rationale for combining acalabrutinib with R-CHOP in patients with untreated DLBCL, and safety of acalabrutinib + R-CHOP has been shown in a phase 1b/2 study (Davies et al. ASH 2020).
Aims: To determine if the addition of acalabrutinib to R-CHOP leads to improved PFS in patients age ≤65y with untreated non-GCB DLBCL.
Methods: ESCALADE (ACE-LY-312; NCT04529772) is a phase 3, randomized, global, double-blind study of acalabrutinib vs placebo in combination with R-CHOP for treatment of newly diagnosed non-GCB DLBCL. The study is recruiting adults ≥18y and ≤65y with previously untreated DLBCL stage II–IV disease with a Revised International Prognostic Index (R-IPI) score of 2–5. Prior to randomization, all patients will receive an initial R-CHOP cycle (cycle 1) as standard-of-care treatment to prevent delays in therapy initiation. Based on central Gene Expression Profile (GEP) testing performed after enrollment, patients with non-GCB DLBCL (activated B-cell like or unclassified) will be randomized into 2 arms to receive acalabrutinib 100 mg twice daily plus R-CHOP or placebo plus R-CHOP from cycle 2 to cycle 6 followed by 2 additional cycles of rituximab + acalabrutinib or placebo (cycles 7 and 8). All patients will receive primary prophylaxis with granulocyte colony-stimulating factors accompanying all R-CHOP cycles. The study aims to randomize 600 patients (~300 per arm). The primary objective is to evaluate whether the addition of acalabrutinib to R-CHOP will prolong PFS. Secondary endpoints include event-free survival, complete response rate, OS, pharmacokinetics, and safety. Key exclusion criteria are central nervous system involvement, primary mediastinal lymphoma, high-grade B-cell lymphoma, diagnosis or treatment of malignancy other than DLBCL, and history of indolent lymphoma. Approximately 250 sites globally will enroll patients. Enrollment began in Q3 of 2020.
Results: Trial in progress.
Summary/Conclusion: Study is currently recruiting.

PB1435 BENDAMUSTINE IS A FAVORABLE LYMPHODEPLETING CHEMOTHERAPY REGIMEN PRIOR TO CAR T CELLS IMMUNOTHERAPY AS FLUDARABINE

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Background: In the process of chimeric antigen receptor (CAR) T cells therapy, it is necessary to carry out pretreatment chemotherapy to reduce lymphocytes called lymphodepleting chemotherapy before infusion of CAR T cells, which makes CAR T cells continuously expanding in *vivo*, plays an anti-tumor effect as well. For the patients of relapsed and refractory B-cell lymphoma (R&R BCL) treated with CAR T, the preferred lymphodepleting chemotherapy should have the dual effect of clearing lymphocytes and reducing tumor load. Bendamustine was reported to treat some R&R BCL, as well acting on lymphocyte clearing.
Aims: To investicate the clinical application of bendamustine as the pretreatment prior to CAR T cells infusion, and to examine its safety and therapeutic effect.
Methods: Twenty-one patients in our cohort were enrolled in this study. All of them were refractory and relapsed patients with poor response to several second-line chemotherapy. The mean age of these 21 patients was 50 years old. Twelve patients were male and 9 patients were female. Nineteen patients were defuse large B cell lymphoma (12 patients were non-GCB and 7 patients were GCB), One patient was follicular lymphoma, and one was Burkitt Lymphoma. About 85.7% patients (18/21) were in stage III-IV, 71.4% patients (15/21) were ECOG≥2. Bendamustine (90 mg/m^2) were used to deplete lymphocytes on days -4~-3 before infusion of CAR T cells (day 0). The CAR T cells for treatment were CD19 or CD20 or CD22 specific chimeric antigen receptor T cells. Average dose of CAR T cells infusion was 2.25×106/kg. CAR T cells in the PB were measured on day 0, 7, 11, 15 and 30, or as necessary by Flow cytometry.
Results: In the bendamustine group, the average peak number of CAR T cells expansion in *vivo* was 1.97×10$^{8/L}$. There were few serious adverse reactions except nausea and vomiting during chemotherapy. The occurrence rate of CRS above grade 2 was 33.3% (7/21) and ICANS above grade 3 was 9.5% (2/21). Three months after CAR T cells infusion, 38.1% patients (8/21) achieved CR, 47.6% patients (10/21) with PR. So the ORR was 85.7%.
Among the 21 patients, 5 patients were treated with CAR T cells twice within 6 months. Fudalabine combined with cyclophosphamide (FC) was chosen for the first lymphodepleting regimen and bendamustine for the second. Bendamustine reduced the number of lymphocytes by 82.3%, while it was 88.6% for FC (P >0.05). Overall the bendamustine regimen was inferior to FC in term of the CAR T cell proliferation rate. There was no significantly difference between these two groups about the occurrence rate of CRS. Regarding CR rate, bendamustine is considered to be superior to FC group.
Summary/Conclusion: Bendamustine can be used as a favorable lymphodepleting chemotherapy drug prior to CAR T.
Key words: Bendamustine, Fludarabine, CAR T, lymphodepleting chemotherapy.

PB1436 DISPARITIES IN LYMPHOMA SURVIVORSHIP ACCORDING TO SOCIO-DEMOGRAPHIC FACTORS; SINGLE CENTER RETROSPECTIVE STUDY IN A COHORT OF 253 DLBCL PATIENTS TREATED WITH RCHOP

M. Symeonidou [1], S. Intzes [1], K. Zagoridis [1], Z. Bezirgiannidou [1], A. Pentidou [1], C. Misidou [1], G. Vrachiolias [1], M. Papoutselis [1], K. Liapis [1], I. Kotsianidis [1], E. Spanoudakis [1,*]

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Background: Diffuse large B cell Lymphoma (DLBCL) is an aggressive histology lymphoma with heterogeneous outcome in the RCHOP immunotherapy era. Although, R-IPI is a useful tool cannot predict accurately outcome for all patients and especially in the real world setting, evidences suggest that sociodemographoc factors are determinants of lymphoma survivorship.
Aims: Our aim was to compare survival in our cohort according to socio-demographic factors.
Methods: In this single center retrospective study we included 253 nodal or extranodal DLBCL patients diagnosed after 2000 and treated with RCHOP. We excluded DLBCL patients with histology of PMBCL n=19, Primary CNS lymphoma n=9, Double hit Lymphoma n=2, Plasmablastic Lymphoma n=1, Lymphoma of the testis n=5 and other than RCHOP first line treatments n=12.
Results: Median age was 67 (16-89 yrs), men to women ratio was 148/92 and among patients in our cohort 186 pts were of Greek origin and 64 were Greek Muslims. Disease characteristics (IPI, Bulky, cell of origin according to Hans Index, stage III-IV) were not different according to ethnic origin except for the presence of ≥ 2 extranodal sites that occurred more frequently in the Greek Muslims cohort (33,5% vs 16,3%% for Greeks, p=0,007, chi-square). Overall survival (OS) according to ethnicity/race was statistically indifferent; median OS for Greeks 96 (61.2-130,8) months vs 63 (49-77,7) months for Greek Muslims (Log Rank p=0,084, Figure 1). Percentage of PET/CT complete metabolic response (CMR) after treatment completion was equal 78,8% vs 81% Greeks vs Greek Muslims (p=0,831, table 1).
The Modified Kuppuswamy scale slightly modified was used for SES assessment and according to this model 100 pts in our cohort were considered low SES and 148 high SES. Disease characteristics were similar between low and high SES cohorts except percentage of 1 extranodal sites (low SES 53,5% vs 42,3 for high SES pts, p=0,004) and ≥ 2 extranodal sites (low SES 27,5% vs 16,8% for high SES pts, p=0,004). Low SES patients had more often B-symptoms (62% vs 47,3% for high SES pts, p=0,023). Overall survival (OS) according to SES was statistically indifferent; median OS for low SES 51 (13,7-88,2) months vs 96 (52-140) months for high SES pts (Log Rank p=0,15, Figure 2). Percentage of PET/CT complete metabolic response (CMR) after treatment completion was equal 87% vs 76,6% for low and high SES respectively (p=0,291).
The Cumulative Illness Rating Scale-Geriatric (CIRS-G) was calculated for all patients and OS according to CIRS-G <3, ≥3 CIRS-G ≤7, and CIRS-G>7 were calculated. Median OS was inferior for DLBCL patients with CIRS-G more or equal to 3; median OS for CIRSG<3 126,5 (103,7-149) months for

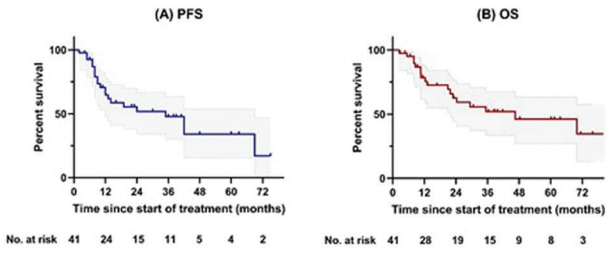
CIRSG 3-7 62,4 (52,1-73,6) months and for CIRSG>7 49,9 (35,2-64,7) months (Log Rank p=0,05, Figure 3).
Summary/Conclusion: In conclusion, lymphoma characteristics, CMR achievement and overall survival, except for percentage of patients with extranodal sites that occurred more often in low SES and Greek Muslims DLBCL patients, were not different according to SES and ethnicity/race. The only factor that is adversely related with overall survival is CIRS-G index more or equal to 3.

PB1437 OUTCOME OF PATIENTS WITH NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA AFTER HIGH-DOSE METHOTREXATE FOLLOWED BY CONSOLIDATION WHOLE-BRAIN RADIOTHERAPY AND CYTARABINE: AN 8-YEAR COHORT STUDY

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Background: Current treatment of primary CNS lymphoma (PCNSL) is a high-dose methotrexate (HD-MTX)-based polychemotherapy. The addition of cytarabine to HD-MTX-based chemotherapy improves clinical outcomes, however the combination therapy increases toxicity. Sequential chemotherapy may decrease toxicity without altering efficacy.
Aims: To analyze efficacy and safety of sequential chemotherapy and cranial radiation for newly diagnosed PCNSL patients.
Methods: This was a single center, retrospective cohort study of consecutive newly diagnosed immunocompetent PCNSL patients treated with HD-MTX (5 cycles of 3 g/m^2 every 2 weeks) followed by consolidation WBRT (total 46 Gy) and cytarabine (2 cycles of 3 g/m^2/d for 2 days every 3 weeks) from January 2013 to December 2020. Initial WBRT before HD-MTX was allowed in patients with Karnofsky performance status less than 70%. Primary outcome was progression-free survival (PFS). Key secondary outcomes were response rate, treatment-related toxicity, and overall survival (OS).
Results: Of 41 patients, 25 patients had complete response (CR) and 10 patients had partial response, which inferred to an overall response rate (ORR) of 85.4% and a CR rate of 60.9%. More than 90% of patients were able to tolerate and complete HD-MTX. Twenty-one patients (51.2%) received initial WBRT before chemotherapy. The incidence of ≥ grade 3 hematologic and non-hematologic toxicities were 4.8% and 17.1%, respectively. Treatment-related mortality rate was 2.4%. There was no difference in toxicity between patients with age < 60 and ≥ 60 years. At the median follow-up duration of 39.8 months, median PFS was 35.2 months (95%CI 12.4 – 69.3) and median OS was 46.5 months (95%CI 21.8 – NR).



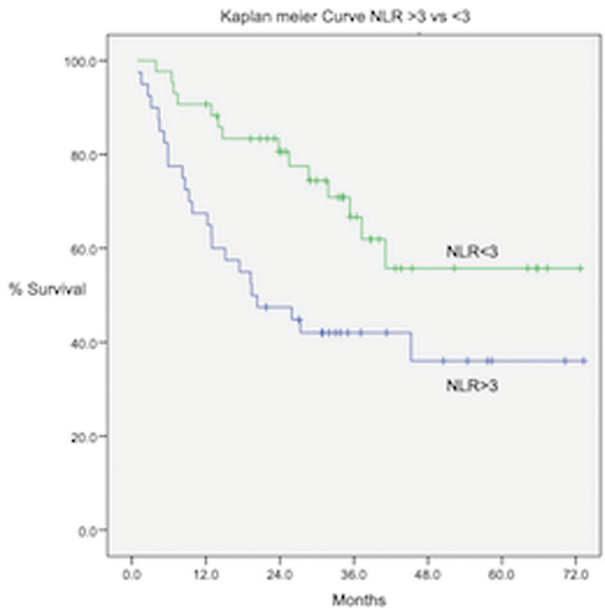
Summary/Conclusion: High-dose methotrexate followed by consolidation whole-brain radiotherapy and cytarabine has acceptable efficacy, great tolerability, and low toxicity in newly diagnosed PCNSL patients.

PB1438 NEUTROPHIL/LYMPHOCYTE RATIO (NLR) ITS A WORSE PROGNOSIS FACTOR IN OVERALL SURVIVAL IN LARGE B CELL LYMPHOMA (DLBCL). EXPERIENCE IN HEMATOLOGY CENTER IN NORTHEAST OF MEXICO

G. Sotomayor Duque [1], M. R. Rios Rodelo [1,*], S. Baltazar Arrellano [1], M. P. Pequeño Luevano [1], W. Nava [1], A. Mecott [1], R. Hernandez Valdes [2], R. E. De Leon Cantu [3], L. G. Avila Contreras [1], I. Borjon [1], D. Cruz Contreras [1], M. L. Guajardo [1], J. A. Carrizales Villarreal [1], H. P. Sorkee [1], J. L. Cedillo de la Cerda [1]

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Background: Diffuse Large Cell Lymphoma B (DLBCL) accounts for up to 62% of all Non-Hodgkin Lymphomas. The prognosis of DLBCL is established by considering patient and tumor factors. Neoplasm cells develop immune escape mechanisms in addition to an inflammatory response associated with Cancer. Tumor cells recruit Tumor Associated Neutrophils (NAT) that exert pro-carcinogenic effects such as inhibition of tumor cell apoptosis, angiogenesis, and suppression of the adaptive immune system.
Aims: To assess the impact on Overall survival of NLR in patients with a diagnosis of DLBCL
Methods: We aimed an observational, retrospective, cross-sectional and analytical study. Patients with Diffuse Large B-Cell Lymphoma, diagnosed between January 2014 and December 2018 were included. The qualitative variables were analyzed with the chi-square test and the quantitative variables with the student's t test. The relative risk was measured with a 95% CI, with a p value <0.05% being significant. A survival analysis was performed with Kaplan-Meier curves.
Results: 83 patients were included, 51 (61.4%) were men and 32 (38.5%) were women, with a median age of 61 (range 26-85) years and a median follow-up of 27 (range 0.9-73.2) months. Patients with NLR >3 was associated with lower response to chemo immunotherapy (p=0.001), higher relapse/refractive disease (P=0.003) and more than two lines of treatment (p=0.016). NLR >3 was associated with lower survival with HR 2.36(p=0.011). The Overall Survival at 6 years of patients with NLR> was 36% compared to those with NLR <3 was 56% (p = 0.009).



Summary/Conclusion: The NLR >3 is a predictor of a lower response to immunochemotherapy and more agresive course in addition to being associated with a lower overall survival in patients with DLBCL.

PB1439 HEALTH-RELATED QUALITY OF LIFE EFFECT OF MOGAMULIZUMAB BY PATIENT BLOOD INVOLVEMENT

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Background: Cutaneous T-cell lymphomas (CTCL) are a rare group of non-Hodgkin lymphomas that present in skin and progress to involve extracutaneous sites in a subset of patients. The most studied subtypes, mycosis fungoides (MF) and Sézary syndrome (SS), together represent around two-thirds of all cases. Disease staging of MF/SS is multi-compartmental and utilises a modified disease specific TNMB classification. Leukemic involvement, present by definition in SS and in a proportion of MF patients, has previously been found to be an independent prognostic factor affecting overall survival, disease-specific survival and increasing the risk of disease progression (Agar 2010, Am Soc J Clin Oncol), although further research is ongoing.
As a chronic and generally incurable disease associated with disfiguring skin lesions, intractable itching, sleep disturbance, and psychosocial problems, CTCL has a serious negative effect on patient quality of life (QoL). Therefore treatment goals include reducing the burden of disease, delaying progression, and improving or preserving QoL.
Aims: This post hoc analysis of MAVORIC trial data sought to determine whether baseline blood tumour burden affected treatment effect on patient QoL, where patients classified as B0 are considered to have no blood involvement and patients classified as B1 and B2 are considered to have blood involvement.
Methods: The Phase 3 MAVORIC trial (NCT01728805) was an open-label study that compared mogamulizumab to vorinostat, with patients randomised 1:1 to each treatment arm. Mogamulizumab patients received intravenous treatment, 1.0 mg/kg weekly for the first 28-day cycle then on days 1 and 15 of subsequent cycles. Vorinostat patients received 400mg daily PO. Patient reported outcome (PRO) assessments of health-related QoL (HRQoL) were assessed using the validated Skindex-29, and FACT-G (Functional Assessment of Cancer Therapy - General) instruments. Pruritus was assessed using ItchyQoL and Pruritus Likert Scale. All PROs were administered at baseline and Skindex-29, and FACT-G were then administered at every other treatment visit (Cycle 1, 3, 5, …), and ItchyQoL and Pruritus Likert Scale were administered every 4 weeks at each cycle. Only results taken up to treatment Cycle 12 were analysed as beyond this point, patient numbers were too low to give meaningful data.
Results: Overall, no statistically significant differences were seen between mogamulizumab and vorinostat for patients with no blood involvement. Statistically significant differences were seen for patients with blood involvement, with mogamulizumab patients seeing statistically significant improvement in Skindex-29 for treatment Cycles 3–11 in all domains (Emotional, Functional, Symptoms); and in the Functional Domain of ItchyQoL at most timepoints. In mogamulizumab-treated patients with blood involvement, the Pruritus Likert Scale Score showed a reduction in itch from Cycle 1 and a trend to reducing levels of itch over 12 cycles. The FACT-G Total Score showed greatest improvement from baseline for mogamulizumab patients with blood involvement compared to those without and all vorinostat patients (Figure 1).

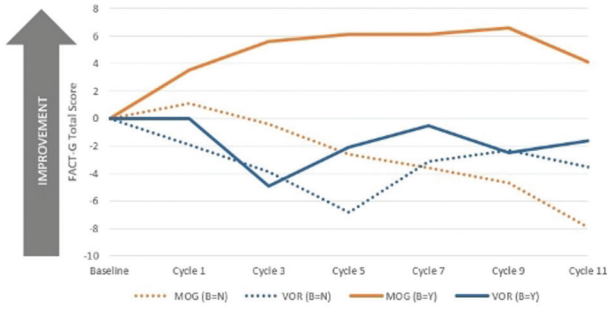


Figure 1. The change from baseline for the FACT-G Total Score by treatment cycle.
B, blood involvement; FACT-G, Functional Assessment of Cancer Therapy-General; MOG, mogamulizumab; N, no blood involvement; VOR, vorinostat; Y, confirmed blood involvement

Summary/Conclusion: Overall, mogamulizumab patients with blood involvement saw greater HRQoL improvement than those without blood involvement. Mogamulizumab offers QoL benefit, assessed across a number of PROs, especially to patients with blood involvement (B1 or B2).

PB1440 PHASE 3 RANDOMIZED STUDY OF LONCASTUXIMAB TESIRINE PLUS RITUXIMAB VERSUS IMMUNOCHEMOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) - LOTIS-5

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Background: Patients (pts) with DLBCL for whom frontline therapy is unsuccessful and who are ineligible for autologous stem cell transplantation have poor outcomes with salvage therapy. Single-agent loncastuximab tesirine (Lonca), an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin, showed antitumor activity and manageable toxicity in pts with R/R B-cell non-Hodgkin lymphoma in a Phase 1 trial (Hamadani *et al*. Blood 2020; blood.2020007512) and in pts with R/R DLBCL in a Phase 2 trial (Caimi *et al*. Blood 2020; 136(Suppl 1):35–37).
Rituximab (R) is part of standard immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments.
Aims: LOTIS-5 aims to evaluate Lonca + R (Lonca-R) versus (vs) standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in pts with R/R DLBCL.
Methods: This is a Phase 3 randomized, open-label, 2-part, 2-arm, multicenter study (NCT04384484). A non-randomized safety run-in (Part 1) will compare the safety of Lonca-R with previous safety data for Lonca after the first 20 pts have completed Cycle 1. Part 2 will be started if no significant increase in toxicity occurs; ~330 pts will be randomized 1:1 to receive Lonca-R or R-GemOx.
The primary objective of the study is to evaluate the efficacy of Lonca-R vs R-GemOx. The primary endpoint is progression-free survival by independent review. Secondary endpoints include overall survival; objective response rate; complete response rate; duration of response; frequency and severity of adverse events; changes from baseline in safety laboratory and clinical variables; concentration and pharmacokinetic parameters of Lonca (conjugated and total antibody, and unconjugated warhead); immunogenicity; and changes in patient-reported outcomes. Time-to-event endpoints will be assessed for the intent-to-treat population using a stratified log rank test. The dosing regimen of Lonca-R in both parts of the study will be 150 µg/kg Lonca + 375 mg/m^2 R every 3 weeks (Q3W) for 2 cycles and then 75 µg/kg Lonca + 375 mg/m^2 R for 6 cycles. The dose regimen of R-GemOx in Part 2 will be 375 mg/m^2 R, 1000 mg/m^2 Gem, and 100 mg/m^2 Ox Q2W for 8 cycles.
Key inclusion criteria include age ≥18 years; pathologic diagnosis of DLBCL (including pts with DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; ≥1 line of prior systemic therapy; not a candidate for stem cell transplantation; and measurable disease per 2014 Lugano Classification.
The study opened in September 2020 and enrollment is ongoing.
The trial design was presented at 62nd American Society of Hematology Annual Meeting and Exposition, December 5–8, 2020.
This study is sponsored by ADC Therapeutics SA.
Results: N/A
Summary/Conclusion: N/A
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PB1441 BRENTUXIMAB VEDOTIN IN COMBINATION WITH LENALIDOMIDE AND RITUXIMAB IN SUBJECTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) (TRIAL IN PROGRESS)

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Background: The majority of patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after HSCT or CAR-T, or who are not candidates for HSCT or CAR-T have poor outcomes and are in need of novel therapies. Brentuximab vedotin (BV) is a CD30-directed ADC and preclinical data provide a strong rationale for combining BV, lenalidomide, and rituximab in the treatment of R/R DLBCL. In addition, in a phase 1 trial in which 37 pts with R/R DLBCL were treated with BV + lenalidomide, the ORR was 56.7% (73.3% in CD30+ pts; manuscript in preparation). The median duration of remission was 13.2 months in pts with a CR or PR and 11.7 months in pts with CR, PR, or stable disease >6 months. The PFS and median OS were 11.2 months and 14.3 months, respectively and results were similar in the CD30+ and CD30 <1% groups. The clinical activity and manageable safety profiles of BV, lenalidomide, and rituximab as single agents, make the combination a potentially viable option in multiply relapsed and heavily pretreated pts.
Aims: To describe the study design and rationale for investigation of the combination of brentuximab vedotin, rituximab, and lenalidomide in a Phase 3 randomized study in R/R DLBCL.
Methods: This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of BV vs placebo, in combination with lenalidomide + rituximab, in subjects with R/R DLBCL (EudraCT: 2020-002686-33). Prior to randomization, there will be a safety and PK run-in period where 6 pts will receive BV, lenalidomide + rituximab, and safety and PK will be evaluated after the first cycle of treatment; 6/6 subjects have been enrolled.
Key eligibility criteria include: pts aged ≥18 with R/R DLBCL with an eligible subtype; ≥2 prior lines of therapy and have relapsed, declined, or are ineligible for stem cell transplant, or chimeric antigen receptor T-cell (CAR-T) therapy; ECOG 0 to 2; fluorodeoxyglucose-avid disease by PET and bidimensional measurable disease of at least 1.5 cm by CT.
Patients (n=400) will be randomized 1:1 to receive either BV or placebo in combination with lenalidomide + rituximab and will be stratified by CD30 expression (positive [≥1%] versus <1%), prior allogeneic or autologous stem cell transplant therapy (received or not), prior CAR-T therapy (received or not), and cell of origin (GCB or non-GCB).
The primary endpoints are PFS per BICR in the ITT and CD30+ populations. Key secondary endpoints are OS in the ITT and CD30+ populations, and ORR per BICR. Other secondary endpoints include CR rate, duration of response, and safety and tolerability of the combination. Disease response will be assessed by BICR and the investigator according to the Lugano Classification Revised Staging System. Radiographic disease evaluations, including contrast-enhanced CT scans and PET, will be assessed at baseline, then every 6 weeks from randomization until Week 48, then every 12 weeks. PET is not required after CR is achieved. The trial is currently enrolling and will be open in 16 countries.
Results: N/A
Summary/Conclusion: N/A

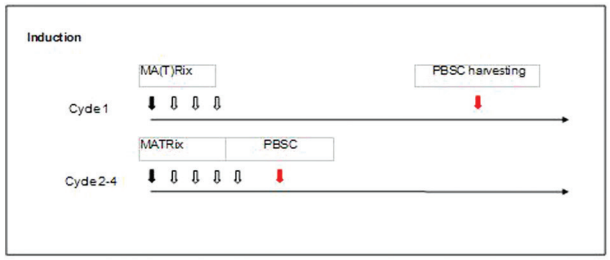
PB1442 SAFETY AND FEASIBILITY OF HIGH DOSE CHEMOTHERAPY WITH PBSC RESCUE AND ASCT CONSOLIDATION IN PCNSL: A SINGLE CENTER EXPERIENCE

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Background: Primary diffuse B-cell lymphoma of central nervous system (PCNSL) is a rare and aggressive non Hodgkin Lymphoma (2-3% of NHL). Currently, the standard of care for young and fit patients (pts), is MATRix regimen (Rituximab, HD-Metotrexate, Cytarabine and Thiothepa) and consolidation therapy with autologous stem cell transplantation (ASCT). The mortality reported in literature is 4-6%.
Aims: To study the safety and tolerability of MATRix regimen with sequential autologous peripheral blood stem cell (PBSC) infusion in young and fit pts with PCNSL.
Methods: We report 10 sequential cases of young (< 70 years old) and fit pts with a PCNSL, treated at Niguarda Hospital with the first cycle of MA(T)Rix followed by PBSC harvesting and 3 MATRix with PBSC rescue. Consolidation with ASCT (thiothepa and BCNU conditioning regimen) was performed in all the population in CR/PR.
Results: Ten pts with new diagnosis of PCNSL were treated between October 2014 and March 2019. The population was composed of 8 women and 2 men, median age at diagnosis was 56 years old. Consolidation therapy with high-dose chemotherapy (HDT) and ASCT was performed in 9/10 pts. One received only radiotherapy for progressive disease (PD).
After the first cycle of chemotherapy all pts had a successful stem cell mobilization and adequate harvesting of hematopoietic progenitor cells (median 33.4 x10^6 CD34/Kg). All the following 3 cycles of MATRix had received a rescue of stem cells (median of PBSC infusion at each cycle: 5.3 x10^6 CD34/Kg) on day + 2.
The median rise of neutrophil count (N >1000/mcl) was 13 days after second cycle and 14 days after third and fourth cycles.
Regarding toxicity the major complication were infections. 10/19 (52%) of all the infections occurred during the first cycle. According to NCCN Guidelines ® we observed 15 (79%) grade 1 and 2 infections and 4 (21%) grade 3 or 4.
Neither TRM nor ICU transferral were observed. No patient experienced cardiac or thromboembolic complication. Despite the higher frequency of complication of the first cycle no dose adjustment were made on the following cycles.
With a median of follow up of 16.1 months 50% of pts are in CR, the median OS is 13.6 months and the median PFS is 9 months.

Figure 1.



Treatment schedule:
Induction:
- Cyde 1: Rituximab 375 mg/sqm, Methotrexate 3.5 g/sqm on day 1, Cytarabine 2 g/sqm on day 2 and 3.
- Cyde 2-4: Rituximab 375 mg/sqm, Methotrexate 3.5 g/sqm on day 1, Cytarabine 2 g/sqm on day 2 and 3, Thiotepa 30 mg/sqm on day 4. PBSC rescue on day +2.

Summary/Conclusion: With the limitation of a small series of cases, MATRix regimen with sequential infusion of PBSC and ASCT consolidation is feasible and safe.

PB1443 ACUTE TOXICITY OF R-CHOP PROTOCOL IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA: ABOUT 551 CYCLES

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Background: The R-CHOP chemotherapy protocol is the gold standard for the treatment of non-Hodgkin's B lymphomas due to its efficiency in terms of therapeutic response and survival. However, this therapeutic combination can cause a significant toxicity.

Aims: The aim of this work is to study the incidence and severity of acute toxicity after R-CHOP, to study predictive factors of hematological or extra-hematological complications after R-CHOP, and to estimate the overall survival and mortality rate associated with this protocol.
Methods: This is a sixteen-year retrospective study at the Clinical Hematology Department of the Military Hospital of Tunis. The clinical and biological data of 89 patients were collected and the study of the side effects of 551 R-CHOP type chemotherapy cycles were detailed. The total number was divided into 407 R-CHOP$_{21}$ and 144 R-CHOP$_{14}$ cycles.
Results: Hematological toxicity was observed in 92% of the cycles, with predominantly grade 1 anemia, thrombocytopenia and lymphopenia. Among the 63 (11.4%) cases of grade 4 neutropenia, 34 (6%) progressed to febrile neutropenia (FN) with only 3 during RCHOP$_{14}$. Among the 65 patients who received RCHOP$_{21}$, 15 had primary prophylaxis with granulocyte colony-stimulating factors (G-CSF), and among these patients, only 3 episodes of FN were described, while the total number of FN episodes during RCHOP$_{21}$ was 31 (7.6% of the total cycles of RCHOP$_{21}$). In univariate analysis, it was found that the presence of more than two comorbidities, a positive Charlson score, hypoalbuminemia, hemoglobin lower than 12 g/dl and neutrophil count less than 1500/mm^3 at the pre-treatment assessment, lymphopenia less than 600/mm^3, thrombocytopenia less than 100 000/mm^3, lack of G-CSF prophylaxis, as well as the type of treatment received (RCHOP$_{21}$), were predictive factors for the occurrence of febrile neutropenia. In multivariate analysis, significant risk factors for FN were hypoalbuminemia (p=0.01), neutrophil count less than 1500/mm^3 on pre-chemotherapy workup (p=0.013), lymphopenia and thrombocytopenia ($p < 0.0001$ respectively). Neurological toxicity was seen predominantly (42.8%) at the end of the 5th cycle. An age over 60 was found to be an independent risk factor for neurological toxicity (p=0.005). Pulmonary, hepatic and renal toxicities were not significant. As for cardiac toxicity, it was observed in 4 patients, and resulted in a deadly heart failure in one case. Fifteen deaths were recorded in our study, including three toxic deaths. The overall survival was influenced by the absence of primary G-CSF prophylaxis (p=0.002), the presence of initial liver damage (p=0.001), and the occurrence of FN during the first cycle (p=0.013). The event-free survival was also correlated with the absence of primary G-CSF prophylaxis (p=0.005), the occurrence of FN during cycle 1 (p=0.039), and the presence of initial liver damage (p=0.001).
Summary/Conclusion: Our results confirms the efficiency of the R-CHOP protocol in terms of therapeutic response. However, an acute toxicity, essentially hematological and cardiac, was noted. Systematic G-CSF prophylaxis and close cardiac monitoring would therefore help reduce these adverse effects.

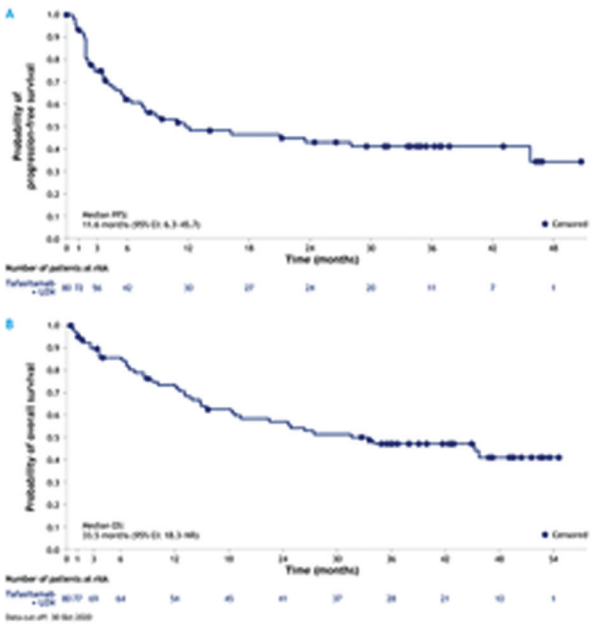
PB1444 LONG-TERM ANALYSES FROM L-MIND, A PHASE II STUDY OF TAFASITAMAB (MOR208) COMBINED WITH LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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Background: Tafasitamab is a humanized, Fc-modified anti-CD19 monoclonal antibody that enhances antibody-dependent cellular cytotoxicity and phagocytosis. It is FDA-approved in combination with lenalidomide for adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), including arising from low-grade lymphoma, who are ineligible for autologous stem cell transplant (ASCT).
Aims: L-MIND (NCT02399085) is an ongoing, open-label, single-arm, Phase II study to characterize the safety and efficacy of tafasitamab + lenalidomide in ASCT-ineligible patients with R/R DLBCL. Primary analyses and 2-year efficacy results were previously presented: we report an updated efficacy analysis with ≥35 months follow up (Data cut-off: October 30, 2020).
Methods: Patients were aged ≥18 years with ASCT-ineligible R/R DLBCL, had 1–3 prior systemic therapies (including ≥1 CD20-targeting regimen), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients received 28-day cycles of tafasitamab (12 mg/kg IV), once weekly during cycles 1–3, with a loading dose on Day 4 of cycle 1, then every two weeks (Q2W) during cycles 4–12. Lenalidomide (25 mg PO) was administered on Days 1–21 of cycles 1–12. After cycle 12, progression-free patients received tafasitamab Q2W until disease progression. The primary endpoint was objective response rate (ORR), assessed by IRC. Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and overall survival (OS).
Results: Eighty of 81 enrolled patients received tafasitamab + lenalidomide and were included in the full analysis set. At data cut-off, the overall ORR was 57.5% (n=46/80), including a complete response (CR) in 40% of patients (n=32/80) and a partial response (PR) in 17.5% of patients (n=14/80). Median estimated DoR was 43.9 months (95% confidence interval (CI): 26.1–not reached [NR]), and was NR in patients who achieved a CR (95% CI: 43.9–NR). Median estimated PFS was 11.6 months (95% CI: 6.3–45.7), with a median follow-up of 33.9 months (Fig.); estimated 36-month PFS was 41.1% (95% CI: 29.1–52.7). Median estimated OS was 33.5 months (95% CI: 18.3–NR), with a median follow-up of 42.7 months.
In patients who had received 1 vs ≥2 prior lines of therapy, ORR was 67.5% (n=27/40; CR rate: 47.5%; PR rate: 20.0%) vs 47.5% (n=19/40; CR rate: 32.5%; PR rate: 15.0%). Median estimated DoR was 43.9 months (95% CI 9.1–NR) in patients with 1 prior treatment and not reached (95% CI 15.0–NR) in those receiving ≥2 prior treatments. Median estimated PFS and estimated 36-month PFS were 23.5 months (95% CI 7.4–NR) and 47.8% (95% CI: 30.2–63.4) in patients with 1 prior treatment vs 7.6 months (95% CI 2.7–NR) and 34.3% (95% CI: 18.6–50.7) in those receiving ≥2 prior treatments. Median estimated OS was 45.7 months (95% CI 24.6–NR) in patients with 1 prior treatment compared with 15.5 months (95% CI 8.6–NR) in those receiving ≥2 prior treatments.
There were no unexpected toxicities or new safety signals.

Kaplan-Meier plot of (A) PFS and (B) OS after 35 months follow-up



Summary/Conclusion: Combination therapy with tafasitamab + lenalidomide followed by tafasitamab monotherapy provided durable responses, achieving a median DoR of 43.9 months in patients with R/R DLBCL not eligible for ASCT, with a manageable safety profile. These long-term data indicate that this chemotherapy-free regimen can achieve prolonged remission and survival benefit in this patient population, especially at first relapse, with a median estimated DoR of 43.9 months and median estimated OS of 45.7 months at second-line.

PB1445 MANUFACTURING COMMERCIAL AXICABTAGENE CILOLEUCEL FOR EUROPEAN PATIENTS: A 2-YEAR RETROSPECTIVE ANALYSIS

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Background: Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor T-cell therapy, was granted marketing authorization by the European Commission on August 28, 2018 for use in adults with relapsed/refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after ≥2 prior lines of systemic therapy.
Aims: To describe 2 years of post–marketing authorization experience in manufacturing from a United States site and supplying commercial axi-cel lots in European countries and Israel.
Methods: From apheresis material collected at a qualified treatment center, peripheral blood mononuclear cells (PBMCs) were manufactured and cryopreserved in The Netherlands and then shipped to the United States (El Segundo, CA) to continue manufacturing. If additional apheresis was needed, the first apheresis was considered for each patient, and is subsequently referred to as that patient's lot. The finished product lot was shipped back to The Netherlands for European Qualified Person (QP) release and then sent to the hospital for administration to the patient.
Results: From first apheresis after marketing authorization, September 6, 2018, until September 5, 2020, 1074 patients were included on the Kite Konnect® website and provided apheresis material for axi-cel manufacturing. The median and mean turnaround times from apheresis to QP release were 25 days and 26.2 days, respectively. The median and mean times from apheresis to shipment were 29 days and 31.5 days, respectively. Despite the transatlantic air travel disruption due to the COVID-19 pandemic, the median turnaround time from apheresis to QP release from March 2020 to August 2020 was not affected (25 days).
For those 1074 patients for whom manufacturing was started, 1040 commercial axi-cel lots (97%) were released, and 1000 (93%) were delivered, including 19 lots (1.8%) that were out of specification. Out of specification commercial axi-cel lots were released exceptionally and on physician's request based on a risk/benefit assessment according to the European Union Advanced Therapy Medicinal Product guidelines.
To obtain this level of manufacturing success, a remanufacturing step was required either from frozen PBMC bags in 19 cases (1.8%) or from new apheresis in 19 cases (1.8%). In addition, 18 patients (1.7%) had batches rejected; 7 patients (0.7%) had production terminated, and 9 patients (0.8%) had orders cancelled.
In June 2020, a new facility in Hoofddorp, The Netherlands opened to engineer cell therapies for European patients with the objective of substantially reducing time from apheresis to QP release and to avoid transatlantic transport.
Summary/Conclusion: In conclusion, the initial 2-year experience in manufacturing commercial axi-cel for European countries shows high manufacturing success, with a reliable time from apheresis to QP release (median, 25 days) and a very low percentage (1.8%) of out of specification lots released on physician's request.

PB1446 RELATIONSHIP BETWEEN PAKT1, PSYK PROTEINS CO-EXPRESSION AND SURVIVAL IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. The clinical criteria characterized by the International Prognostic Index (IPI) provide a standard model for risk stratification. However, there is variability in outcomes in IPI risk groups, which indicating the biological and clinical heterogeneity of the DLBCL and does not allow to accurately assess the individual risk of therapy failure. Development of the additional biological prognostic criteria of disease could allow to lower unfavorable outcome cases. Dysregulation of key molecules (pAKT1, pSyk) of the PI3K/AKT/mTOR and BCR signaling pathways involves the biological behavior of tumor cells and may affect on the course of DLBCL. It worth noting that monotypic overexpression of pAKT1 and pSyk is associated with low overall (OS) and progression-free (PFS) survival in DLBCL patients. Nevertheless, the combined expression of these proteins still has not yet been studied, thus indicates the relevance of the research.
Aims: Assesment of relationship between co-expression pAKT1, pSyk proteins in tumor cells with OS and PFS in DLBCL.
Methods: Formalin fixed, paraffin-embedded lymph node and other organ and tissue samples of 100 patients with newly diagnosed DLBCL were used. All the patients were treated in the clinic of institute from 2012 to 2018 using standard R-CHOP regimen. Determination of the relative number of pAKT1-, pSyk-positive tumor cells was performed by immunohistochemical and morphometric methods. OS and PFS were calculated by the Kaplan-Meier method using the log-rank test. Threshold values for the expression of these proteins were calculated using ROC-analysis: pAKT1-positive tumor cells - 70%; pSyk-positive tumor cells - 28%. According to the established thresholds, all subjects were divided into groups with high [≥70% (+) for pAKT1; ≥28% (+) for pSyk] and low [<70% (-) for pAKT1; <28% (-) for pSyk] protein expression. The interrelation of different variants of pAKT1 and pSyk co-expression with the course of DLBCL was analyzed.
Results: The highest OS (90.2%) was recorded in the group of patients (n=41) with simultaneously low expression of markers (pAKT1-/pSyk-). In the presence of co-expression of pAKT1+/pSyk- and pAKT1-/pSyk+, it was 52% (n=29) and 60% (n=15), respectively. The lowest OS values (26.7%) were observed in patients (n=15) with a combination of pAKT1+/pSyk+, which significantly differed from other variants of co-expression of markers (p<0.001; HR=5.2; 95% CI=2.49-10.9). A similar pattern was found in the analysis of PFS. The proportion of patients without disease progression with the option of co-expression of pAKT1-/pSyk- was 78.1% (n=41), and in the presence of combinations of pAKT1+/pSyk- and pAKT1-/pSyk+ - 55% (n=29) and 53% (n=15), respectively. The lowest PFS (40%) was recorded in patients with simultaneous overexpression of biomarkers (n=15; p=0.002; HR=3.3; 95% CI = 1.54-7.30).
Summary/Conclusion: Combined overexpression of pAKT1/pSyk proteins is associated with a poorer prognosis of DLBCL compared with other variants of their co-expression.

PB1447 THE PROGNOSTIC ROLE OF PD-L1 PROTEIN EXPRESSION IN A COMBINED MODEL FOR PREDICTION OF THE SURVIVAL OF DIFFUSE LARGE B CELL LYMPHOMA PATIENTS

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Background: Diffuse large B-cell lymphoma (DLBCL) is characterized by molecular biological heterogeneity and variability of the clinical course, which casts doubt on the use of a single standard of patient care and promotes the search for risk-adapted approaches in the first line of therapy for patients with DLBCL. The search for new predictors of effectiveness of induction therapy and survival are of significant scientific and practical importance
Aims: The research is aimed at the assessment of prognostic value of PD-L1 protein expression in a combined model for predicting the course of DLBCL in patients receiving induction therapy according to the RCHOP therapy

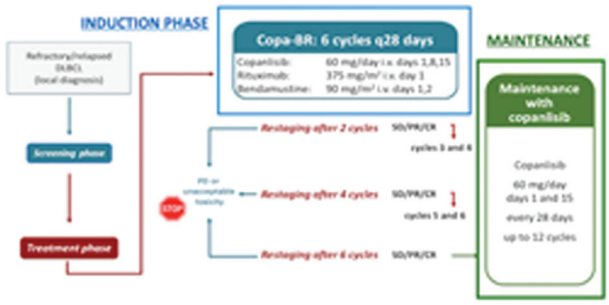
Methods: A retrospective analysis of the data of 85 DLBCL patients who were treated at the Kirov Scientific Re-search Institute of Hematology and Blood Transfusion was carried out. The median age was 59 (18-80) years. All the patients received no less than 4-6 courses of RCHOP chemotherapy. The median follow-up was 17 (1-168) months. The optimal cut-off threshold for assessing the proportion of cells expressing the PD-L1 protein was determined using the CART (Classification and Regression Tree) machine learning method
Results: The patients were divided into three groups according to the immunohistochemical subtype and IPI risk. In group 1 with GCB type tumors and any risk except high 21 (84%) and 4 (16%) patients, respectively, showed low or higher PD-L1 expression. Low level of PDL1 provided two-year PFS in 76% of all the cases, while higher level of PDL1 – in 100% (p=0,628). Two-year OS was 100% in both groups.
In Group 2 with nonGCB subtype and any risk except high 27 (67,5%) and 13 (32,5%) patients had low and high PD-L1 expression, respectively. Two-year PFS didn't differ much: 46% - in high PDL1 expression level and 49% - in low PD-L1 expression level. At the same time the patients with high PD-L1 expression had shorter OS than those with low expression: 52% and 87%, respectively (p=0,049).
In Group 3 with high IPI risk 9 (45%) and 11 (55%) patients had high and low PD-L1 expression level, respectively. In cases of high PD-L1 two-year OS was 0%, with 46% in cases of low PD-L1 (p=0,002). Two-year OS was 66% in the patients with low PD-L1 expression level (p=0,008).
Summary/Conclusion: High PD-L1 expression level in combination with high IPI and non-GCB tumor subtype is associated with low OS and PFS in DLBCL patients. This is probably due to the low efficacy of induction therapy according to the RCHOP regimen in patients with high IPI risk. This allows us to consider the assessment of the proportion of PD-L1 expressing cells as an additional criterion for stratification of patients into risk groups for predicting the response to treatment and a differentiated approach to the choice of therapeutic tactics at the onset of the pathological process

PB1448 COPANLISIB IN COMBINATION WITH RITUXIMAB-BENDAMUSTINE IN PATIENTS WITH RELAPSED-REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A MULTICENTRIC PHASE II TRIAL OF THE FONDAZIONE ITALIANA LINFOMI (FIL_COPA-RB)

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Background: Diffuse large B cell lymphoma (DLBCL) are curable in 50-60% of cases with frontline immunochemotherapy. Salvage therapy for relapsed/refractory (R/R) DLBCL is able to cure roughly 40-50% of patients, and includes high dose-chemotherapy plus autologous stem cell transplant (ASCT) in chemosensitive fit patients, and chimeric antigen receptor T-cells (CAR-T), permitted only after ≥2 prior systemic regimes in patients with no major comorbidities. Therefore, there is an urgent need to investigate new salvage treatments for R/R DLBCL unresponsive or ineligible to ASCT or CAR-T. Rituximab plus bendamustine (RB) is active in R/R DLBCL with an overall response rate (ORR) ranged from 40 to 60% but usually of short duration. Copanlisib is an intravenous pan-class I PI3K inhibitor with predominant activity against PI3K-α and -δ isoforms, active as single agent in indolent lymphomas and DLBCL with ORR of 59% and 25%, respectively (NCT01660451) (NCT02391116). Most frequent treatment-emergent adverse events are transient hyperglycemia and transient hypertension. The association of copanlisib plus RB (Copa-RB) has been showed a safe treatment in R/R indolent lymphomas (NCT02626455).
Aims: To assess the efficacy and safety of Copa-RB followed by copanlisib maintenance in R/R DLBCL not eligible or relapsed after ASCT or CAR-T
Methods: FIL Copa-RB is a multicentric open-label single arm, single stage, phase II trial. An estimated 81 patients will be enrolled, from 30 centers in Italy. Inclusion criteria are: patients aged 18 or older with histologically confirmed DLBCL (including de-novo DLBCL, DLBCL transformed by indolent lymphomas and high-grade lymphoma) R/R after 1 to 3 previous lines of therapy, considered not candidate or R/R to ASCT or CART, ECOG PS ≤ 2. Exclusion criteria include primary mediastinal B cell lymphoma histology, significant organ dysfunction, uncontrolled hypertension and hyperglycemia (HbA1c> 8.5%). Treatment consists of an induction phase with six 28-day cycles of copa-RB (copanlisib 60 mg intravenously on day (D) 1, D8 and D15, rituximab 375 mg/m2 on D1, bendamustine 90 mg/m2 on D1-D2) followed by a maintenance phase of twelve 28-day cycles of copanlisib 60 mg given on D1 and D15 (Fig.). The primary endpoint is progression free survival (PFS) defined as the time between the date of enrolment and the date of disease progression, relapse or death from any cause, whichever occurs earlier, with an expected improvement of 12-month PFS from 20% to 35%. Secondary endpoints include overall survival, ORR, complete response (CR) rate, duration of response and rate of response improvement during maintenance. Exploratory analysis will include correlation between outcome and cell of origin, MYC, BCL2 and BCL6 overexpression and rearrangements, and mutational analysis of selected genes possibly involved in predicting response to copanlisib. The expected study duration from first patient's first visit to last patient's last visit is approximately 4 years.
Results: The recruitment started in November 2020; at March 1st, 8/81 patients have been enrolled. Results for this study are not yet available.



Summary/Conclusion: The treatment of R/R DLBCL ineligible or unresponsive to ASCT or CAR-T is still an unmet clinical need and new treatment options are warranted. Copanlisib as single agent has been already shown a moderate activity in DLBCL and the association Copa-RB plus copanlisib maintenance could be a new strategy to improve the outcome of these patients. Biomarkers studies would further elucidate patients who are more likely to respond to this treatment.

PB1449 RADIOTHERAPY FOR SYSTEMIC B-CELL LYMPHOMA WITH CUTANEOUS INFILTRATION: IS IT WORTHY?

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Background: Cutaneous infiltration by systemic B-cell lymphoma is rare and frequently associated with advanced-stage disease. Radiotherapy is recommended as consolidation therapy in some extranodal B-cell lymphomas and as front-line treatment in primary cutaneous B-cell lymphoma. Studies that address the role of radiotherapy in the treatment of cutaneous infiltration by systemic B-cell lymphoma are lacking.
Aims: 1) to compare response to treatment in patients treated with and without radiotherapy;
2) to analyse disease-free survival (DFS) and relapse location after cutaneous infiltration in systemic B-cell lymphoma.
Methods: Retrospective unicentric cohort study including patients with systemic B-cell lymphoma with cutaneous infiltration treated on a tertiary hospital from 2010 to 2021. Patients were divided in 3 groups according to type of treatment after cutaneous infiltration: chemotherapy (CHEMO), radiotherapy (RT) and chemotherapy followed

by consolidation radiotherapy (CHEMO+RT). Primary outcome was response to treatment and secondary outcomes were DFS and relapse location after cutaneous infiltration. We used Fisher's exact test for group comparisons and survival analysis for DFS calculation. Data was collected by clinical records consultation and SPSS was used for statistical analysis.

Results: Twenty one patients were included in the analysis, 12 were female and median age at diagnosis was 67 years [Q1-Q3 58.5-75.0]. Median follow-up was 22 months [Q1-Q3 12.5-109.0]. Cutaneous infiltration was present at diagnosis in 15 patients (71%); in the 6 patients without infiltration at diagnosis, the median number of treatment lines was 1.5 [Q1-Q3 0.75-3.25]. The most frequent type of lymphoma was diffuse large B cell (DLBCL) (n=13), followed by follicular (n=3) and lymphocytic lymphoma (n=2). Eighty percent of patients had advanced-stage disease at diagnosis (AA stage IV); 2 patients were HIV positive. The head & neck region was the most frequently involved (n=11) and the most frequent types of lesion were nodules (n=8) and tumours (n=8). 6 patients had extensive/distant cutaneous disease. First line of treatment after cutaneous infiltration was CHEMO in 15 patients (R-CHOP in10, R-CVP in 4, GEMOX followed by autologous bone marrow transplant in 1 patient), CHEMO+RT in 3 patients (R-CHOP in 2 and Rituximab in 1; RT dose 25-36 Gy) and RT in 3 patients (12-40 Gy). There were no differences between the groups regarding age at presentation, gender, staging or DLBCL predominance. Complete response (CR) rate was higher in the CHEMO group (80%) than in the RT group (0%) *(p=0.025)*; no difference in CR rate was found between the CHEMO and CHEMO+RT group (67%)(*p=1.00)*. Of the 14 patients that achieved CR, 5 relapsed in the skin and 1 in the skin and nodes. Two of these patients were in the CHEMO+RT group and 4 were in the CHEMO group. All the cutaneous relapses occurred in the site of initial cutaneous infiltration. There were no differences in median DFS between CHEMO and CHEMO+RT (*p=0.638*).

Summary/Conclusion: Radiotherapy as consolidation treatment and as single treatment is not associated with better CR rates or more prolonged DFS than isolated chemotherapy. Relapse after CR in these patients is frequently located in the same cutaneous territory of the initial infiltration. These findings raise the question of the utility of skin radiotherapy in systemic B-cell lymphoma with cutaneous involvement, although more studies with larger sample sizes are needed to confirm our conclusions.

PB1450 DOSE-ADJUSTED EDOCH-RITUXIMAB IN ELDERLY PATIENTS WITH HIGH GRADE DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The standard first-line therapy for diffuse large B-cell lymphoma (DLBCL) is CHOP-R. Many studies have shown the efficacy of EDOCH-R (etoposide, dexamethasone, vincristine, cyclophosphamide, doxorubicin and rituximab) regimen in this pathology with an acceptable toxicity. However, there is few evidence supporting the efficacy and safety in elder patients.

Aims: The aim of this study is to analyze the results of EDOCH-R as first line therapy in patients over 60 years old with de novo DLBCL diagnosis at Hospital Universitario de Guadalajara (HUG).

Methods: The medical records of all the patients with DLBCL over the age of 60, treated with EDOCH-R as first-line therapy at HUG from 01/01/2014 to 31/12/2020 were review, identifying 25 patients in total. Baseline data was collected at diagnosis, including patient demographics, Eastern Cooperative Oncology Group (ECOG), staging, IPI, PET-TC and histologic subtypes. Germinal center B-cell (GCB) and non-GCB DLBCL subtypes were classified based on the algorithm proposed by Hans et al. EDOCH-R administration was planned every 21 days for 6 cycles. None of the patients received radiotherapy. Pegfilgrastim was administered at day 6 of therapy. Adverse events were reported according to the National Cancer Institute reviewed criteria. Statistical analysis was carried out with SPSS software. Overall survival (OS), progression-free survival (PFS) and response rate were the primary end points of this study. The secondary clinical objective included patient safety.

Results: The diagnostic parameters obtained for all the patients are recorded in Table 1. All the patients exhibited a high Ki-67 expression (≥ 80%). Two patients (8%) patients were classified as double expressor (DE) and another 2 (8%) individuals resulted double-hit lymphomas (DHL).

All the patients received EDOCH-R regimen as first-line chemotherapy with a median of 6 cycles. Complete remission (CR) was achieved in 79% of the patients that completed the 6 cycles, and partial remission was achieved in 10% of the patients. One patient (5%) exhibited progressive disease after 4 cycles of therapy. With a median follow-up of 36 months the OS was 65% and PFS was 52%. OS was lower in the group of patients older than 70 years and in those with an IPI greater than 3, although a significant difference was not encountered.

The major side effect of the EDOCH-R regimen was hematologic toxicity. Grade 4 neutropenia, anemia and thrombocytopenia were observed in 76%, 36% and 24% of the patients, respectively. Neutropenic fever developed in 76% of the patients. One patient exhibited a decrease in the cardiac ejection fraction, which led to change the treatment. Three patients (12%) over 70-years-old died of progressive lymphoma, and 2 patients (8%) had to end therapy due to comorbidity factors.

PARAMETER	DATA
Gender, n (%)	
Male	14 (56)
Female	11 (44)
Age (years)	
Median	57
Range	34-81
ECOG, n (%)	
0	3 (12)
1	14 (56)
2	8 (32)
3-5	0
Estage, n (%)	
1	2 (8)
2	5 (20)
3	5 (20)
4	14 (52)
IPI, n (%)	
1	5 (20)
2	5 (20)
3	8 (32)
4	5 (20)
5	2 (8)
DLBCL subtypes, n (%)	
Non-Germinal center B-cell	16 (64)
Germinal center B-cell	8 (32)
No data	1 (4)

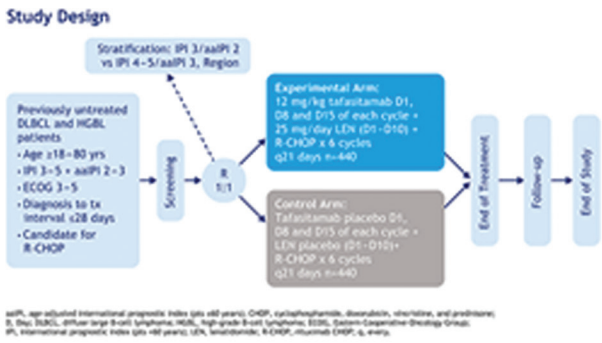
Summary/Conclusion: EDOCH-R is an effective therapy for DLBCL in elderly patients, although it has shown a high hematological toxicity.

PB1451 FRONT-MIND: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING EFFICACY AND SAFETY OF R-CHOP + TAFASITAMAB + LENALIDOMIDE VS R-CHOP ALONE FOR NEWLY-DIAGNOSED HIGH-RISK DLBCL

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Background: Tafasitamab is an Fc-modified, humanized monoclonal antibody targeting CD19+ tumor cells, which enhances *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis. Lenalidomide (LEN) has anti-proliferative and anti-angiogenic activities. Tafasitamab + LEN is indicated in adult patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including arising from low-grade lymphoma, who are ineligible for autologous stem cell transplantation. The L-MIND study (NCT02399085) showed that tafasitamab + LEN is well tolerated, with an ORR of 57.5% at ≥35 months f/up (reported at this meeting) in pts with R/R DLBCL. R-CHOP is the current standard of care for pts with newly-diagnosed DLBCL. In preclinical studies, tafasitamab + rituximab and tafasitamab + LEN were shown to increase anti-tumor activity compared to either single agent alone. Data from FIRST-MIND (NCT04134936), a Phase Ib, open-label, randomized study of tafasitamab + R-CHOP or tafasitamab + LEN + R-CHOP in pts with newly-diagnosed DLBCL, are reported elsewhere at this congress.
Aims: The Front-MIND study aims to assess the efficacy and safety of tafasitamab + LEN + R-CHOP vs R-CHOP alone in previously untreated, high-intermediate and high-risk pts.
Methods: Front-MIND is a Phase III, multicenter, randomized, double-blind, placebo-controlled study (Fig.). An estimated 880 pts will be enrolled, from 350 centers in America, Europe and Asia-Pacific. Eligible pts are aged 18 to 80 yrs with previously untreated (diagnosis to start of treatment ≤28 days [D]) local biopsy-proven, CD20-positive DLBCL (International Prognostic Index [IPI] ≥3 if >60 yrs/age-adjusted IPI 2–3 if ≤60 yrs), and ECOG PS 0–2. Pts with transformed lymphoma are excluded. Pts will be randomized 1:1 based on stratification factors: IPI intermediate-high vs high risk and geographic region. The experimental arm will comprise six 21-D cycles of tafasitamab (12 mg/kg intravenous D 1, 8 and 15) + LEN (25 mg orally, D1–10) + R-CHOP. The control arm will comprise six 21-D cycles of tafasitamab placebo (0.9% saline solution IV, D1, 8 and 15) + LEN placebo (D1–10) + R-CHOP. Pre-planned Central Nervous System prophylaxis with intravenous high-dose methotrexate is allowed after response assessment at end of treatment. The primary endpoint is investigator-assessed progression-free survival. Secondary endpoints include investigator-assessed event-free survival and overall survival. A large set of translational studies is planned, analyzing the relationship between potential biomarkers and efficacy. Pts will be followed up from their end-of-treatment visit until the end of the study, including clinical evaluation every 3–6 months and imaging every 3–12 months up to 60 months. The expected study duration from first pt's first visit to last pt's last visit is approximately 5 years. The study is conducted with the scientific support of the Fondazione Italiana Linfomi and the German Lymphoma Alliance.
Results: Results for this study are not yet available.



Summary/Conclusion: There remains a high unmet need to improve treatment options for newly diagnosed pts with high-risk DLBCL. The combination of tafasitamab, LEN and R-CHOP may have synergistic potential. Preliminary data from the First-MIND study suggest that tafasitamab ± LEN + R-CHOP is tolerable in pts with treatment-naïve DLBCL. The Phase III Front-MIND study will provide further evaluation of clinical benefits and safety in a high-intermediate and high-risk population of pts with newly diagnosed DLBCL.

PB1452 PRIMARY GASTRIC LARGE B CELL LYMPHOMA:EXPERIENCE OF THE HEMATOLOGY DEPARTMENT OF SFAX

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Background: Primary gastric lymphoma (PGL) is a rare disease. It is, however, the most common extra nodal non-Hodgkin lymphoma (NHL). Diffuse large B cell lymphoma (DLBCL) is the common aggressive subtype of gastric NHL.
Aims: The purpose of our study is to analyze its epidemiological aspects, clinical features, endoscopic aspects, therapeutic methods and prognostic factors in our center.
Methods: This retrospective study involved untreated patients with primary gastric large B cell lymphoma diagnosed between January 2006 and December 2019 in the hematology department of Sfax in Tunisia. The Musshoff-modified Ann Arbor System was used for clinical staging. We used the Revised International Prognostic index (R-IPI) score to evaluate prognosis.Patients were treated with chemotherapy (CHOP+/-R, ACVBP+/- R or mini CEOP/CHOP +/- R) alone or followed by radiation or autologous stem cell transplantation. The International Working Group Response Criteria for NHL 1999 was used to evaluate the response. To confirm complete remission, gastric lesions were evaluated by Endoscopy combined to Biopsy. Kaplan-Meier method was used to estimate overall survival (OS) and event free survival (EFS).
Results: A total of 24 eligible patients were identified. Sex ratio was 1.2.Median age was 59 years (17-82). The mean consultation delay was 9 months (1-48 months). Epigastric abdominal pain was the most common revealing symptom (83% of patients), it was associated to B symptoms in 75% of the cases. Performance Status of 2 or greater was noted in eight patients (33%). In Endoscopy, lesions were found more in gastric body and antrum (25%), there were 1 patient who had multiple located lesions and 1 who had diffuse gastric lesions. One patient had stenosis. Nasopharyngeal biopsy was performed on 10 patients and was positive in one case. Elevated LDH level were observed in 5 patients (21 %). 63% of the patients had localized disease (IE or IIE). Half of the patients were screened for Helicobacter Pylori Infection, it was present in 7 patients (58%). A quarter of gastric DLBCL were associated to low-grade mucosa associated lymphoid tissue (MALT) lymphoma. R-IPI was high in 12% of the cases, intermediate in 71% and low in 17%. The Median follow up was 120 months. One patient died of hemorrhagic shock before treatment and 4 patients died while undergoing chemotherapy. The treatment

response was determined in 18 patients, among them:71% achieved complete remission, 24% were evaluated partial response and 5% were in progression. Five Years OS and EFS rates were respectively 61% and 57%.
Summary/Conclusion: The rarity of PGL has left many aspects of this neoplasm to remain unknown. In our study, the initial presentation was with nonspecific symptoms, which often leads to misdiagnose and delay of treatment similarly to data from literature. The most frequent site of lesions in our patients was the antrum of the stomach (29%) which is similar to literature data. The majority of the cases had localized disease (63%) which remains lower than the other reported series (75-84%). Complete remission rates (71%) and five years OS rates (61%) were lower than the values reported in other series in literature and which were respectively 80% and 70-75%. Early diagnosis, availability of Rituximab and autologous stem cell transplant in high risk forms may help to improve our results.

PB1453 FRONTLINE BRENTUXIMAB VEDOTIN AND CHP (A+CHP) IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA WITH LESS THAN 10% CD30 EXPRESSION (SGN35-032, TRIAL IN PROGRESS)

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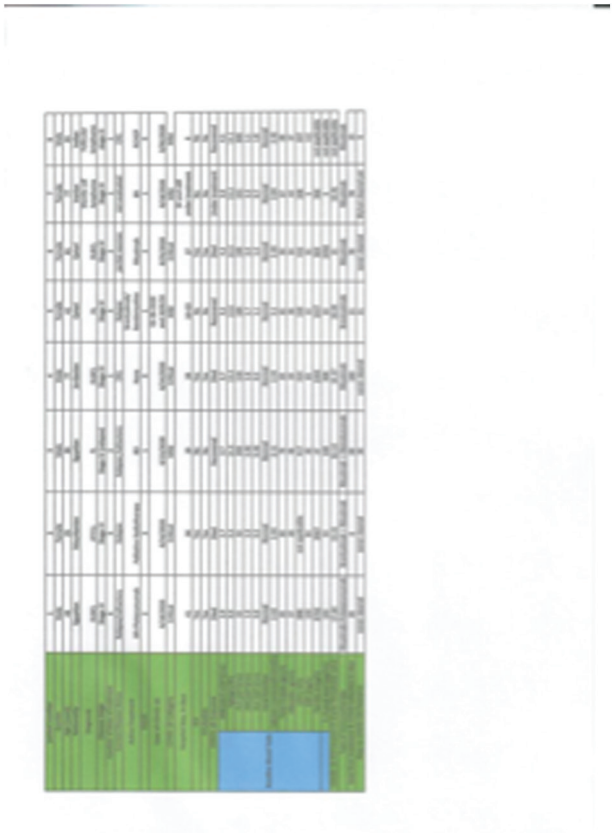
Background: In the ECHELON-2 phase 3 clinical trial, brentuximab vedotin, a CD30-directed antibody-drug conjugate, combined with cyclophosphamide, doxorubicin, and prednisone (A+CHP) showed efficacy in patients (pts) with peripheral T-cell lymphoma (PTCL) across a range of CD30 expression levels, including the lowest eligible level of 10% by IHC.
It is expected that A+CHP will demonstrate efficacy in PTCL with <10% CD30 expression because: i) clinical responses to brentuximab vedotin occurred in pts with low and undetectable CD30 expression (Jagadeesh 2019); and ii) the activity of CHP chemotherapy in PTCL is unrelated to CD30 expression. This study will include subjects with PTCL subtypes other than systemic anaplastic large cell lymphoma (sALCL).
Aims: To describe the rationale and study design of SGN35-032 (EudraCT 2020-002336-74), a study of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP) for patients with previously untreated PTCL with <10% CD30 expression.
Methods: This is a dual-cohort, open-label, multicenter, phase 2 clinical trial (EudraCT 2020-002336-74) designed to evaluate the efficacy and safety of A+CHP in subjects with non-sALCL PTCL and CD30 expression <10% on tumor cells. Up to approximately 40 subjects will be enrolled in each of the CD30 negative (expression <1%) and the CD30 positive (expression ≥1% to <10%) cohorts. Only subjects with CD30 expression <10% per central confirmation will be analyzed for the primary and secondary endpoints. Subjects will receive 21-day cycles of A+CHP for a target of 6-8 cycles.
The primary endpoint of this trial is objective response rate (ORR) per blinded independent central review (BICR) using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Key secondary endpoints include complete remission (CR) and progression-free survival (PFS) per BICR and overall survival.
Key inclusion criteria include adults with newly diagnosed PTCL, excluding sALCL, per the WHO 2016 classification; CD30 expression <10% by local assessment; and FDG-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.
Lymphoma response and progression will be assessed by BICR per Cheson 2007 and modified Lugano criteria (Cheson 2014). A PET scan is required at baseline, after Cycle 4, and after the completion of study treatment. Follow-up restaging CT scans will be performed over the next two years.
Efficacy and safety endpoints will be summarized with descriptive statistics by cohort, for both the CD30 negative and the CD30 positive cohorts. Time-to-event endpoints, such as PFS, will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be presented. Medians for time-to-event analyses (eg, median PFS),will be presented and two-sided 95% confidence intervals will be calculated using the log-log transformation method.
The trial currently is open at sites in the US. Sites in Europe are expected to open in early 2021.
Results: N/A
Summary/Conclusion: N/A

PB1454 IMPLICATIONS OF IMMUNOMODULATORY MEDICATIONS IN COVID-19 INFECTED HEMATOLOGICAL MALIGNANCY PATIENTS IN QATAR

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Background: Immunomodulatory medications including monoclonal antibodies are widely used in the treatment of many hematological malignancies, however their use during the COVID-10 pandemic was associated with worse outcome for some patients.
Aims: To evaluate the immune & hematologic characteristics of patient demographics, time from last chemo-immunotherapy, cancer status at time of infection, severity of COVID-19 infection, COVID-19 CT value, time of clearance, Immunoglobulin levels & IL-6 levels
Methods: To evaluate the immune & hematologic characteristics of patient demographics, time from last chemo-immunotherapy, cancer status at time of infection, severity of COVID-19 infection, COVID-19 CT value, time of clearance, Immunoglobulin levels & IL-6 levels
Results: during the study period we reviewed 50 patients with hematological malignancy who were diagnosed with confirmed COVID-19 since March 2020, 8 patients fit the inclusion criteria, all of them were having advanced stage lymphoma at some point.
4 patients died, 75% of them had ECOG ≥2 & all of them never cleared the COVID-19 virus, 3 patients recovered, 1 is still recovering but still has reactive COVID PCR test, remains in very stable condition.
the other 4 patents who recovered, 2 cleared their infection within 14 days, 1 patient had reinfection within 3 months & 1 still has positive COVID PCR after 30 days of infection, all of them were in complete remission at time of COVID-19 infection & all of them has mild infection



Summary/Conclusion: Treatment with monoclonal antibodies including regimens during COVID-19 pandemic should be used with caution in regards of its outstanding benefits vs risk of severe & fatal COVID-19 infection in this critical point of time. It was noticed that achieving hematologocal remission is an important factor in patient survival & recovery from COVID-19 infection, patient who died had lower COVID-19 PCR CT values than the patients who survived & never cleared the virus, however survivors mostly had delayed viral clearance than general population in general

PB1455 TREATMENT PATTERN AND PROGNOSIS ANALYSIS OF NEWLY DIAGNOSED T / NK CELL LYMPHOMA PATIENTS

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Background: Mature T / NK cell lymphoma account for 10 to 20% of all malignant lymphomas, and their treatment results are poor compared to B-cell lymphomas. The standard treatment is CHOP therapy, but the therapeutic effect is not sufficient. Here, we examined the treatment results of mature T / NK cell lymphoma in our institution.
Aims: To characterize treatment patterns and outcome for newly diagnosed mature T / NK cell lymphoma patients.
Methods: We retrospectively analyzed 123 cases of mature T / NK cell lymphoma who visited our institution from April 2007 to December 2017 based on medical records.
Results: 81 men and 42 women, with median age 68, range 31-90 years. Diagnosis was PTCL-NOS 34 (27.6%), AILT 24 (19.5%), ENKL 23 (18.7%), ALCL 15 (12.2%), ATL 17 (13.8%), MEITL 6 (4.9%) and others 4 (3.3%). Clinical stage I-II 39 (31.7%), extranodal involvement 93 (75.3%), B symptoms 21 (17.7%), bone marrow infiltration 21 (17.1%). Chemotherapy was performed in 109 (88.6%), CHOP 52 (47.7%), CyclOBEAP 17 (15.6%), and 2/3 DeVIC + radiotherapy 14 (12.8%). 9 (7.3%) received only palliative care. The median observation period was 17 months, and the 3-year OS and PFS were 51.6% and 40.2%, and the 3-year PFS of chemotherapy patients was 46.8%. By histological subtype, ALCL ALK+ 100%, ALCL ALK- 66.7%, ENKL 46.5%, AILT 39.7%, PTCL 34.2%, ATL 22.5%, MEITL 0%. By multivariate analysis, PIT, response to initial therapy and MEITL were associated with PFS(P=0.011, P<0.001, P=0.006). PIT, response to initial therapy and Age was associated with OS (P=0.011, P<0.001,P=0.009).
Summary/Conclusion: Mature T / NK cell lymphoma generally have a poorer prognosis than DLBCL, but the prognosis differs depending on the histological subtype, and it is important to determine a stratified treatment policy in the future.

PB1456 SUCCESSFUL TREATMENT BRENTUXIMAB VEDOTIN OF CD30-NEGATIVE ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA: CASE REPORT

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Background: Angioimmunoblastic T-cell lymphoma (AITCL) is one of the aggressive histological variants of peripheral T-cell lymphomas. About 70% of patients receiving first-line treatment develop a relapse or a refractory course. There are currently no treatment standards for relapsed/refractory (r/r) AITCL. A number of new therapeutic approaches aime to improve the results in patients with r/r AITCL, including immunotherapy with an effect not only on tumor cells, but also on cells of the microenvironment.
Aims: We want to demonstrate a case of successful treatment Brentuximab vedotin of CD30-negative angioimmunoblastic T-cell lymphoma.
Methods: A 55-year-old woman was diagnosed with angioimmunoblastic T-cell lymphoma who presented with IVB stage of disease with involvement of the cervical, supraclavicular lymph nodes, palatine tonsils, intrathoracic, axillary lymph nodes, intra-abdominal, retroperitoneal lymph nodes, iliac, inguinal lymph nodes, spleen, skin and bone marrow. The patient underwent several lines of chemotherapy and immunotherapy without achieving an effect (CHOP, GDP, CsA, 5-Azacytidine). After treatment, the therapeutic effects were evaluated by PET-CT. The tumor cells did not have CD30 expression, but due to the presence of CD30 expression on healthy cells of the microenvironment, it was decided to use Brentuximab vedotin (Bv) as a salvage-therapy.
Results: On Bv therapy, a partial response was achieved with an improvement in the quality of life (13 injections were performed in total - 4 in combination with Bendamustine and 3 with Rituximab). Therapy was continued with lenalidomide, resulting in a complete response.
Summary/Conclusion: This clinical case demonstrates that complete response was achieved by the effect of drugs on microenvironment but not on tumor cells, which emphasizes the immune dependence of this histological variant of PTCL.

PB1457 DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE B-CELL LYMPHOMA: THERAPEUTIC RESPONSE - UNICENTRIC RETROSPECTIVE DESCRIPTIVE ANALYSIS

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Background: Relapse/refractoriness (R/R) in diffuse large cell B lymphomas (DLBCL) and high grade (HG- DLBCL) affects more than 1/3 of patients and the existence of a poor prognosis poor prognosis and therapeutic challenge is well known.
Aims: This unicentric retrospective analysis aims to describe the response to 1st-line treatment and relapse of patients with DLBCL and HG- DLBCL.
Methods: Retrospective analysis of DLBCL or HG- DLBCL patients diagnosed and treated at a center between 2015 and 2019. We identified 125 with the diagnosis of DLBCL or HG- DLBCL between 2015-2019. Among this group, 58 did not undergo in curative chemoimmunotherapy (CIT). We report the results of a statistic analysis.
Results: The DLBCL group comprised 47 patients (81%), 13% G-DLBCL (13%) and 6% PTLD; 9% with involvement of extranodal sites. 55% were men; median age of 61 years (52% >60 years); 10% with ECOG ≥2. 10% were HIV+. The International Prognostic Index (IPI) was calculated: low: 26%; low intermediate: 30%; high intermediate: 33%; high: 7%.
The CIT schemes were R-CHOP (n=44), R-CNOP (n=10), R-mini-CHOP (n=8), others (n=5). The dose/replacement adjustment of anthracycline was made in patients aged > 60 years, high ECOG and/or comorbidities. 25% were treated with radiotherapy alone. 67% achieved complete response (CR).
R/R was 44.8% (recurrence n=10; refractoriness n=20). The median time to relapse was 10.5 months. At diagnosis these patients had IPI ≥2 in 87%, mass >7cm in 50% and 73% were CD5+. The activated B Cell subtype was identified in 1/3 of the cases. Five were double/triple-expressor and two double-hit.
Twenty-four patients underwent in second-line therapies. Only 29% (n=7) achieved CR (R-ICE n=3; R-DHAP n=2; R-Bendamustine n=1; CVP n=1). Four patients underwent autotransplantation. Eight performed ≥3 therapeutic lines.
The median follow-up was 19.3 months. The mortality rate was 36%. 71% died from disease progression. The median overall survival of patients undergoing 1st CIT was 39 months.
Summary/Conclusion: By advanced age, commorbidities and/or high ECOG, only 54% of patients with DLBCL or HG- DLBCL were elected to curative CIT. Of the remaining, only 9 are alive with follow-up time ≥ 18 months. The patients studied presented characteristics, risk factors and unsatisfactory responses to CIT in R/R, as described in the literature. Thus, we emphasize the need for therapeutic strategies adapted to improve prognosis.

PB1458 MYD88 EXPRESSION IN PRIMARY AND SECONDARY CNS LYMPHOMAS

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Background: Myeloid differentiation primary response 88 (MYD88) is a common adaptor protein that is responsible for signaling from several receptors; is encoded by the *MYD88* gene. [1].

Aims: Aim: We aimed to document the level of MYD88 expression, and their associations with clinicopathological parameters in CNS Lymphomas.
Methods: Methods: A total of 9 patients were included in the study. MYD88 protein expression was evaluated by immunohistochemistry (IHC) using two different scoring systems. All samples were diagnosed and selected by a hematopathologist. Tissue samples were collected from all patients before treatment.
MYD88 cytoplasmic expression was classified as four categories according to the staining intensity on a scale from 0 to 3 as follows: 0, no reaction; 1, weak reaction; 2, moderate reaction; and 3, strong reaction. This classification was called the first classification model. In the second classification model, the extent of staining scored as 0 (0% of tumor area stained), 1 (< 10%), 2 (10–50%), or 3 (> 50%) [2]. Staining intensity and the percentage of tumor cell positivity were evaluated and recorded by a hematopathologist.
Results: A majority of the patients in our CNSL cohort had an ABC-like immunophenotype, as has been previously reported [3]. MYD88 protein expression was seen in 8/9 cases (88,8%) and varied widely by intensity and density of expression. Five patients (55,5%) showed high-level MYD88 expression.1 patient didn't show protein expression. 3 of patient (patient 2,3and 9) dead after the diagnose who shows low expression of MYD 88.

Patient	MYD 88 first cl.	MYD 88 second cl.	pathology	localization	Lymphoma type
1	3+	90% (3)	Dlbcl-abc	Temporal lobe	Primary cns
2	1+	20% (2)	Extranodal marginal zone lymphoma	Spinal mass	Patient was lost before evoluation
3	1+	30% (2)	Dlbcl-abc	cerebellum	Primary cns
4	-	-	Dlbcl-abc	Foramen luschka mass	Primary cns
5	2+	100% (3)	Follicular lymphoma -3a	Epidural mass	Secondery cns
6	3+	95% (3)	Dlbcl-abc	Parietal lobe	Primary cns
7	1+	100% (3)	Dlbcl-abc	Temporal lobe	Secondery cns
8	3+	100% (3)	Dlbcl-abc	cerebellum	Secondery cns
9	1+	40% (2)	Dlbcl-abc	Occipital lobe	Primary cns

Summary/Conclusion: Conclusion: MYD 88 protein expression was found both of primary and secondary CNS lymphomas regardless of lymphoma subtype. Further studies are needed for its relationship with prognosis.

PB1459 SUCCESSFUL MANAGEMENT OF EARLY CENTRAL NERVOUS SYSTEM RELAPSE IN A PATIENT WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Background: Secondary central nervous system involvement as a relapse of primary mediastinal large B-cell lymphoma (PMLBCL) is an infrequent complication that drastically diminishes survival of the affected patients. Whole-brain radiotherapy and high-dose methotrexate (HD-MTX) were reported to improve the disease outcome, nevertheless, the median overall survival varies from 2 to 19 months, according to different authors. Here we present a case of complete cure of this condition.
Aims: The aim of the study was to outline the features of the disease course and management that could lead to long-term survival in case of primary mediastinal large B-cell lymphoma with secondary central nervous system involvement.
Methods: The 19-years-old male patient developed dyspnea and pain in the shoulder in June 2011. There were palpable subclavicular and left axillar lymph nodes revealed, and CT showed conglomerate in the mediastinum sized 160x135x190 mm together with contrast accumulation in both lungs and pleural effusion. Histological and immunohistochemical findings supported the diagnosis of PMLBCL. IPI was considered as low-intermediate. Initially patient received 2 CHOP-Bleo followed by 6 R-CHOP cycles, resulting in CR. Initially patient had received 2 CHOP-Bleo cycles of chemotherapy, followed by 6 R-CHOP cycles resulting in CR. One month later, however, intensive headaches developed. MRI revealed 71x62mm tumor in the right hemisphere (see picture). Right craniotomy with subtotal tumor resection had been performed, followed by 50 Gy ^{60}Co γ-therapy that was used locally on the bed of the removed tumor with subsequent 42 Gy total brain irradiation. After resolution of cytopenia, 2 cycles of HD-MTX 3.5g/m^2 and rituximab 0.375g/m^2 were initiated with 3-week interval between cycles. Immunochemotherapy had been stopped due to the acquisition of acute viral hepatis B, and therapy with peg-interferon-α-2b (peg-IFN) 0.12g weekly was started and lasted 6 months.
Results: The decision to perform subtotal CNS tumor resection instead of biopsy was made intraoperatively by the surgeon, as the result of the macroscopical resemblance of the tumor to glioblastoma. Nevertheless, histology confirmed extranodal PMLBCL in the resected tissue. In the post-operative period, the patient developed secondary epilepsy, successfully controlled with carbamazepine. HD-MTX caused neutropenia with mild infectious complications. The switch from peg-IFN to tenofovir in the treatment of hepatitis B resulted in improvement of the symptoms of epilepsy. Residual dysmorphic changes in the right hemisphere have diminished spontaneously on the further MRI examinations. Body PET-CT after the stop of peg-IFN showed metabolically negative residual tumor mass in the mediastinum, sized 37x24x36mm. Biopsy revealed no bone marrow infiltration with PMLBCL. On the last PET-CT, performed 5 years after the CNS relapse, mediastinal residual tissue was slightly decreased to the maximal size of 29 mm. After the combined therapy the patient remains disease-free for 97 months. He has healthy biological son, born 3 years after the last cycle of HD-MTX.



Summary/Conclusion: Combination therapy including both surgical subtotal resection of localized CNS tumor instead of biopsy and subsequent local and whole brain irradiation followed by HD-MTX-containing regimens, can lead to the long-term remission and could possibly be curative for CNS relapse in some patients with PMLBCL. Further studies are needed to confirm the feasibility of this strategy.

PB1460 BELINOSTAT IS WELL TOLERATED AND EFFICACIOUS IN A PATIENT WITH EARLY RELAPSED PERIPHERAL T-CELL LYMPHOMA: A CASE REPORT.

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Background: Background: Peripheral T-cell lymphomas (PTCLs) are an aggressive and heterogeneous group of lymphomas with a T-cell origin. They are a rare entities, accounting for 10-15% of Non- Hodgkin lymphomas. The disease is generally incurable if refractory in the absence of transplantation and treatment is aimed at prolonging life and reducing disease-related symptoms. Belinostat is a histone deacetylate inhibitor that was granted accelerated approval by the US Food and Drug Administration on July 3, 2014, for the treatment of patients with relapsed or refractory PTCLs. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.
Aims: Case report.

Methods: Case Summary: 60 year old male patient with PTCL not otherwise specified (PTCL-NOS), Ann Arbor stage IVE B, was being treated with four cycles of chemotherapy with CHOEP-21; he achieved a partial remission and a complete remission of disease after completing six cycles CHOEP-21. About 7 months after the end of treatment, he achivied a first relapse. The patient was treated with three courses of GemOX obtained a stable disease. A third line chemotherapy regimen with three cycles of DHAP protocol did not result in lymphoma remission. Subsequent treatment with Belinostat. After three cycles of belinostat, the patient achieved a partial response. After 6 months of belinostat therapy (8 cycles), the patient has maintained a PR. Belinostat therapy was well tolerated for all eight cycles with mild hematological and no hematological toxicities without any toxicity more than CTC grade 2. Belinostat therapy the patient in PR refused to continue the treatment. Two months later we observed a progression of disease and died.
Results: Monotherapy with belinostat has efficacy in Peripheral T-cell lymphomas.
Summary/Conclusion: Discussion: monotherapy with belinostat has comparable efficacy to other agents used in this setting and it is well tolerated in regard to hematologic events, but there is limited data on patient-reported outcomes, reduction in disease-related symptoms, or quality of life.

PB1461 INCIDENTAL DIAGNOSIS OF BURKITT LYMPHOMA ON CECAL APPENDIX: CASE REPORT AND LITERATURE REVIEW

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Background: Primary lymphoid organs are bone marrow and thymus. The secondary lymphoid organs are spleen,lymphonodes and lymphoid tissue associated to mucous membranes.Cecal appendix,therefore,can be site of NHL such as Burkitt lymphoma.BL is an aggressive NHL characterized by translocation and deregulation of the MYC gene on chromosome 8 and the heavy chain gene on chromosome 14.The t(8;14) is the most common translocation in BL occurring in 70-80% of cases.BL is derived from germinal center B cells and hystologicaly is characterized by a monomorphic population of matur lymphocytes with basophilic cytoplasm and prominent vacuoles.The result is a "starry sky" apparence due to macrophages containing cellular debris.The malignant cells express B-cell markers including CD19-CD20-CD79A-PAX5 and for germinal center markers CD10 and bcl6 but are negative for bcl2.There are only 30 cases of appendiceal Burkitt lymphoma in literature.In this cohort,the patients are predominantly male with an average age of 20 years.The majority of cases clinically presented as classical acute appendicitis,the remainder of cases presented atypical clinic but radiological signs of appendicitis.
Aims: In february 2020,a 44-years old man underwent appendicectomy for the diagnosis of acute appendicitis.Intraoperatively,a significant inflamed,edematous appendix without perforation was identified.Biopsy histology demonstrated marked expansion by lymphoid infiltrate composed by monomorphic intermediate-sized and the characteristic starry sky appaerance.In immunochemistry,the cells are CD20+ CD10+ BCL6+ BCL2- cMyc + with Ki67 proliferative index equal to 90%.The translocation t(8;14) in FISH confirms the diagnosis of Burkitt lymphoma.The patient had no B syntoms and was subjected to bone marrow biopsy without marrow infiltration by Burkitt Lymphoma.Total body CT and whole body PET did not demonstrate evidence of residual disease at any nodal or extranodal side.CSF was negative for neoplastic cells.LDH was normal.The Ann Arbor staging classification corresponde to stage IE, low risk.
Methods: The patient was started on a multiagent steroid and chemotherapy regimen(R-CODOX-M-IVAC)and medicated lumbar punctures.Our therapeutic program is to subject the patient to other cycles of therapy and to peripheral stem cells collection according to NCCN guidelines.
Results: Ours is one of the rare cases of appendiceal BL.This case allows us to underline the importance of hystology after appendicectomy to discover incidental diagnosis of NHL and other pathology with poor prognosis if not treated.
Summary/Conclusion: Approximately 1% of appendicetomies have an incidental finding of an appendiceal neoplasm.A primary appendiceal lymphoma is extremely rare. The predominant PAL histological subtype was DLBCL followed by Burkitt lymphoma.Treatment for Burkitt Lymphoma is stratified on patient age and stage.In adult,current recomandations include multiagent regimens with intensive chemotherapy and immunotherapy with anti CD20.Newer anti-CD20,anti-CD19,CD22 monoclonal antibody are under investigation.Follow up is carried out in the basis of the disease responce according to the Lugano criteria.

Bleeding disorders (congenital and acquired)

PB1462 INHIBITORS IN MILD HAEMOPHILIA A: EXPERIENCE OF A SINGLE SPANISH CENTER

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Background: In mild hemophilia A (HA) (F8: C> 5%), Desmopressin (DDAVP) is the 1st therapeutic option. When DDAVP fails (40-50%) FVIII Concentrates (CF8) are of choice with the risk of development of "inhibitors" against F8. Previously, the incidence of inhibitors in non-severe (NS) HA was estimated between 3% and 13%. Recently, certain F8 genotypes eas associated with higher rates of inhibitors (even for some the incidence close to that of severe HA). On the other hand, there are limited data on the optimal therapeutic approach to eradicate inhibitors in these patients
Aims: To report the incidence of inhibitors -as well as their management- in a population of patients with mild HA, attended in a 3rd level center in the last year (2020/1 /1- 2020/31/12) in relation to surgical procedures
Methods: 15 Surgical procedures performed on 10 patients with mild HA (F8: C> 5%), all on demand treatment, and the replacement treatments were recorded. The interventions were 5 tooth extractions (2 multiple), 3 major surgeries, 3 minor surgeries and 4 minor procedures. Only 2 patients had a genetic study. The age, type of surgery, number of previous days of exposure (ED) and duration of treatment are recorded (Table 1).The inhibitor is dislodged 15 days and 2 months after the end of treatment.
Results: Two patients (40% of those who received CF8) developed an inhibitor antiF8; In both cases, it was detected in the 2nd control: patient **4** presented it with maximum titer of 2.56 uBT (N <0.6) and patient 7 reached 12.8 uBT, both *type 1* kinetics. Both patients lost response to DDAVP. In **patient 4**, a "watch and wait" strategy was chosen, with progressive clearance until negative titer at day (d) + 57, without bleeding symptons. For **patient 7**, an immunosuppression (IS) strategy was made (Prednisone 1 mg / Kg / day (5 weeks) and descent to suspension + AntiCD20 375 mg / m2 / weekly, 4 weeks) with progressive decrease in inhibitor titer (1st negative control to d + 51); suffered a retroperitoneal hematoma (treatment: Novoseven®, 7 d). At d+162 we certified the success of IS (Response to DDAVP, Inhibitor <0.4 uBT, F8: C 17%, Pharmacokinetic F8 (35 IU/Kg pdF8): recovery 2.25 and terminal half-life 8.75 h-WAPPS Hemo®)



Summary/Conclusion: The incidence of inhibitors in NS-HA increases progressively with the cumulative number of ED to CF8, apparently without reaching a plateau, unlike that observed in severe HA with estimated risk after 20, 50 and 100 SD at 3.5% (95% confidence interval (CI) 2.1–4.9), 6.7% (CI 4.5–8.9) and 13.3% (CI 9.6–17.0), respectively. The development of inhibitors in NS- HA is a relevant problem being important to establish strategies to reduce the risk: knowing the responsible mutation in order to estimate the risk, maximizing the use of DDAVP and antifibrinolytics,.. among other measures. Furthermore,

it is imperative to know more about the treatment regimens aimed at the eradication of inhibitors in NS-HA. IS seems a valid option, as reported by Kempton in a cohort of 32 patients. The "wait and watch" strategy allows confirming the clearance of the inhibitor, but the confirmation of eradication is also influenced by clinical behavior, since, as we are reminded in the INSIGHT Study, many patients are not re-exposed to CF8. Therefore, it is necessary to deepen the registration and modeling of simple and effective therapeutic strategies to manage this problem, in addition to the invaluable contribution of Emicizumab for the management of these patients, specially in cases in which suppression success is not achieved.

PB1463 ANALYSIS OF SURVIVAL IN PATIENTS WITH ACID SPHINGOMYELINASE DEFICIENCY TYPE B USING A LARGE, DEIDENTIFIED US ELECTRONIC HEALTH RECORD DATABASE

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Background: Acid sphingomyelinase deficiency (ASMD, historically known as Neimann Pick disease types A and B) is a rare metabolic disease characterized by the accumulation of sphingomyelin in cells and tissues. ASMD is divided into subtypes A, A/B and B. Type B (also known as chronic visceral ASMD) is characterized by onset in childhood or adulthood, hepatosplenomegaly, interstitial lung disease, liver dysfunction, thrombocytopenia, and bone disease, whereas type A has onset in infancy, prominent CNS involvement, and death before age 3. ASMD is sometimes confused with Nieman Pick disease type C (NPC), which shares some clinical features but is separate and biochemically distinct. The most common causes of morbidity and mortality in ASMD type B are respiratory and liver failure. Hematologists are often instrumental in the recognition of this underdiagnosed and often life-threatening disease.
Aims: To describe overall survival (OS) in ASMD type B patients in a real-world setting using data from electronic health records (EHRs).
Methods: Patients with ≥ 2 records of of ICD-10 diagnosis codes for ASMD (E75.241 [Type B],E75.248 [Other], or E75.249 [Unknown]) were identified in Optum's deidentified Market Clarity database between January 1, 2007 and December 31, 2019. Patients were excluded if there was any record of an ICD-10 code for NPC or ASMD type A; any evidence of neurological symptoms prior to age 40 years (typical of NPC & ASMD type A/B), or death prior to age 3 (typical of ASMD type A). Additional cohorts with varying inclusion/exclusion criteria were used for sensitivity analyses. The first ASMD diagnosis was the index date. Follow-up period was from the index date until death, end of patient record, or December 31st, 2019. OS was estimated by Kaplan-Meier time to event analyses and a standardized mortality ratio (SMR) - the ratio of the observed number of deaths in the study population divided by the number of expected deaths based on the age- and-sex-specific mortality in a general population.
Results: We identified 46 patients who met the study criteria. Median age was 35 years, 65.2% were female, and median follow-up was 2.3 years. During follow-up, the most common disease manifestations were respiratory disease (60.9%), headache (50%), cardiovascular events (28.3%) and cirrhosis (23.9%). Six patients died during follow-up. The SMR was 17.69 (95% CI: 3.54, 31.84) when compared to a 2007 general population in the database. When compared to a 2017 general population, which more closely approximates the average follow-up time of the ASMD cohort, the SMR was 57.35 (95% CI: 1.15, 113.55). These data suggest that although survival varied widely, ASMD type B patients are substantially more likely to die compared to the general population.
Summary/Conclusion: This study extends our knowledge of survival in ASMD type B patients. Although limited by the small sample size and the lack of a validated algorithm for identifying ASMD type B in an EHR database, results were consistent with known characteristics of the disease. SMRs could be considered as an alternative approach for OS in rare diseases, when sample sizes are small, and the amount of censoring is large. Our data suggest a high risk of premature death in ASMD type B. Additional studies are needed to confirm these findings and investigate factors associated with mortality in this population and explore methods for addressing limitations in time-to-event statistics in rare diseases.

PB1464 TRANSTHORACIC AORTIC VALVE IMPLANTATION (TAVI) IN HEMOPHILIA

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Background: The increase in life expectancy of hemophiliac patients leads to the appearance of health problems whose proper managment is not clearly defined. Cardiac Surgery presents a major hemostatic challenge for a multitude of reasons, particularly in patients suffering from congenital or acquired hemostatic disorders. Acknowledging that, evidence from the literature suggests that cardiac surgery can be performed safely in this patient population
Aims: We reported the first TAVI performed in our hospital in hemophiliac patient, the management during and after hospital discharge
Methods: Male, 74 years, mild hemophilia A (F8:C 9%, F8 chromogenic 5,4%) without inibitor AntiF8(< 0.6 Bethesda Units, uBT). We not know the responsible mutation. In the past, he received treatment with different Concentrates of F8 (the last, ReFacto AF®). Previous surgeries: Total Hip Prostesis. CV Risk Factors: Arterial Hypertension (Medical treatment), Obesity, Diet-controlled hyperglycemia. He has a chronic liver disease due Virus C.
He had an Severe Aortic stenosis who needed surgical replacement and the chosen option was TAVI to reduce the surgical risks, among which bleeding
Results: 30 minutes before the procedure, ReFacto AF® 50 IU / kg was administered; A 29 mm Corevalve Evolut® R prosthesis was implanted, for which access was required through both femoral and right jugular veins to place a temporary pacemaker, a procedure that required the use of Unfractionated Heparin (5000 IU) without complications. At 3 hours, a 2nd dose of ReFacto AF® of approx. 10 IU / Kg was administered and the plasma levels of F8 were monitored using the chromogenic technique (level 110%). 8 hours after the 1st administration, ReFacto AF® started every 8 hours to maintain a trough level of approx 80% for first 48 hours, then adjusted every 12 hours (trough level of 50%) up to 7 days, then 30% (Desmopressin and ReFacto AF, alternate days) until completing 12 days of treatment. Simultaneously, antithrombotic prophylaxis was started with Enoxaparin® 40 mg (from day +1 to discharge) and simple antiplatelet therapy (ASA 100 mg / day), which he currently maintains. Hospital dischage was at day +14.
The inhibitor was removed 15 days and 2 months after the procedure - according to the protocol of our service - resulting negative. The patient reports an improvement of his quality of life, compared with the previous one, with disappearance of associated symptoms and progressive increase of physical activity, more according to his age and general condition
Summary/Conclusion: We present a succesfully case of TAVI in mild haemophiliac patient. TAVI is a safe and effective option versus open heart surgery in high-risk patients as haemophiliac patients. A search in PuBmed® database, crossing 2 topics: Aortic Stenosis and Haemophilia, showed 5 citations, 1 for Haemophilia B and 4 Haemophilia A; just case reports, so we consider it interesting to communicate our experience in order to generate scientific evidence so as not only to recomend this therapeutic option as of choice in these patients but also to guide the performance of the procedure, in close collaboration with cardiologists and anesthetists

PB1465 EVALUATION OF THE EFFICACY OF MOROCTOCOG ALPHA DURING THE PREVENTIVE TREATMENT OF PATIENTS WITH HEMOPHILIA A

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Background: The emergence of modern concentrates of coagulation factor VIII (FVIII) has changed the management tactics and improved the quality of life of patients with hemophilia A, compared to the period before 2005, when such patients in Russia received therapy with cryoprecipitate and fresh frozen plasma (FFP).
Aims: The objective of the observational study was a retrospective analysis (2017 - 2019) of the efficacy of using a recombinant

antihemophilic factor (coagulation factor VIII drug with a deleted B domain) - Moroctocog alpha for the prophylactic treatment of patients with severe and moderate forms of hemophilia A living in the Amur Region and in the Khabarovsk Territory of the Far Eastern Federal District of Russia.
Methods: Patients with hemophilia A over the age of 20 were divided into 2 groups. In group 1 - 21 patients received substitution therapy with Moroctocog alpha; age composition: 40-50 years old (n = 10), 30-39 years old (n = 6), 20-29 years old (n = 5). All patients were diagnosed with hemophilic arthropathy: deforming arthrosis of the knee (n = 21), ankle (n = 12), elbow (n = 16) joints. Group 2 included 21 patients who received plasma FVIII and octocog alpha at the age of 40-50 years (n = 8), 30-39 years (n = 8), 20-29 years (n = 5). All patients were diagnosed with hemophilic arthropathy: deforming arthrosis of the knee (n = 21), ankle (n = 13), elbow (n = 17) joints. In both groups, there were 13 patients with severe and 8 with moderate forms of hemophilia A. In both groups, FVIII concentrates at a dose of 20-40 IU / kg of body weight were injected every 2-3 days (2-3 times a week).
Results: Until 2005, when patients of both groups received therapy with cryoprecipitate or FFP "on demand", all of them had frequent hemorrhagic complications from 52 to 6 episodes per year, bleeding and hemorrhage were of all severity, including life-threatening; patients with a severe form were hospitalized 8-10, and with a moderate form - 4 times a year. During the study period, against the background of prophylactic use of the Moroctocog alpha drug and other FVIII drugs no more than 2 episodes of bleeding (spontaneous and post-traumatic) of mild and moderate severity were noted in 7 patients of the first group and 6 patients of the second group. Spontaneous bleeding was diagnosed only in patients with low adherence to treatment, which was stopped by the administration of the drug in therapeutic doses, mainly on an outpatient basis, and rarely required hospitalization. The desired indicators of clinical control were achieved - no more than 2 cases of spontaneous hemarthrosis or other bleedings per year. In both groups, it was possible to achieve a 98% reduction in the number of bleedings compared to the period before 2005, when these patients received treatment with cryoprecipitate and FFP "on demand". When using Moroctocog alpha there were no adverse reactions in patients.
Summary/Conclusion: It was concluded that Moroctocog alpha is not inferior to plasma concentrates FVIII and Octocog alpha in terms of efficacy and safety, and can be effectively used for the preventive treatment of bleeding in hemophilia A.

PB1466 COVID INFECTION REVEALING FACTOR XI DEFICIENCY IN ELDERLY PATIENT

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Background: Factor XI deficiency, acquired or constitutional, constitutes a pathology
moderate hemostasis
The hemorrhagic symptomatology of factor XI deficiency varies between patients and
even in the same patient, and requires a triggering factor.
Coagulation disturbances are commonly seen in patients with COVID19. If thrombosis is a clinical feature
predominantly of COVID 19 contributing to visceral failures, events bleeding is infrequent and is probably related to vascular coagulation disseminated.
Aims: We report the case of an 84-year-old subject in whom a covid 19 would have
allowed the late revelation of a constitutional factor XI deficiency.
Methods: We report the case of an 84-year-old subject in whom a covid 19 would have
allowed the late revelation of a constitutional factor XI deficiency.
Results: An 84-year-old patient was admitted to an intensive care unit for the management of acute respiratory distress. He does not report any history of hemorrhage and no similar case in the family.
The clinical examination on admission found signs
respiratory struggle, 90% saturation in ambient air, a syndrome mucocutaneous hemorrhagic disease consisting of clot hematuria, epistaxis and a
extensive hematoma of the rectus abdominis muscles measuring 14 cm / 6 cm, the chest scanner suggested pneumonia COVID type classified CORADS 5 extended over 50-75% of lung surface associated with right proximal pulmonary embolism. an isolated prolongation of the activated partial thromboplastin time at 1.38 without thrombocytopenia, elevation of dimers or consumption of fibrinogen. Wilbrand factor antigen and activity were normales. The exploration of coagulation factors of the endogenous pathway has objectified
a factor XI deficiency estimated at 36%. The hypothesis of a constitutional factor XI deficiency
decompensated by SARS cov 2 infection was therefore raised
The treatment was based on
symptomatic treatment with oxygen therapy and replacement with fresh plasma
frozen. The evolution was marked, after regression of the SARS cov 2 pneumonia,
by the control and the absence of recurrence of hemorrhagic manifestations.
Summary/Conclusion: Constitutional factor XI deficiency is a rare deficiency in coagulation but its incidence
remains underestimated, as it is rarely responsible for a hemorrhagic syndrome and requires a triggering factor for the hemorrhagic syndrome. In our patient, infection with Covid 19 was the viral infection responsible for triggering hemmoragic syndrome secondary to factor XI deficiency.

Bone marrow failure syndromes incl. PNH - Biology & Translational Research

PB1467 APLASTIC ANEMIA PATIENTS COULD BE DIVIDED INTO TWO SUBGROUPS BASED ON THE GENE EXPRESSION IN THEIR BONE MARROW MULTIPOTENT MESENCHYMAL STROMAL CELLS

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Background: Aplastic anemia (AA) is caused by hematopoietic stem cells (HSC) damage resulting in a bone marrow (BM) failure. An autoimmune attack is the most frequent but probably not the only origin of it.
Aims: The aim of the study was to analyze stromal microenvironment in BM of untreated AA patients through the multipotent mesenchymal stromal cells (MMSC).
Methods: The study included 21 AA (8 with severe AA (SAA) and 13 with non-severe AA (NAA)) patients in the debut. In all patients BM was aspirated after informed consent at diagnostic punctures. MMSC were isolated and cultivated by the standard method. RNA was extracted on passage 1 by the standard protocol. Gene expression was analyzed with Taqman modification of RT-PCR. As a control BM samples of 19 healthy donors of according age were used.
Results: Comparison of gene expression in MMSC from SAA and NAA patients revealed the significant decrease in the expression of *FGF2*, *SDF1*, and *IL1R* in SAA patients. The expression of *FGFR2*, *PTGES*, and *ANGPT1* was significantly decreased in SAA patients compared to donors. MMSCs from NAA patients, on the contrary, revealed increased expression of *FGFR1*, *TGFB2*, and *CFH* in comparison with donors. Thus, stromal precursors in NAA and SAA are altered differently. Probably, it reflects initial differences in the pathogenesis of these forms of AA.
In MMSC of 6 AA patients (3 with NAA and 3 with SAA) there was no expression of *TGFB1*, *ANGPT1*, *IDO1*, and *PTGES*. Moreover most of the other studied genes were dramatically down-regulated in these MMSC (Table). In 5 out of 6 patients these changes were detected even after 6 months of immunosuppressive therapy, while all these patients had responded to the treatment and reached partial remission or hematological improvement within 6 months. So the disrupted expression of these genes may be permanent. Despite of the absence of expression *TGFB1* and *ANGPT1*, which are factor crucial for the hematopoiesis,

the hematopoiesis was partly restored. Both TGFB1 and ANGPT1 regulate quiescence of HSC. Therefore, the lack of these factors could induce HSC activation. The determination of these factors expression in long-term observation may explain mechanisms of HSC survival in such patients. What factors are responsible for the maintenance of hematopoiesis in these patients is the subject of ongoing study.

Table. Relative gene expression level in MMSC from AA patients, subdivided on the absence or presence of *TGFB1* expression

	donors(n=19)	No TGFB1 expression (n=6)	TGFB1 expression is detected (n=15)
FGF2	1.76±0.35	1.03±0.19	4.96±1.37* **
FGFR1	0.07±0.02	0.49±0.06*	0.18±0.07 **
FGFR2	0.24±0.06	0.04±0.02*	0.76±0.44
CFH	0.69±0.14	0.25±0.06*	1.65±0.32 **
TGFB1	0.91±0.12	0±0	1.19±0.12 **
TGFB2	1.64±0.3	0.002±0.001*	6.26±1.19* **
HGF	0.41±0.08	0.07±0.03*	1.65±0.32* **
PDGFRA	0.05±0.03	0.36±0.17	1.26±0.38* **
PDGFRB	0.62±0.1	0.02±0.01	0.16±0.08
PTGES	0.17±0.03	0±0	0.2±0.05 **
IDO1	0.002±0.001	0±0	0.02±0.01
JAG1	1.08±0.47	0.004±0.002*	2.77±1.1 **
IL1R	1.29±0.69	0.0002±0.0002*	1.27±0.3 **
SDF1	2.84±0.42	0.001±0.001	1.04±0.26 **
ANG1	0.68±0.19	0±0	2.18±0.71 **

* - significant differences from donors, ** - significant differences from the subgroup without *TGFB1* expression

Summary/Conclusion: Stromal precursors in BM of untreated NAA and SAA patients are impaired differently. This effect could reflect the different causes of these forms of AA or be the consequence of compensatory reaction of stromal microenvironment to the various levels of hematopoiesis failure. Two subgroups of AA patients had been revealed, which dramatically differ in the pattern of gene expression in MMSCs.

PB1468 IDENTIFICATION OF A NOVEL DELETION IN THE RPS26 GENE IN A GREEK CHILD WITH THE DIAGNOSIS OF BLACKFAN-DIAMOND ANEMIA

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Background: Blackfan-Diamond Anemia (BDA) is a rare congenital bone marrow failure (BMF) syndrome characterized by selective aplasia of the erythroid progenitor lineage. Typically BDA is diagnosed within the first year of life, with the presentation of normochromic, microcytic anemia accompanied by reticulocytopenia. BDA is caused by inherited or de novo mutations in ribosomal proteins and is recognised as the first known human ribosomopathy. Symptoms are heterogenous, even between affected family members carrying the same mutations. Most often the genes involved are RPS19, RPS24, RPS 17, RPL35A and RPS 26. RPS 26 is responsible for 2.5-6% of DBA patients and to date 30-disease causing variants have been reported. Many of the patients affected present with clinical malformations, and there seems to be a correlation between the phenotype and genotype.
Aims: We describe a case of DBA presenting with heart failure secondary to a serious severe anemia.
Methods: A 3 month old male infant, due to poor feeding and marked paleness undertook a full blood count which revealed remarkable anemia (Hb 1.8 g/dL). The infant was born at 35w gestation age and admitted in NICU due to low birth weight and jaundice though phototherapy was not applied. In the newborn period the infant was feeding well and presented no respiratory distress. Prenatal history was unremarkable and there was no history of anemia. Physical examination revealed no dysmorphic features and normal appearing with no evident anomalies.
The infant was immediately transfused, however, due to deterioration of its clinical condition with gasping and cardiac failure accompanied by bradycardia, was transferred to PICU and eventually intubated. The infant presented kidney failure, with reduced diuresis and hypertension and received anti-hypertensive treatment. The reticulocyte index upon admission was 3.4 percent and all other hematologic parameters and bilirubin levels were normal. A peripheral smear showed the presence of all white blood cell lineages with normal morphology; platelets were increased and displayed variable size (small to large). Red blood cells were decreased and schistocytes, elliptocytes, spherocytes, and Heinz bodies were not present.
The infant had no signs of hemolysis and the presence of infectious etiologies or structural abnormalities was excluded-negative studies for HIV, parvovirus, toxoplasmosis, and cytomegalovirus infection. Since there was no compensatory reticulocytosis, a congenital anemia associated with BMF, such as Diamond Blackfan anemia, was suspected.
Results: Morphologic review of the bone marrow aspirate exhibited complete absence of the erythroid lineage with the presence of hemophagocytic islets. Taking under consideration the bone marrow morphology in conjunction with the low reticulocyte count, a Blackfan-Diamond analysis was performed for the RPS19, RPL11, RPL5 which was negative. Due to the high index of suspicion, whole exome sequencing was performed which revealed a nucleic substitution of c181+1del IG of the RPS26 gene. The mutation was in heterozygosis with a possible formation of a non functional proteic molecule and not described in literature. Upon confirmation of diagnosis, due to the age (<12m), the infant was commenced on regular transfusions in order to avoid side effects from the use of the corticosteroid treatment. The infant has moderate transfusional needs (approx. once every 3 months).
Summary/Conclusion: As the WES/NGS testing becomes more accessible, novel mutations can be identified providing the possibility of the gene therapy in the future.

Bone marrow failure syndromes incl. PNH - Clinical

PB1469 PROFILE OF HEMOPHAGOCYTIC LYMPOHISTIOCYTOSIS (HLH) – PROSPECTIVE OBSERVATIONAL STUDY

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Background: Hemophagocytic Lymphohistioctosis(HLH) is characterised by fever, splenomegaly, cytopenias,hepatitis, altered mental status and neurological involvement. There is marked increase of Histiocytes in bone marrow.
Aims: To study epidemiology, clinical features, laboratory findings & diagnosis of underlying disease associated with HLH and also to assess their response to the treatment
Methods: We enrolled 53 consecutive patients diagnosed with HLH from January 2012 to march 2015 who satisfied the HLH 2009 diagnostic criteria and were between the age of 1 month and 15 years
Results: Most children belonged to age group 31 days -12 months (47.16%). Mean age was 35 months, male (54.71%) children were slightly more affected than female (45.29%) children. The most common presenting symptom in our series was fever (96.2%) and most common sign was pallor (100%). Bone marrow hemophagocytes were demonstrated in 92.15%. Raised S.Ferritin levels >500ng/ml was seen in 98.11% with mean ferritin levels of 4146ng/ml. Transaminitis was seen in 84.9%.Bicytopenia was noticed in 62.26% and pancytopenia in 35.84%. With respect to etiology, Infection was the most common, noticed in 75% of cases. Dengue was found in 14 patients (26.1%). Primary HLH was seen in 5 (9.5%) of children. Out of 53 children enrolled in the study only 47 children received some form of therapy, with prephase steroid alone therapy (n=31) (65.9%) had a improvement in clinical parameter, however on follow up 3 (9.6%) children died and 1 left against medical advice. Among 16 children who had no improvement with steroids were advised complete HLH protocol, but only 12 (25.5%) children parents gave the consent, during course of therapy 7 children died (14.8% in 47) (58.3% in 12 who completed protocol), 3children discharged against medical advice (6.3%) at the time of completion of protocol only 2 (4.2% in 47) (16.6%) in 12 who completed protocol.
Summary/Conclusion: Infection associated HLH has better outcome with early diagnosis and prompt treatment. Primary HLH should be suspected and genetic analysis should be sent for patients <3 yrs, with history of consanguinity and sibling death due to similar condition, those presenting with CNS signs and symptoms & patients who deteriorated rapidly on treatment with Dexamethasone alone

PB1471 LONG-TERM EFFECTS IN SUBGROUPS OF PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA TREATED WITH PEGCETACOPLAN VERSUS ECULIZUMAB: 48-WEEK ANALYSIS OF PEGASUS PHASE 3 TRIAL

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Background: Pegcetacoplan (PEG), a PEGylated peptide targeting proximal complement protein C3, can control both intravascular and extravascular hemolysis. In the PEGASUS trial (NCT03500549), a phase 3, randomized, open-label, active-comparator controlled study, PEG was shown to be superior to eculizumab (ECU) after 16 weeks in improving hemoglobin (Hb) levels and clinical outcomes in patients with PNH *(Hillmen P et al, EHA 2020)*.

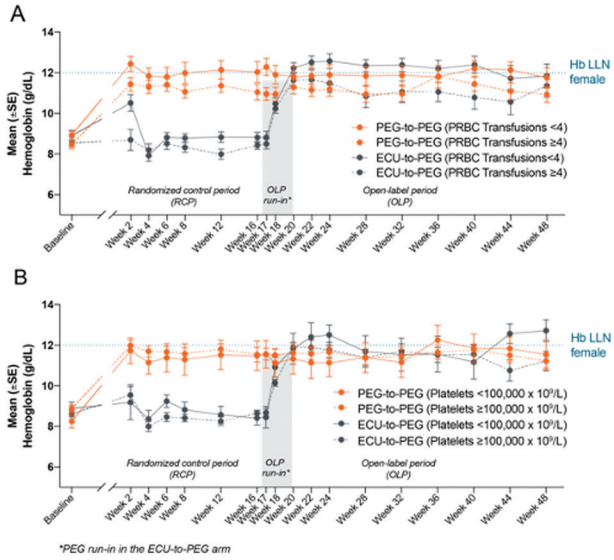
Aims: To identify if the prespecified strata (transfusion history and platelet count) of PEGASUS patients showed additional benefit from PEG vs ECU at 48 weeks.

Methods: Eighty PNH patients (≥18 years) with Hb levels <10.5 g/dL and ECU treatment (≥3 months) were enrolled. Patients entered a 4-week run-in period (RIP) with ECU+PEG (1080 mg subcutaneously 2x/week), then were stratified based on baseline platelet count and prior transfusion requirements, and randomized 1:1 to PEG or ECU monotherapy. The primary endpoint was change in Hb level from baseline to Week 16. Patients could continue to an open label period (OLP) of PEG monotherapy, which included a 4-week RIP (ECU+PEG) for ECU patients (ECU-to-PEG) but not for patients continuing PEG (PEG-to-PEG). Key secondary endpoints were transfusion avoidance and adverse events (AEs). Here, primary and key secondary endpoints were analyzed by subgroups (<4 vs ≥4 packed red blood cell transfusions within 12 months prior to baseline; platelet count at screening [<100,000x10^9/L vs ≥100,000x10^9/L]).

Results: PEG treatment was associated with significantly greater increases in Hb levels from baseline than ECU at Week 16, which were maintained in the PEG-to-PEG arm through Week 48 regardless of baseline subgroup. The ECU-to-PEG arm demonstrated increased Hb levels regardless of prior transfusions (Figure A) or baseline platelet count (Figure B). At Week 48, Hb levels were similar in the <4 (mean [SD]; PEG-to-PEG: 11.8 [1.9] g/dL; ECU-to-PEG: 11.8 [2.2] g/dL) and ≥4 transfusion strata (PEG-to-PEG: 10.9 [1.6] g/dL; ECU-to-PEG: 11.4 [2.2] g/dL). Similar Hb levels were also seen for the <100,000x10^9/L (PEG-to-PEG: 11.5 [2.2] g/dL; ECU-to-PEG: 12.7 [1.4] g/dL) and ≥100,000x10^9/L platelet strata (PEG-to-PEG: 11.2 [1.6] g/dL; ECU-to-PEG: 11.2 [2.3] g/dL).

At Week 48, on PEG monotherapy, both arms had similar proportions of transfusion free patients during the OLP in the <4 (PEG-to-PEG: 80%; ECU-to-PEG: 88%) and ≥4 transfusion strata (PEG-to-PEG: 67%; ECU-to-PEG: 61%). Similar trends were seen in the <100,000x10^9/L (PEG-to-PEG: 75%; ECU-to-PEG: 78%) and ≥100,000x10^9/L platelet strata (PEG-to-PEG: 72%; ECU-to-PEG: 70%).

The most common AEs by physician reported preferred term throughout the study for all patients who received PEG were injection site reactions (36%), hemolysis (24%), and diarrhea (21%). Of all study patients, 30% experienced serious AEs, 6% possibly related to PEG. No cases of meningitis were reported. One COVID-19 death was reported, unrelated to study treatment. Six patients discontinued due to hemolytic events: 5 classified by the treating physician as "hemolysis" and 1 as "hemolytic anemia." Overall, 12 patients (15%) discontinued PEG: 3 in RCP, 8 in OLP due to TEAEs (6 in ECU-to-PEG, 2 in PEG-to-PEG), and one during follow-up; one patient withdrew due to physician decision.



Summary/Conclusion: In the prespecified stratified analysis of PEGASUS, PEG showed treatment effect durability in Hb level with transfusion avoidance in most PNH patients regardless of prior transfusions or baseline platelet count during the OLP through Week 48. The safety profile of PEG was consistent with previously reported data.

PB1472 RHTPO IMPROVES THE OVERALL SURVIVAL OF PATIENTS WITH APLASTIC ANEMIA IN CHINA: RETROSPECTIVE ANALYSIS OF A SINGLE-INSTITUTION

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Background: Hematopoietic stimulation therapy is one of the most important dimensions for the treatment of aplastic anemia. The recovery of platelets is the plight of AA recovery.

Aims: To analyze the total effect of rhTPO and(or) rhIL-11 combined with immunosuppressive therapy (IST) for AA patients and compare the effects between them.

Methods: we enrolled 131 AA patients who were divided into 4 groups: the IST group (36 cases), the rhIL-11+IST group (14 cases), the rhTPO+IST group (42 cases), and the rhIL-11+rhTPO+IST group(39 cases). Survival time as well as bone marrow hematopoiesis, peripheral blood cells, immune cell subsets of patients in each group at the 3, 6, and 9 months after ATG/ALG treatment were collected and analyzed.

Results: Patients who were applied IST coupled with rhTPO (including rhTPO+IST group and rhIL-11+rhTPO+IST group) performed much better than without rhTPO group in terms of ORR, improvement of bone marrow hematopoietic, megakaryocyte recovery and overall survival (OS). rhTPO collaborated by rhIL-11 could influence mDC number and help humoral immune reconstitution. Among all the parameters, bone marrow cellularity at 3 months is the only multivariate that affects OS.

Summary/Conclusion: rhTPO is a powerful supplement to IST in treatment of AA, patients could benefit from several aspects, including elevating ORR, shortening bone marrow hematopoietic and magekarocyte recovery time, helping humoral immune reconstitution, and prolonging OS. IL-11 and TPO have a synergistic effect on the mechanism, the combination of these drugs may be the "icing on the cake" for IST treatment of AA.

PB1473 MUTATION ANALYSIS OF CHINESE SPORADIC DIAMOND-BLACKFAN ANEMIA BY NEXT GENERATION SEQUENCING

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Background: Diamond-Blackfan anemia (DBA) is the second most common congenital bone marrow failure syndrome, after Fanconi anemia, characterized by erythroid aplasia. The estimated prevalence was 5~7 cases per 1000,000 live births in European population and 12 per 1000,000 live births in Japanese population in one year. It is typically occured during infancy and associated with physical abnormalities, such as short stature, craniofacial, upper limb, heart and genitourinary defects. DBA patients also have the tendency of tumor susceptibility, the incidence of which is lower than that in Fanconi anemia or dyskeratosis congenita patients. DBA is commonly diagnosed based on a positive family history, age of onset less than one year old and laboratory findings such as macrocytic anemia, reticulocytopenia, myeloproliferative activity with erythroid precursor cell reduction, elevated erythrocyte adenosine deaminase activity (eADA), and persistence of hemoglobin F (HbF), as well as associated congenital malformations. The phenotypic expression of DBA varies greatly, even in the same family.
Aims: We aimed to expand DBA-related gene mutations library and investigate the relationship between clinical phenotype and genotype in DBA.
Methods: Genomic DNA of 14 clinically suspected congenital DBA patients was selected to detect 71 known genes closely related to congenital bone marrow failure by next-generation sequencing (NGS). The relationship between clinical phenotype and genotype in DBA was analyzed.
Results: We have identified 13 pathogenic variants of 7 genes (RPL11, RPL5, RPS19, RPS26, RPL35A, RPS27, and TSR2) in 14 clinically suspected DBA patients. The ratio of male to female is 1:1. We have identified RPS19 mutations in six patients, and RPL11 and RPS26 mutations in two patients respectively. Among the mutations identified, five were previously reported, and eight variants were novel. Particularly, we have identified one stop-gain mutations, one splicing mutation, four frameshift variants, six missense variants, as well as one start-loss mutation. Except for two adult patients, the other patients were infants, and the median age of onset was one year old. There was no significant difference in gender and age. Among the cases, female patients are more prone to congenital dysplasia or tumor susceptibility. Compared with the European and American patients, the Asian patients with RPS19 and RPL5 gene mutations have a higher rate of congenital dysplasia.
Summary/Conclusion: Our study further fills genetic disease mutation database and enriches the corresponding clinical manifestations. Our results suggested that genetic diagnosis by NGS is a fast, economic and accurate way to detect and identify pathogenic alterations of inherited diseases like Diamond-Blackfan anemia.

PB1474 IDIOPATHIC APLASTIC ANEMIA – ARE THERE OTHER PROGNOSTIC FACTORS?

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Background: Idiopathic aplastic anemia (AA) is a rare entity characterized by reduced bone marrow cellularity and consequent pancytopenia due to an immune destruction of the hematopoietic stem cells. Currently there are no defined prognostic scores and therapeutic decision is based on disease severity [according to Camitta's criteria (CC)] and patient's fitness.
Aims: Assessment of prognostic factors in AA.
Methods: Unicentric retrospective analysis of patients (pts) diagnosed with AA between 2008 and 2019. Cox proportional hazard regression analysis was used to analyze factors affecting overall survival (OS) and overall response rate (ORR). OS obtained using the Kaplan-Meyer method was compared by the log-rank test. P<0,05 were considered statistically significant.
Results: 41 pts diagnosed – 37% male, median age at diagnosis 59 years (18-83 years). No cytogenetic abnormalities were identified and 11 pts had a concomitant paroxysmal nocturnal hemoglobinuria clone [PNH – expression defect >0,1% in ≥2 markers (CD55, CD59, CD16, CD24, CD14) in 2 distinct hematopoietic cell lines]. According to CC, 22 % were classified as moderate AA, 42% severe and 36% very severe.
Six pts under 40 years had a matched sibling donor and underwent allogeneic stem cell transplantation as first line treatment - all of then achieved a complete remission (CR).
Twenty-two pts were treated with immunosuppressive therapy [16 antithymocyte globulin (ATG) + cyclosporine (CsA) and 6 CsA], 3 eltrombopag monotherapy and 8 supportive care only. Two pts did not require therapeutic intervention. ORR in non-transplanted pts was 60%. Although ORR was not statistically different between groups, it appears to be superior with ATG+CsA (75% vs 33% CsA vs 33% eltrombopag; p=NS), with inferior outcomes in pts ≥60 years (33% vs 54%; p=0,047; HR 3,22). Regarding ATG source, ORR was superior with horse vs rabbit origin (89% vs 57%; p=0,017; HR 7,07). In non-transplanted pts, only 3 achieved CR, all treated with ATG+CsA. Macrocytosis (MCV>97fL, excluding vitamin deficit) was associated with superior ORR (40% vs 88%; p=0,042; HR 7,07). Also normal LDH at diagnosis was associated with superior ORR (p=0,019; HR 5,52).
Treatment response is one of the main factors influencing OS - pts with ORR had a superior OS (p<0,001). Median OS of pts with treatment response was 70 months vs 4 months in pts without response vs 1,5 months in pts on supportive care only. There were also differences on OS between pts without treatment response and pts only on supportive care (p=0,023). The presence of PNH clone is also associated with superior OS (p=0,049). Age ≥60 years had a negative impact on OS (p<0,001).
Regarding the CC, only absolute neutrophil count (ANC) <0,5x10^9/L had a significant impact on OS in both univariate (p=0,009; HR 3,92) and multivariate analysis (p=0,018; HR 4,02), with a negative impact.
Currently, 53,7% of pts are alive. The main cause of death was infection (63%).
No other variable significantly affected prognosis.
Summary/Conclusion: Age ≥60 years and ANC <0.5x10^9/L negatively affected OS. Since ANC was the only statistically significant component of CC to have an impact on OS (pts with low ANC might have a high rate of infection), raises questions regarding the statistical power of the different CC, that maybe should be reviewed.
Treatment response is associated with favorable OS, with macrocytosis and normal LDH appearing associated with a superior ORR. Also the presence of PNH clone is associated with a superior OS.
More robust studies are needed to validate these prognostic factors.

PB1475 INJECTION-SITE REACTIONS AT WEEK 48 IN THE RANDOMIZED PHASE 3 PEGASUS TRIAL OF PEGCETACOPLAN COMPARED WITH ECULIZUMAB FOR INDIVIDUALS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Background: Pegcetacoplan (PEG), a PEGylated peptide targeting proximal complement protein C3, can control both intravascular and extravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH). In the PEGASUS trial (NCT03500549), a phase 3, randomized, open-label, active-comparator controlled study, PEG was shown to be superior to eculizumab (ECU) after 16 weeks in improving hemoglobin (Hb) levels and clinical outcomes in patients with PNH *(Hillmen P et al, EHA 2020)*. PEG is self-administered twice weekly via two 10-mL subcutaneous injections at two distinct sites, which may lead to injection-site reactions (ISRs).
Aims: Our aim was to compare ISR safety outcomes from the PEGASUS trial to ISR incidences from similarly administered treatments based on published literature.
Methods: PEGASUS subjects received twice-weekly subcutaneous injections of 1080 mg PEG plus their current intravenous ECU dose in an initial 4-week run-in period (RIP), followed by a 16-week 1:1 randomized controlled period (RCP) where participants received PEG (n=41) or ECU monotherapy (n=39). Patients receiving ECU during the RCP entered another 4-week RIP (ECU+PEG), followed by an Open Label Period (OLP), in which all patients received PEG monotherapy.
The primary endpoint was the mean change from baseline in Hb levels at Week 16. Safety was a secondary endpoint and included monitoring incidence of ISRs, adverse events (AE), and treatment-emergent AEs (TEAEs). Therapies comparable to PEG were identified in order to establish a context for PEG-associated ISRs. Inclusion criteria were subcutaneously administered drugs with similar injection volumes (≥10 mL) or PEGylation (with ≥0.5-mL injections). ISR incidences and management strategies reported with identified drugs were evaluated from the prescribing information and published literature.

Results: Total reported TEAEs were as follows: i) RIP and open-label RIP (71 subjects, 89%); ii) RCP (PEG arm: 36 subjects [88%]; ECU arm: 36 subjects [92%]); iii) OLP (71 subjects [92%]). Most ISRs occurred during treatment initiation, as 59% of PEG patients experienced ISRs during the initial RIP compared to 37% in the RCP and 26% in the OLP. 2.6% of ECU patients experienced ISRs. In the total cohort, most ISRs were mild; there were a few moderate ISRs (4 in RIP, 3 in RCP+OLP PEG group; minimal intervention indicated) and no ISRs that were severe or led to study drug discontinuation.
Five drugs with comparable mode of delivery to PEG were identified and evaluated for ISR data (see Table). The percent of patients who experienced ISRs for evaluated drugs varied from 5–67% but were generally mild, resolved quickly, and were less likely to occur with subsequent treatments, according to published studies. Prevention or management strategies for ISRs included ice packs, injection-site rotation, and empowering patients to gain confidence in self-administration through training and other initiatives.

Table. Comparative Analysis of ISRs

Drug name	Drug type	Volume per site (mL)	Delivery	Frequency	Most frequent ISRs[a]	ISR incidence[b]
Pegcetacoplan	PEGylated peptide	~10	20-40 min over 2 sites	Twice weekly	Erythema, pruritus, bruising, induration, reaction, swelling[c]	36%[c]
Immunoglobulin with hyaluronidase	Immunoglobulin	≤600	~1-2 mL/min over 2 sites	Monthly	Discomfort, pain, erythema, swelling, itching	38-65%
Deferoxamine	Small molecule	10-20	Continuous pump over 8-24 hours	Daily	Pain, swelling, reddening, itching, blistering, burning	45%
Daratumumab and hyaluronidase[d]	Monoclonal antibody	15	Injected over 3-5 min	Weekly to monthly	Erythema, itching, swelling, bruising	11-67%
Certolizumab pegol	PEGylated antibody fragment	~1	Short injections at up to 2 sites	Monthly	Erythema, bruising, discoloration, pain, swelling	5%
Pegfilgrastim	PEGylated growth factor	0.6	Single injection at 1 site	Once per Chemo-therapy cycle	Pain, redness	8%

[a]Per prescribing information
[b]From published literature
[c]From PEGASUS randomized controlled period + open-label period
[d]Administered by healthcare provider only, whereas all others could be self-administered or administered by healthcare provider
ISR, injection-site reaction

Summary/Conclusion: PEGASUS trial ISRs observed with PEG treatment were more frequent in the initial treatment period and decreased over time, potentially because patients became more experienced with self-injection. ISRs were often mild or manageable and PEG patients on average reported better quality of life than ECU-treated patients at Week 16, indicating these events are likely not a barrier to treatment. Comparable trends for reported ISRs have been observed with other drugs delivered similarly to PEG; management strategies for ISRs with these drugs may potentially be useful for reactions observed with PEG.

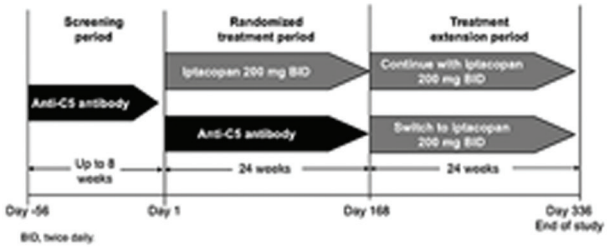
PB1476 PH3 STUDY OF EFFICACY AND SAFETY OF IPTACOPAN (LNP023), AN ORAL COMPLEMENT FACTOR B INHIBITOR, IN PTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND RESIDUAL ANEMIA DESPITE ANTI-C5 ANTIBODY TREATMENT

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Background: The standard of care in PNH is anti-C5 monoclonal antibody (MAb) treatment (tx) with eculizumab (ECU) or ravulizumab (RAV) but hematological responses can be heterogenous. Iptacopan (LNP023) is a first-in-class, oral, small-molecule, selective and reversible complement factor B inhibitor that inhibits both intra- and extravascular hemolysis. In an ongoing Ph2 study (NCT03439839), iptacopan add-on tx has demonstrated improvements in hematological response and biomarkers of disease activity in adult patients (pts) with PNH with active hemolysis despite ECU tx.
Aims: The Ph3 APPLY-PNH study (NCT04558918) will assess the efficacy and safety of iptacopan monotherapy in adult pts with PNH with residual anemia despite prior anti-C5 MAb tx by evaluating its superiority to anti-C5 MAb tx.
Methods: The study comprises an ≤8-wk screening period; a 24-wk, randomized, open-label, active-controlled, parallel-group tx period; and a 24-wk tx extension period (Fig. 1). Pts (N≈91) will be randomized (8:5) to iptacopan monotherapy 200mg orally BID (seamless switch from prior tx) or intravenous ECU/RAV (continue prior tx). Pts will be stratified based on prior anti-C5 tx and transfusion history. On completion of the Wk 24 visit, pts may enter the 24-wk iptacopan tx extension period. Eligible pts must have a confirmed diagnosis of PNH (red blood cells [RBCs] and white blood cells [granulocyte/monocyte] clone size ≥10%) and residual anemia (mean Hb <10g/dL) despite receiving a stable regimen of ECU/RAV in the 6 months preceding randomization. Key exclusion criteria include ECU dosing interval ≤11 days; known or suspected hereditary complement deficiency; hematopoietic stem cell transplantation; laboratory evidence of bone marrow failure; active, systemic infection ≤14 days preceding study drug tx; and history of recurrent, invasive infections caused by encapsulated microorganisms. Primary endpoints are the proportion of pts achieving 1) a sustained increase in Hb levels from baseline (BL) of ≥2g/dL (between D126 and D168) in the absence of RBC transfusions (between D14 and D168); and 2) a sustained increase in Hb levels to ≥12g/dL (between D126 and D168), in the absence of RBC transfusions (between D14 and D168). Potential superiority of iptacopan vs ECU/RAV in the analysis of the primary endpoints will be determined using an odds ratio and tested using a conditional logistic regression model, accounting for stratification factors used at randomization and adjusted for age, sex, and BL Hb. The study α will be split equally between the two endpoints and will determine rejection of each based on the permutation distribution of the *P*-values. Secondary endpoints include RBC transfusion-avoidance between D14 and D168 (except D1-14); and changes from BL in Hb levels, FACIT-Fatigue score, and reticulocytes (per weighted testing approach). The primary and secondary endpoints will be tested using a graphical multiplicity adjustment, where α weights are assigned to the different tests. If all of the above hypotheses (including both primary endpoints) are rejected, the following will be tested at full study α, also in a weighted fashion: % change from BL in lactate dehydrogenase, occurrence of breakthrough hemolysis, and occurrence of major adverse vascular events (including thrombosis). Additional endpoints include safety assessments, PNH clone size, C3d deposition on RBCs, and PROs (PGI-S, EORTC QLQ-C30, EQ-5D-5L).
Results: NA

Figure 1: APPLY-PNH design



Summary/Conclusion: This study will be the first head-to-head comparison of iptacopan vs an anti-C5 MAb in patients with PNH.

PB1477 CATEGORIZED HEMATOLOGIC RESPONSE TO PEGCETACOPLAN VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: POST HOC ANALYSIS OF PEGASUS PHASE 3 RANDOMIZED TRIAL DATA

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Background: Pegcetacoplan (PEG), a PEGylated peptide targeting proximal complement protein C3, can control both intravascular and extravascular hemolysis. In the PEGASUS trial (NCT03500549), a phase 3, randomized, open-label, active-comparator controlled study, PEG was shown to be superior to eculizumab (ECU) after 16 weeks in improving hemoglobin (Hb) levels and clinical outcomes in patients with paroxysmal nocturnal hemoglobinuria (PNH) *(Hillmen P et al, EHA 2020)*.
Aims: This post-hoc analysis categorized the hematologic response to PEG versus ECU treatment in PEGASUS patients with PNH up to Week 48.
Methods: Hematologic response to PEG or ECU in PEGASUS patients (≥18 years) with PNH and Hb <10.5 g/dL (despite stable ECU treatment for ≥3 months) was categorized as complete, major, good, partial, minor, or no response at baseline, Week 16, and Week 48 using the number of packed red blood cell transfusions required, Hb level, lactate dehydrogenase (LDH) level, and absolute reticulocyte count assessed in the last 6 months of treatment (ARC; categorization criteria per Risitano AM, et al. *Front Immunol*. 2019;10:1157). Hematologic response criteria are as follows: Complete response, no transfusions required, stable Hb (normal range), and no evidence of hemolysis (LDH≤1.5×upper limit of normal [ULN] U/L, ARC≤150,000/μL); Major response: no transfusion, normal Hb, but with evidence of hemolysis (LDH>1.5×ULN U/L and/or ARC>150,000/μL); Good response: no transfusions, but with chronic mild anemia or evidence of hemolysis; Partial response: chronic moderate anemia and/or occasional transfusions (<3 units/6 months); Minor response: regular transfusions required (3-6 units/6 months); No response: regular and frequent transfusions required (>6 units/6 months). Statistical tests were performed to determine significance for patient responses of 'Good,' 'Major,' or 'Complete', collectively (McNemar's test within arms; Chi-squared between arms).
Results: Of 80 enrolled patients, 41 and 39 were randomized to the PEG-to-PEG and ECU-to-PEG study arms, respectively (Figure A). Mean Hb levels for each arm at baseline, Week 16, and Week 48 are shown below (Figure B). At baseline, 7% (PEG-to-PEG) and 3% (ECU-to-PEG) of patients exhibited a Good/Major/Complete hematologic response. At Week 16, 73% (PEG-to-PEG) and 5% (ECU-to-PEG) of patients exhibited this response (p<0.0001), while the proportion of patients who achieved this response was similar between arms at Week 48 (p=0.4390). In total at Week 48, 63% of patients in the PEG-to-PEG arm (p=0.4142 vs. Week 16) and 54% of patients in the ECU-to-PEG arm (p<0.0001 vs. Week 16) achieved a Good/Major/Complete hematologic response, demonstrating a significant increase in the percent of ECU-to-PEG patients achieving at least a Good response after switching to PEG (Figure C).
Overall, 13 left the study; 12 patients discontinued PEG: 3 in the randomized controlled period, 8 in the open label period due to TEAEs (6 in ECU-to-PEG, 2 in PEG-to-PEG), and one during follow-up; one additional patient withdrew due to physician decision. These 13 patients (12 discontinuations and 1 withdrawal) were not included in statistical analyses.

(A)

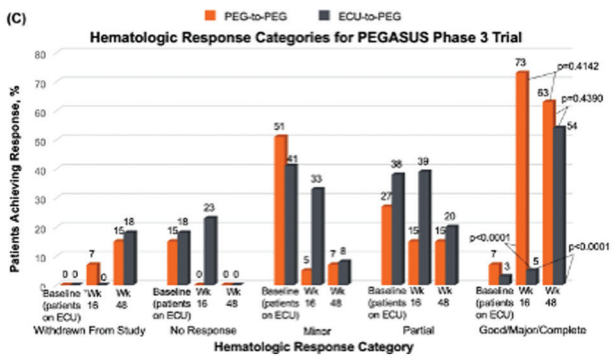


(B) Mean Hemoglobin Levels for Each Study Arm at Baseline, Week 16, and Week 48

	PEG-to-PEG			ECU-to-PEG		
	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48
Hb level, g/dL; NRR, 12.0-18.0 g/dL Mean (SD)*	8.7 (1.1)	11.5 (2.0)	11.3 (1.8)	8.7 (0.9)	8.6 (1.0)	11.6 (2.2)

*NRR: normal reference range

(C)



Summary/Conclusion: In this post-hoc analysis of the PEGASUS study, PEG treatment resulted in a significantly greater proportion of patients with Good or better hematologic responses after switching from ECU treatment. These results further support that proximal complement inhibition, by preventing EVH in addition to controlling IVH, leads to clinical and hematologic improvement in PNH treatment.

PB1478 ASSOCIATION BETWEEN HLA AND BONE MARROW FAILURE DISEASES

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Background: The bone marrow failure diseases include a group of disorders that can be either inherited or acquired, involving either 1 cell line or all of the cell lines. Acquired aplastic anemia and myelodysplastic syndrome are common diseases, manifested as bone marrow failure. Acquired aplastic anemia (aAA) is thought to be driven by Human Leukocyte Antigen (HLA)-restricted T cell immunity, with earlier studies favoring HLA class II-mediated pathways. Owing to the association of autoimmune disease with pathognomonic HLA, we hypothesized that part of the MDS and aAA patients could associate with HLA genotype and thus those patients are prone to develop bone marrow failure diseases.
Aims: To characterize the association between HLA genotype and bone marrow failure disease, we therefore designed a study to investigate the association of HLA genotype and its correlation with bone marrow failure disease.
Methods: A total of 12 patients with acquired severe aplastic anemia (aSAA) and 10 patients with myelodysplastic anemia (MDS) were enrolled in this study, as well as 10 health controls. The enrolled patients were diagnosed in our department from 2019.07 to 2020.12. All subjects underwent blood sampling on EDTA as anti-coagulant for DNA extraction. We used a next-generation sequencer (MiSeq, Illumina, CA, USA) to identify the HLA of HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DP, and HLA-DQ genes in each patient and heath control. Informed consent was obtained from the study participants for the genetic analyses. The diagnosis and severity of AA and MDS were determined according to standard criteria. Tests of proportions were used to compare allelic frequencies.
Results: We found HLA-C*14:02:01, HLA-C*04:01:01, HLA-DQB1*06:01:01 might be involved in the pathogenesis in bone marrow failure diseases (all $p<0.05$). As for HLA-C*14:02:01, frequency of this gene in MDS and SAA is 20% and 0%, respectively. ($p=0.0357$) This serotype of HLA-C might be a biomarker to distinguish MDS from SAA. As for HLA-C*04:01:01, frequency of this gene in SAA and HC is 0% and 20%, respectively. ($p=0.0357$) This serotype of HLA-C might be a major protective factor in the pathogenesis of aSAA. Similarly, the frequency of HLA-DQB1*06:01:01 in SAA and HC is 4.17% and 30%, respectively. ($p=0.0353$) This serotype of HLA-DQ might be a major protective factor in the pathogenesis of aSAA (Table 1). Supporting by previous study, we found high risk HLA-DR alleles such as DRB1*15:01 is highly expressed in patients with MDS or SAA (35%, 41.6%, respectively), compared with health control (25%). However, we did not find a statistical significance between three groups.

Table 1. Identified genotype with statistical significance

	Frequency in MDS	Frequency in aSAA	Frequency in HC	p1	p2	p3
C*14:02:01	4	0	1	0.3416	0.4545	0.0357
C*04:01:01	2	0	4	0.6614	0.0357	0.2008
DQB1:06:01:01	3	1	6	0.4506	0.0353	0.3155
	Note: p1:MDS compared with HC; p2: SAA compared with HC; p3: MDS compared with aSAA					

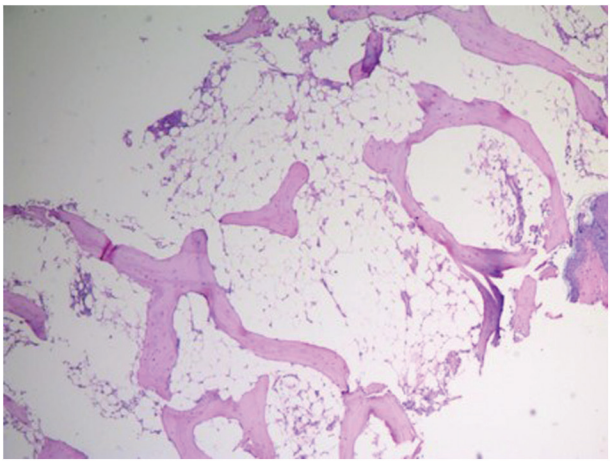
Summary/Conclusion: HLA genotype could be a surrogate marker to monitor the disease severity and predisposition to bone marrow failure disease.

PB1479 POST COVID 19 APLASTIC ANEMIA: CASE REPORT

O. Fahmy [1], A. Ayad [1], M. Marie [2], E. S. Saber [1], M. T. Hamza [3], D. El Demerdash [1,*]

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Background: The most common symptoms seen in COVID-19 patients are fever, fatigue, and dry cough, and dyspnea. Although there is comparatively few rising reports on the hematological sequelae. Hematological changes commonly described in patients with COVID-19, include reduced lymphocyte count and platelet count but normal white blood cell count. we present a case of pancytopenia and hypocellular marrow which is not a commonly known sequalae of COVID 19 infection.
Aims: To describe a novel case of coronavirus disease 2019 (COVID-19)-associated aplastic anemia in a patient known to have primary glomerulonephritis.
Methods: we described a case report of hematological sequalae of a COVID 19 case including the clinical presentation, management, and response to therapy
Results: A 25-year-old lady with a background of primary membranous glomerulonephritis with crescent formation required therapy with rituximab monoclonal anti CD20, presented with anemia, mucocutaneous bleeding. 25 days before her presentation she had subjective fever, cough, and dyspnea with radiological findings highly suspicious for COVID 19 and she tested positive for COVID-19 by PCR on nasopharyngeal swab. Isolation at home was recommended for her as she had mild-moderate COVID19 and her swab turned negative after 15 days of onset of the respiratory symptoms. she experienced pallor and muco-cutaneous bleeding in form of ecchymosis all over the body, wet purpura but the rest of her clinical examination was free, her CBC revealed hemoglobin: 6.9 g/dl; WBC: $2.67\times10^3/mm^3$; platelets: $10\times10^3/mm^3$. MCV 79 with reticulocytopenia, all immunological profiles as well as virology screening for HCV, HBV, HIV, CMV and EBV were negative. Bone marrow aspirate and biopsy revealed marked hypocellular marrow (cellularity 20%) with all bone marrow element were markedly depressed. Cyclosporine was prescribed for her as well as eltrombopag in the dose of 50 mg/day orally which titrated gradually according to platelet response to 100 mg/day PO with repeated irradiated packed RBCs and platelet transfusion during hospital stay.
During her hospital stay her liver enzymes (AST & ALT) were elevated so doses of cyclosporine and eltrombopag were decreased till the normalization of her liver enzymes then reiterated again according to the hematological response. She is maintained on this protocol now for 2 months with minimal hematological response. she prepared now for HLA matching and hematopoietic stem cell transplantation.



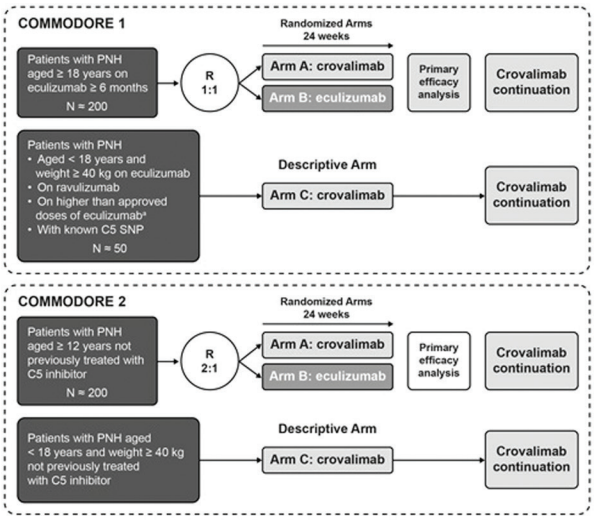
Summary/Conclusion: Further exploration of potential COVID-19-related hematological abnormalities is needed and requires extensive collaboration to collect large, organized data sets. The possibility of an immune-mediated process and its therapeutic implications also warrants greater study.

PB1480 TWO CURRENTLY RECRUITING PHASE III TRIALS: COMMODORE 1 AND 2 EVALUATING CROVALIMAB VS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WITH OR WITHOUT CURRENT ANTI–COMPLEMENT THERAPY

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Background: Crovalimab is a novel anti–complement C5 antibody currently being studied as a treatment for paroxysmal nocturnal hemoglobinuria (PNH), a life-threatening disease associated with hemolytic anemia and thrombosis. Treatment with approved C5 inhibitors eculizumab or ravulizumab is effective but can be limited by breakthrough hemolysis (BTH) due to unsustained C5 inhibition, inadequate efficacy in patients with C5 mutational variants and the requirement of regular intravenous (IV) infusions. Crovalimab is unique in that its properties allow for subcutaneous (SC) injections once every 4 weeks (Q4W) that can be self-administered. Additionally, crovalimab binds to C5 mutational variants. Promising results were obtained in the Phase I/II COMPOSER trial (NCT03157635; Röth et al, *Blood*. 2020) conducted in patients with PNH, with or without prior anti–C5 treatment.
Aims: The efficacy and safety of crovalimab vs eculizumab will be evaluated in two Phase III, randomized, open-label trials in patients with PNH, with or without current complement inhibition.
Methods: COMMODORE 1 (NCT04432584) will enroll patients who are receiving complement therapy. This trial is divided into 2 parts: 2 randomized arms (Arms A and B) for primary and secondary efficacy analyses and an exploratory descriptive arm (Arm C) (Figure). Patients eligible for the randomized arms will be randomized 1:1 to receive either crovalimab (Arm A) or eculizumab (Arm B). Arm A and C patients will receive crovalimab loading and subsequent SC Q4W maintenance dosing from week 5. Arm B patients will receive eculizumab IV maintenance dosing from D1 Q2W for a total of 24 weeks. Patients from each treatment arm can continue or switch to crovalimab after 24 weeks of treatment as determined by the treating physician. The primary efficacy objective is to determine the noninferiority of crovalimab vs eculizumab based on mean percent change in lactate dehydrogenase levels from baseline to week 25. Secondary efficacy objectives are to determine the proportion of patients who experience BTH, achieve transfusion avoidance (TA) or hemoglobin stabilization, as well as determine mean change in fatigue according to the Functional Assessment of Chronic Illness Therapy–Fatigue questionnaire from baseline to week 25. Safety and tolerability of crovalimab will also be evaluated along with pharmacokinetic, immunogenicity and health status utility objectives.
COMMODORE 2 (NCT04434092) will enroll patients not previously treated with complement inhibitors. This trial is also divided into 2 parts (Figure). Patients aged ≥ 12 years will be randomized 2:1 to receive either crovalimab (Arm A) or eculizumab (Arm B). Arm A and C patients will receive crovalimab loading and subsequent SC Q4W maintenance dosing from week 5. Arm B patients will receive induction doses of eculizumab IV QW for 4 weeks followed by maintenance dosing Q2W up to 24 weeks. Patients from each treatment arm can continue or switch to crovalimab as determined by the treating physician. The co-primary efficacy objectives are to determine the noninferiority of crovalimab vs eculizumab, based on the proportion of patients 1) who achieve TA from baseline to week 25 and 2) with hemolysis control from week 5-25. Safety and tolerability of crovalimab will also be evaluated along with pharmacokinetic, immunogenicity and health status utility objectives.
Results: COMMODORE 1 and 2 are now enrolling.



[a]Those receiving > 900 mg per dose and/more frequently than Q2W.
C5, complement component 5; PNH, paroxysmal nocturnal hemoglobinuria; Q2W, once every 2 weeks; R, randomized; SNP, single nucleotide polymorphism.

AK and AR are co-first authors. TM and J-IN are co-senior authors.

Summary/Conclusion: The COMMODORE 1 and 2 studies aim to assess the efficacy and safety of crovalimab in patients with PNH, compared with eculizumab, in patients with or without prior complement inhibition.

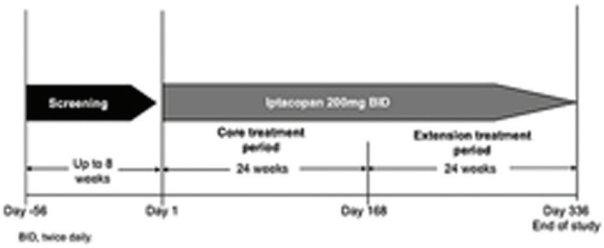
PB1481 PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF IPTACOPAN (LNP023), AN ORAL FACTOR B INHIBITOR, IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NAÏVE TO COMPLEMENT INHIBITOR THERAPY

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Background: The standard of care treatment (tx) in PNH is based on complement C5 inhibition with anti-C5 monoclonal antibodies (MAbs). Anti-C5 MAbs are generally effective at treating intravascular hemolysis (IVH) but unmet medical needs remain. Hematological responses to anti-C5 antibody tx can be heterogenous and a substantial number of pts experience residual anemia associated with breakthrough hemolysis (BTH). Anti-C5 MAbs are also not available in all countries and, where available, pt access can be limited. Iptacopan (LNP023) is a first-in-class, oral, small-molecule, selective, and reversible complement factor B inhibitor that inhibits both IVH and extravascular hemolysis (EVH). In an ongoing Ph2 study (NCT03439839), iptacopan has demonstrated improvements in both hematological response and biomarkers of disease activity in adult pts with PNH who had active hemolysis despite tx with eculizumab. These findings warrant further Ph3 studies to assess the efficacy of iptacopan in a wider population of pts with PNH, including those who are naïve to anti-C5 MAbs tx.
Aims: The Ph3, single-arm, open-label APPOINT-PNH study (CLNP023C12301) will assess the efficacy and safety of iptacopan in adult pts with PNH who are naïve to complement inhibitor therapy, including anti-C5 MAbs.
Methods: The study comprises an ≤8-wk screening period; a 24-wk, single-arm, open-label core tx period; and a 24-wk, open-label tx extension period (Fig. 1). On completion of the Wk 24 visit, pts who show benefit from iptacopan tx can enter the extension period. Eligible adult pts (N≈40; ≥18 years old) must have a confirmed diagnosis of PNH (red blood cells [RBCs] and white blood cells [granulocyte/monocyte] clone size ≥10%); anemia (mean Hb <10g/dL) and active hemolysis (lactate dehydrogenase [LDH] >1.5×upper limit of normal). Key exclusion criteria: prior tx with a complement inhibitor; known or suspected hereditary complement deficiency; history of hematopoietic stem cell transplantation; laboratory evidence of bone marrow failure; active, systemic infection ≤14 days preceding study drug tx; and history of recurrent, invasive infections caused by encapsulated microorganisms. The primary objective is to assess hematologic response, defined as achieving a sustained increase in Hb levels ≥2g/dL (in the absence of RBC transfusions). The primary endpoint is to evaluate the proportion of pts achieving an increase from baseline (BL) in Hb levels ≥2g/dL, between D126–D168 (in the absence of RBC transfusions between D14–D168). The analysis of the primary endpoint will be a logistic regression model including BL covariates: sex, age (categorical), Hb >8g/dL, and presence of transfusion dependence at enrollment. Secondary endpoints include: proportion of pts reaching Hb levels ≥12g/dL; absence of RBC transfusions; changes from BL in Hb levels; changes in patient-reported fatigue scores (FACIT-Fatigue); changes from BL in reticulocytes; % change from BL in LDH; occurrence of BTH; occurrence of major adverse vascular events (including thrombosis). Additional analyses include safety assessments; evolution of PNH clone size and C3d deposition on RBCs; and other PROs (PGI-S, EORTC QLQ-C30, EQ-5D-5L).
Results: NA.

Figure 1: APPOINT-PNH design



Summary/Conclusion: Ph2 study data suggest that iptacopan may control EVH and IVH, thereby reducing anemia in pts with PNH previously treated with anti-C5 MAbs. Data from a further Ph2 study of iptacopan in patients with treatment-naïve PNH (NCT03896152) are awaited. Ph3 studies to assess the efficacy of iptacopan in a wider population of pts with PNH are planned.

PB1482 PHENOTYPE-GENOTYPE RELATIONSHIP IN PATIENTS WITH FANCONI ANEMIA AND VACTERL-H ASSOCIATION FREQUENCY

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Background: Fanconi anemia is mainly an autosomal recessive syndrome and more than 60% of the patients have physical anomalies. In the follow-up of the patients, bone marrow failure, AML and solid tumors develop. Pathological changes have been identified in at least 22 genes. FANCA 60%, FANCC 14% and FANCG 10% genes have been identified most frequently. VATER association, in its broader form, is an abbreviation of VACTERL or VACTERL-H, vertebral anomaly, anal atresia, cardiac anomalies, trecea-esophageal fistula, renal anomaly, extremity (radius and thumb) anomaly and hydrocephalus. It is a disease defined by a combination of three or more. It is seen sporadically and its frequency is reported as one in ten thousand or forty thousand in the general population. The probability of being diagnosed with Fanconi anemia simultaneously or later with VACTERL-H association has been reported to be 5-30%. In these patients, the risk of early-onset midline brain tumors, Wilms' tumors and AML is greatly increased.
Aims:
Our aim is to investigate the phenotype-genotype relationship of our patients with Fanconi anemia.
Methods: In our department, the phenotype-genotype relationship was investigated by studying the genetic mutations of patients diagnosed with Fanconi anemia with clinical, laboratory and mitomycin C test positivity. Our patients were evaluated especially in terms of VACTERL-H association.
Results: Mutations were detected in 14 patients out of 40 Fanconi anemia followed in our clinic. Four of our patients were male and other was female. Their age was between 2-21 and the median age was 10. Two siblings were identified in three families. Mutations were detected in the FANCA gene of 13 patients. Compound heterozygosity was detected in four patients, large homozygous deletion in six patients, and homozygous missense mutation in three patients. Eleven different pathological alleles were shown in the FANCA gene. In a patient with VACTERL-H association, c.2504+1G> C homozygous mutation was found in the FANCG gene.

Summary/Conclusion: Fanconi anemia is common in our country. However, genotype determination studies have started in recent years. Fanconi anemia are the results of this study genotype the first reported from Turkey. By obtaining genotype results in more of our patients, the frequency of Fanconi genotype in our country should be determined and its relation with phenotype should be investigated. In addition, patients with VACTERL-H association should be evaluated in terms of Fanconi anemia.

PB1483 DIAGNOSIS OF HEMATOPOIETIC MALIGNANCIES WITH GERMLINE PREDISPOSITION: A FILTERED WHOLE EXOME SEQUENCING APPROACH

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Background: Inherited Haematological Malignancies are a heterogeneous group of malignancies not yet fully understood and in constant evolution.
Patients suffering of suspected inherited malignancies are often faced to poor access to rapid diagnosis due to a restricted number of analytical sites or the current use of non-comprehensive targeted panels.
Aims: We aim at developing a new NGS panel for the analysis of several haematological diseases based on a filtered whole exome sequencing approach.
Haematological diseases incorporated in the panel include myelodysplasic syndromes, acute myeloid leukemia, inherited bone marrow failure syndromes, Fanconi anemia, Diamond Blackfan anemia, dyskeratosis congenita, Telomeropathies and severe congenital neutropenia.
Methods: Clinical exome is sequenced with the SureSelect Hulan Exome V6, recovering information for about 20k genes, representing ca. 180k exons. A newly designed variant filter based on an in-house pipeline tree (Alissa Interpret) for the flagging of retained variants, allows for the selection and labeling of ca. 100 variants per patient. Variants are categorized following the ACMG guidelines for the interpretation of inherited variants and reported in the context of the patient malignancies.
The set of genes has been selected from a deep insight to the most recent literature and guidelines and covers 85 full (exonic) genes. The ncRNA gene TERC and intronic regions from RETL1 are also included in the set.
The analytical pipeline considers the analysis of single patients, corroboration of relevant inherited germline mutations from fibroblasts and/or trio analysis including first or second relatives. Applications cover from simple diagnostic from single patients to familiar studies or donor compatibility analysis.
Results: The proposed analytical method provides a solution for the detection of mutations in a large panel of genes involved in the cited haematological diseases. Due to the constant evolution and updates in this malignancies area, flexibility is a key concept to avoid analytical obsolescence. Due to the wide range of genes covered by the WES approach, significant genes could be further updated, with a minimal effort, to the panel.
Summary/Conclusion: We therefore aim to provide physicians with a comprehensive diagnostic panel for the diagnostic work-up of patients affected (or suspected to be affected) by inherited haematological malignancies, and related diseases enhancing the patient's chances to benefit from a personalized medicine approach; together with a view to increase the knowledge about those (rare) conditions.

PB1484 REAL WORLD SINGLE CENTRE EXPERIENCE OF USE OF ELTROMBOPAG ADDED TO STANDARD IMMUNOSUPPRESSION AMONG INDIAN PATIENTS WITH APLASTIC ANEMIA

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Background: Acquired aplastic anemia results from immune-mediated destruction of haematopoietic stem cells of bonemarrow. Immunosuppressive therapies are effective, but reduced numbers of residual stem cells may limit their efficacy. In patients with aplastic anemia that was refractory to immunosuppression, eltrombopag, a synthetic thrombopoietin-receptor agonist, led to clinically significant increases in blood counts in almost half the patients. We combined standard immunosuppressive therapy with eltrombopag in previously untreated patients with severe aplastic anemia.
Aims: To evaluate the Effectivness and Safety of Eltrombopag, Added to Standard Immunosuppression in Indian patients with Acquired Aplastic Anemia.
Methods: Patients (>5 years) of either gender with Acquired Aplastic Anaemia, who had received Eltrombopag, in addition to standard Immunosuppression with ATG/Cyclosporin from Jul-2019 to Oct-2020, at Department of Clinical Hematology, Nizam's Institute of Medical Sciences, Hyderabad, India, were included. The primary outcome was complete/partial hematologic response at 6 months. Secondary end points included overall response, survival, adverse events{platelet response (platelet count: ≥50000/μL).}
Results: Of 17 patients, majority (%) were females. The mean age was… years. Seven (…%) patients had severe Aplastic Anaemia, two (12.5%) had non-severe aplastic Anaemia, 6 (37.5%) had Megakaryocytic thrombocytopenia. For newly diagnosed patients, the frontline use of eltrombopag (concomitant medications: anti-thymocyte globulin, ATG, and cyclosporin, N = 4; cyclosporin, N = 5; nil, N = 1) at a median maximum dose of 150 (50–300) mg/day led to an overall response rate (ORR) of 90% (trilineage: 60%; neutrophil: 20%; platelet: 10%). Adverse effects included dyspepsia, and liver function derangement. Eltrombopag was well tolerated without significant side-effects mandating drug withdrawal.
Summary/Conclusion: In a routine haematological practice, the use of eltrombopag in AA patients was feasible, safe, and associated with favourable responses.

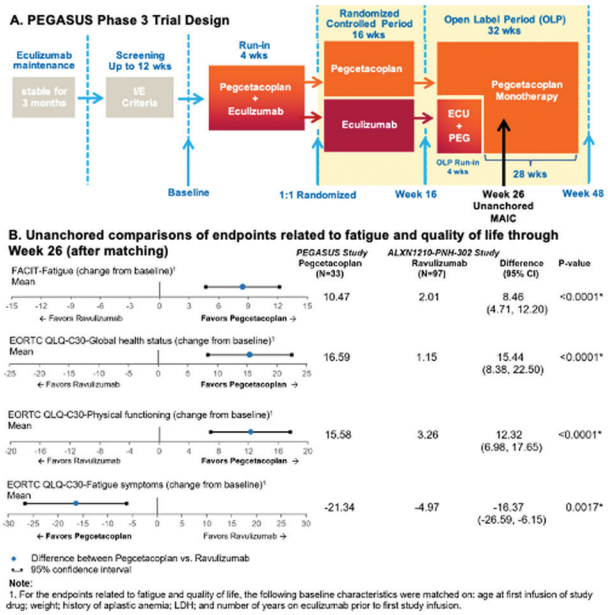
PB1485 COMPARATIVE EFFECTIVENESS OF PEGCETACOPLAN VERSUS RAVULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A MATCHING-ADJUSTED INDIRECT COMPARISON USING 26 WEEK PEGASUS PHASE 3 TRIAL DATA

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Background: Pegcetacoplan (PEG), a PEGylated peptide targeting proximal complement protein C3, can control both intravascular and extravascular hemolysis. In the PEGASUS trial (NCT03500549), a phase 3, randomized, open-label, active-comparator controlled study, PEG was shown to be superior to the C5 inhibitor eculizumab (ECU) after 16 weeks, improving hemoglobin (Hb) levels and clinical outcomes in patients with PNH (*Hillmen P et al., EHA 2020*).
Aims: We assessed the comparative effectiveness of PEG to the C5 inhibitor ravulizumab (RAV) using matching-adjusted indirect comparison (MAIC) methodology to conduct cross-trial comparisons.
Methods: Individual patient data from PEGASUS were used to adjust for baseline differences compared to aggregate, published results from the randomized ALXN1210-PNH-302 ("302") study (NCT03056040) which compared RAV and ECU at 26 weeks among patients with PNH with previous ECU treatment (Kulasekararaj et al., *Blood* 2019). In PEGASUS, patients completed a 16-week randomized controlled period (RCP) with 1:1 PEG and ECU randomization followed by PEG monotherapy for all patients for 28 weeks (Figure A). PEGASUS and 302 had similar eligibility criteria; however, PEGASUS required Hb <10.5 g/dL and absolute reticulocyte count >1x upper limit of normal while 302 did not. Propensity score weighting was used to balance demographic and clinical characteristics between the PEG arm from the PEGASUS trial and the RAV arm from the 302 trial. To compare to RAV results at Week 26, unanchored MAIC was used for PEGASUS patients from the RCP PEG group, using a proxy for Week 26 (mean of Week 24 and Week 28). Mean change from baseline (CFB) was calculated for Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score and for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC QLQ-C30) global health status, physical functioning, and fatigue symptoms questionnaires. Weighted Wald tests and 95% confidence intervals (CIs) were computed for comparisons of categorical and continuous outcomes.
Results: Thirty-three PEG patients from PEGASUS and 97 RAV patients from the 302 study were included. At Week 26, PEG patients experienced a clinically meaningful (>3 points) improvement in FACIT-Fatigue (higher score indicates less fatigue; mean CFB: 10.47 [95% CI: 6.98-13.95]) that was significantly greater (P<0.001) than the improvement for RAV patients (2.01 [95% CI: 0.64-3.38]) (Figure B). PEG patients also experienced clinically meaningful (>10 points) improvement in

EORTC QLQ-30 global health status (higher score indicates improved patient health; mean CFB: 16.59 [95% CI: 10.34-22.84]) that was greater than in RAV patients (mean CFB: 1.15 [95% CI: -2.14-4.44], P<0.001). Similarly, PEG patients showed clinically meaningful (>10 pts) improvement in EORTC QLQ-30 physical functioning (mean CFB: 15.58 [95% CI: 10.53-20.62]), but RAV patients did not (mean CFB: 3.26 [95% CI: 1.53-4.99], P<0.001), indicating that PEG patients experienced higher levels of physical functioning. For EORTC QLQ-30 fatigue symptoms, in which a negative score indicates a decrease in fatigue, PEG patients experienced a clinically meaningful (>10 points) decrease in levels of fatigue (mean CFB: -21.34 [95% CI: -30.96 to -11.72]), but RAV patients did not (mean CFB: -4.97 [95% CI: -8.40 to -1.54], P<0.010).



Summary/Conclusion: MAIC results indicated that when compared with RAV, PEG treatment is associated with improvements in FACIT-Fatigue and EORTC QoL scores, evidencing an improvement in fatigue, physical functioning, global health, and quality of life.

PB1486 TRIAL IN PROGRESS: QUANTIFYING THE HUMANISTIC AND SOCIOECONOMIC BURDEN OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA IN THE COMMODORE BURDEN OF ILLNESS STUDY

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease associated with major complications such as thrombotic events and impaired renal function. Prior to the introduction of C5 inhibitors in 2007, PNH had been fatal in about 35% of patients within 5 years of diagnosis; yet this fatality rate continues in countries without access to these medications. Worldwide access to the C5 inhibitor eculizumab is hindered by the unavailability of treatment, and in places where treatment is approved, cost of treatment, reimbursement issues, infrastructure, or patient restrictions may further impede access (Risitano et al, *Am J Hematol*. 2018; Risitano et al, *Front Immunol*. 2019). PNH treatment places a significant economic burden on healthcare systems. In many countries, this has resulted in negative health technology appraisals (HTAs), indicating that optimal care and resource utilization are not being achieved (Coyle et al, *Med Decis Making*. 2014). New therapies with more convenient modes of administration may improve how PNH is clinically treated and positively impact access to C5 inhibitors globally. Further, treatments that allow for home administration may reduce patient and healthcare systems costs. Robust data on the real-life burden and cost of PNH are needed to assess the impact of current therapies and establish a baseline for new therapeutic approaches. Data derived from this study, which to our knowledge is the first socioeconomic study in PNH, will be used to support HTA processes and inform the value of new PNH therapies.

Aims: The COMMODORE burden of illness (BOI) study will quantify the direct medical costs (eg, treatment and hospitalization), direct nonmedical costs (eg, travel), and indirect costs (eg, impact on work productivity and family burden) associated with PNH for patients and care providers and determine the impact of PNH on health-related quality of life (HRQOL).
Methods: This is an international, prevalence-based, bottom-up, BOI study containing both retrospective and prospective data collection. The study will be overseen by an expert reference group consisting of multidisciplinary stakeholders. The study protocol and materials will be submitted for ethical approval to the University of Chester in the United Kingdom. Physicians will provide information on sociodemographic, clinical, and medical resource utilization using electronic case record forms (eCRFs). Through patient and public involvement and engagement, patients, after giving informed consent, will provide further information on the economic and HRQOL impact of PNH by completing patient-reported outcome surveys. Patients from France, Germany, the United Kingdom, and China will be included.
The aim is to recruit 94 physicians who will report 350 patient eCRFs with an expected return of 140 patient surveys and longitudinal data collection after 6-12 months for each patient. Mean per-patient costs, including direct medical and nonmedical costs, and indirect resource utilization will be calculated by multiplying the individual resource utilization by country-specific unit costs. National economic burden will be extrapolated by applying national prevalence estimates of PNH. Additionally, the impact of PNH on patient HRQOL will be assessed.
Results: Final results are expected in spring 2022.
Summary/Conclusion: The COMMODORE BOI study aims to characterize current PNH treatment via quantification of the humanistic and socioeconomic burden at the patient, healthcare system, and societal level to enhance the evidence base for treatment and decision-making in this community.

PB1487 EPIDEMIOLOGY OF ACQUIRED APLASTIC ANEMIA: A RETROSPECTIVE 10-YEAR SINGLE CENTRE EXPERIENCE

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Background: Aplastic Anemia (AA) is a syndrome characterized by peripheral blood pancytopenia with hypo cellular marrow. Acquired idiopathic AA is still the most common variety. Aplastic anemia's incidence varies in different geographic areas. In Albania the epidemiology of Acquired AA has not been identified by any study up to now.
Aims: The aim of this study is to identify and describe the epidemiology, including the incidence of Acquired AA in Albania.
Methods: The following study is a retrospective study. Patients diagnosed for the first time between January 2010 and December 2020, at the University Hospital Center (UHC) 'Mother Teresa' Tirana, Albania, aged 14 years old and up, were included in this study. The diagnosis of AA patients was confirmed by the bone marrow biopsy hypo-cellularity (less than 25% of cellularity), immunohistochemistry, and by the peripheral blood cytopenias (ANC, Hgb, Plt). The patients were classified into three severity subgroups using the International Aplastic Anemia Study Group. Statistical analysis for this study was performed using SPSS. Categorical and continuous parameters were analyzed using the x^2 test and the T test respectively.
Results: A total of 35 patients were diagnosed as Aplastic Anemia between 2010-2020. The median age was 51 (15-80) years, and 19 (54.3%) were females. Males' age was slightly higher than the females, mean 54.7 and 49.4 years old respectively. Most of the cases fell under the Non-severe AA group and the Very-severe AA group, 16 and 12 patients respectively. Out of the 35 patients, two were lost to follow, 5 died within the first year following the diagnosis. The incidence of Acquired Aplastic Anemia in Albania is 1.35 per million inhabitants.

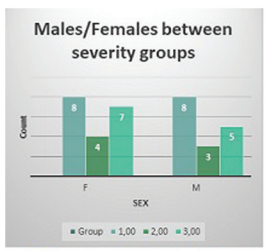


Figure 1. Bar chart showing the distribution of men and women between the three groups.Left to right 1st group NSAA; 2nd group SAA; 3rd group VSAA.

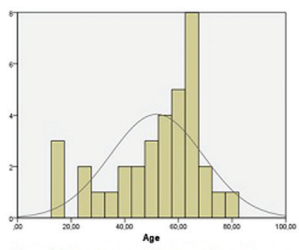


Figure 2. Histogram of the age distribution of the AA patients.

Summary/Conclusion: The incidence of AA in Albania is lower compared to other studies performed in Europe. In this study the median age of the AA patients was 51 years old, which could be due to environmental factors, whereas other studies have reported a younger median age varying between 19 to 35 years of age. In this study females' numbers were slightly higher compared to males. In other studies, males were predominant.

PB1488 RETROSPECTIVE ANALYSIS OF ROMIPLOSTIN IN SEVERE MEDULLARY APLASIA

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Background: Thrombopoietin analogs (aTPO) are used due to effectiveness in megakaryocytes stimulus and bone marrow multipotent hematopoietic progenitor cells. Thus, are widely used as second row treatment in patients with refractory medullary aplasia. Currently, it could be used as first contact treatment with immunosuppressive therapy enhacing in order to increase the response to treatment.
Aims: Analyze of Romiplostim use after inmunosuppressive therapy in patients with severe medullary aplasia.
Methods: Data analysis of all the patients diagnosed with medullary aplasia between 2019 - 2021 and with Romiplostim treatment has been done taking into account the effiency of the treatment in two terms:
- Parcially response to treatment: neutrophils higher than 0.5x10e9/L, platelets higher than 20x10e9/L and haemoglobin higher than 8 g/dL.
- Complete response to treatment: neutrophils higher than 1.5x10e9/L, platelets higher than 150x10e9/L and haemoglobin higher than 12-13 g/dL.
Results: In table 1 below, characteristics of 4 patients treated with Romiplostim has been shown. Three of them had platelets lower than 20x10e9/L with transfusional dependency and neutrophils lower than 1x10e9/L. All of them had have immunosuppressive therapy + Eltrombopag without response. Two of them had refraction to platelets transfusion. One of them only had been received previous treatment with Eltrombopag. After 6,5 months of tracking, all the patients treated with Romiplostim achieve parcially response to treatment without serious complications.

Summary/Conclusion: Adjuvant use of Romiplostim with patients without immunosuppressive therapy response must be taken into account. This option decrease transfunctional needs and improve all the blood series (hemoperipheral level) without serious complications.

PB1489 BONE MARROW METASTASIS: A CASE SERIES

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Background: In bone marrow metastasis, the search of primary tumor is important as prompt treatment dictates prognosis of patient. However, site of primary tumor remains elusive in 10-30% of metastatic cancer despite extensive search.
Aims: At Clinical Referral Haematology Laboratory, Hospital Ampang, which is the tertiary referral laboratory for all hospitals within the Ministry of Health in Malaysia, we performed a retrospective review on the cases with a trephine diagnosis of metastatic carcinoma between 2010-2020.
Methods: A bone marrow trephine biopsy was performed based on patients' clinical presentation and cytopenia from full blood count. We analyzed each report individually and extracted the patients' clinical data from our cases and report, including the primary tumor and or possible metastasis site as well as survival rates.
Results: There were 14 cases of tumors metastatic to the bone marrow comprising of 9 women and 5 men, with median age of 60.3-year-old. Metastasis was made upon a bone marrow trephine biopsy was performed. Preliminary of 6 cases who we manage to identify the site of primary tumor whereas the rest of the cases with unknown primary bone marrow metastasis.
Summary/Conclusion: Bone marrow metastasis is an infrequent event. Close collaboration between clinician and pathologist is essential for diagnosis, identification of tumour subtype and even primary site of tumour for management and prognostication for cancer of unknown

Table 1. Characteristics of patients treated with Romiplostim.

Pacient	Age	Gender	Diagnosis	Immunosuppressive therapy	Refractariedad plaquetaria	Eltrombopag treatment
1	73	F	Severe medullary aplasia	YES	YES	YES (No response)
2	52	F	Severe medullary aplasia	YES	YES	YES (No response)
3	68	M	Severe medullary aplasia	YES	NO	YES (No response)
4	33	M	Severe medullary aplasia	YES	NO	NO

Table 2. Results of the use of Romiplostim in medullary aplasia in our hospital.

Pacient	Start of Romiplostim	Response	Complications	At present
1	22/05/2019 *Hb: 9.5 g/dL* *N: 0.7x10e9/L* *Pla: 21x10e9/L (transfused)*	At 2 months at doses of 8 mcg/Kg	NO	Sustained partial response at doses of 10 mcg/Kg *Hb: 12.9 g/dL* *N: 1.7x10e9/L* *Pla: 150x10e9/L*
2	31/01/2020 *Hb: 10.1 g/dL* *N: 0.98x10e9/L* *Pla: 41x10e9/L (transfundidas)*	At 4 months at doses of 7 mcg/Kg	NO	Sustained partial response at doses of 7 mcg/Kg *Hb: 9.4 g/dL* *N: 2.34x10e9/L* *Plaq: 152x10e9/L*
3	23/10/2020 *Hb: 11 g/dL* *N: 0.59x10e9/L* *Pla: 26x10e9/L (transfundidas)*	At 8 months at doses of 10 mcg/Kg	NO	Sustained partial response at doses of 10 mcg/Kg *Hb: 12.1 g/dL* *N: 1.72x10e9/L* *Pla: 50x10e9/L*
4	23/09/20 *Hb: 7.8 g/dL* *N: 0.79x10e9/L* *Pla: 18x10e9/L*	At 2 months at doses of 6 mcg/Kg	NO	Sustained partial response at doses of 8 mcg/Kg. *Hb: 13,4 g/dL* *N: 1,87x10e9/L* *Pla: 66x10e9/L*

primary. Outcome of unfavourable cancer of unknown primary is poor even with recommended treatment.

Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

PB1490 GENETIC LESIONS IN CLL PATIENTS WITH STEREOTYPE ANTIGENIC RECEPTORS MOST COMMON IN RUSSIA.

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Background: Tumor B-cells in chronic lymphocytic leukemia possess extreme narrowing of the IGHV gene repertoire comparing to other lymphoproliferative diseases. B-cell receptors with a highly homologous structure (SARs) - account for more than 40% of all CLL cases, with 29 such most common subgroups accounting for more than 13% of all CLL cases. CLL#1, CLL#2, and CLL#8 SARs are associated with an extremely aggressive course of the disease, while CLL#4 - with indolent. It was also suggested that tumor cells expressing certain SARs may also differ in the frequency and patterns of genetic lesions.
Aims: To determine the frequency of TP53, NOTCH1, and SF3B1 gene mutations in CLL#1, CLL#6, CLL#3, CLL#99, and CLL#28A subgroups of patients from the Russian cohort.
Methods: The study included 88 CLL patients admitted to the National Research Center for Hematology (Moscow, Russia) from 2012 to 2020. Rearranged IGHV gene sequences and SARs were determined according to the procedure recommended by ERIC. NOTCH1 gene (exon 34) mutations were studied by fragment analysis or by NGS as described by Campregher et al. TP53 gene mutations (exons 2-11 exons) were determined by NGS according to Pavlova et al. SF3B1 gene (exons 14-16) mutations were assessed by NGS.
Results: Peripheral blood DNA samples from CLL#1 (N=32), CLL#6 (N=17), CLL#3 (N=15), CLL#99 (N=12), and CLL#28A (N=12) patients were studied. TP53 gene mutations were detected with a high frequency in the CLL #6, CLL#1, CLL#99, and CLL#28A subgroups in 6 (35.3%), 11 (34.3%), 4 (33.3%) and 2 (16%) cases respectively. It should be noted that in all patients with CLL#99 and CLL#28A, only minor VAF (<5%) mutations were found. Most CLL#1 and CLL#6 patients have VAF>10%. Two patients with CLL#6 and one with CLL#99 had 2 clones simultaneously. In the CLL#3 subgroup, only 2 cases with mutations in this gene were identified, however one had 2 clones, and the other - 4. Mutations in the NOTCH1 gene were detected in patients with CLL#99, CLL#6, CLL#1, CLL#28A, and CLL#3 with a frequency of 3 (25%), 4 (23.5%), 7 (21.8%), 2 (16%) and 2 (13%) respectively. In most cases, the widespread c.7544_7545delCT mutation was detected. Also, c.7558_7561delCTTC and p.Q2444X mutations were found in two cases with CLL#1 and c.7547_7551del deletion in a patient with CLL#28A. SF3B1 gene mutations were detected in 8 (53.3%) CLL#3 patients. In CLL#6 (11 patients studied), CLL#99, and CLL#28A no SF3B1 gene mutations were found and in CLL#1 subgroup these mutations have not been assessed yet.

	CLL#1	CLL#99	CLL#28	CLL#3	CLL#6	CLL in general
IGHV	Clan I	Clan I	IGHV1-2	IGHV1-69	IGHV1-69	--
U-CLL	100%	100%	100%	100%	100%	50-60%
TP53 mutation	34,3%	33,3%	16%	13,3%	35,3%	7-10%
NOTCH1 mutation	21,8%	25%	16%	13,3%	23,5%	4-10%
SF3B1 mutation	--	0	0	53,3%	0	4-10%

Table 1. Genetic lesions frequency in Russian CLL subsets studied and in CLL in general

Summary/Conclusion: Here we present the data concerning the higher frequency of mutations in CLL#1, CLL#6, and CLL#3 subgroups than have been reported so far. Perhaps this is since some of our patients were tested after they already received FCR treatment and subsequently relapsed. It should be noted that CDR3 in subgroups CLL#1 and #99 have a similar motif, differ only by 1 amino acid, and are formed using the IGHV genes of the clan 1 (mostly IGHV1-2). CLL#28A is also based on IGHV1-2, and CLL#3 and CLL#6 are based on IGHV1-69. In the CLL#99 subgroup, as well as in the CLL#1 subgroup of a similar receptor structure, mutations in the TP53 gene are abnormally common, but with low VAF, which currently has no proven negative clinical significance. Interestingly, the two SARS subgroups with the IGHV1-69 gene usage demonstrate an opposite TP53, NOTCH1, and SF3B1 gene mutation pattern. Further study of genetic lesions in diverse SARs subgroups CLL patients should help to improve understanding of the pathogenesis, prognostication, and therapy of the disease.

PB1491 TARGETED MULTIGENE PANEL: NEXT-GENERATION SEQUENCING IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Next-generation sequencing (NGS) technologies have revolutionized approaches in molecular genetic studies making possible to spell out the mutational status, the genetic and epigenetic variability of chronic lymphocytic leukemia (CLL). The driver mutation's identification allows for a deep understanding the pathogenesis of CLL, stratifying patients (pts) into prognostic groups and select the appropriate treatment matching it with the genetic lesions.
Aims: We aimed to develop the Lymphoid Targeted NGS Panel for assessing the mutations of pts with CLL and to study the possible correlation of the mutational status with the clinical characteristics of the disease.
Methods: In study were enrolled 26 pts with CLL: treatment-naïve (n=18) and relapsed/refractory (n=8). All cases were diagnosed according to iwCLL criteria (iwCLL, Hallek et al., 2018). According to cytogenetic assay, pts were divided into 3 prognostic groups: favorable (n=16), neutral (n=2) and unfavorable (n=8). Although, 20/26 pts were divided into 2 prognostic groups taking into account the data on the mutational status of *IGHV*: favorable (n=8) and unfavorable (n=12). Six patients have no available data of *IGHV* mutational status. Treatment regimens: standard rituximab-containing (n=15) and targeted drugs (n=11). The Lymphoid Targeted NGS Panel was designed as a comprehensive gene panel and covered 117 genes, part of which plays a core role in cellular pathways. DNA samples were extracted from peripheral B-cell lymphocytes via the standard phenol-chloroform method. An average reading depth of 1000x is produced on a MiSeq platform (Illumina, USA). The 2% threshold of allele frequency (VAF) was used. The clinical significance of mutations was established using the following databases: COSMIC, ClinVar, gnomAD with application *in silico* analysis (Cscape, Cancer Genome Interpreter, SNPs&Go).
Results: Sequencing of 15 pts samples was performed. Genetic aberrations were detected in all DNA samples. We identified 722 variants in 83/117 genes. Frequent mutations were *FAT1* (13.9%), *KMT2C* (13.6%) and *RYR1* (4.4%). The clinical significance of 82% of variants was identified as likely benign (n=348) and benign (n=244), 16.2% (n=116) of the mutations was uncertain. Regarding associations, pathogenic and likely pathogenic mutations were identified in 80% pts (12/15) with an unfavorable prognosis. The pathogenic mutations 1.7% (n=12): *SF3B1* K700E (n=3), *SF3B1* G742D, *TP53* Lys120Glu, *NOTCH1* P2514fs*4, *BRAF* D594G, *BRAF* K601N, *PTEN* (c.1321-2A>T),*MGA* R1246X, *JAK3* V722L, *IDH2* T352P. Likely pathogenic variants (n=2) were *ATM* Y2080C and *NF1* M2217V. The detected variant of the mutation Lys120Glu in the *TP53* gene was associated with the presence of del17p13, and correlated with the unfavorable clinical course of the disease in patient CLL-024. Three pts with del13q14 had *SF3B1* K700E pathogenic mutation, which accelerated the development of CLL by alternative splicing of RNA and activation mTORC1. It should be noted that 2 pts (CLL-023, CLL-024) with unfavorable prognosis had mutations both in *BCR* and *NOTCH2* genes of uncertain significance. The existing approach to the interpretation of the results does not allow making an unambiguous conclusion about the clinical significance of variants in the *IDH2* and *JAK3* genes, despite its pathogenic effect.
Summary/Conclusion: The obtained data demonstrate the possibility of applying NGS in clinical practice and the approbation of The Lymphoid

Targeted NGS Panel. Whereas the clinical significance of some mutations is currently uncertain, further research using NGS technology is required.

Chronic lymphocytic leukemia and related disorders - Clinical

PB1492 CLINICAL FEATURES OF LARGE GRANULAR LYMPHOCYTIC LEUKEMIA-ASSOCIATED PURE RED CELL APLASIA: RESULTS FROM A SINGLE CENTER IN CHINA

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Background: Large granular lymphocyte leukemia (LGLL)-associated pure red cell aplasia (PRCA) is a rare lymphoproliferative disorder. Only a few case series have been reported in the literature. so that the features and optimal treatment of the disease remains unclear.
Aims: We conducted this retrospective study to assess clinical features, immunological profiles and the outcome of treatment in patients with LGLL-associated PRCA.
Methods: A cohort of 20 patients with LGLL-associated PRCA who referred to our hospital from January 2013 to April 2020 was reviewed.
Results: The clinical characteristics of 20 patients included in this study showed that no differences were evident based on sex. The median age of the patients was 50 years old (range, 28-76 years). Splenomegaly was observed in 45% of cases, most of which were characterized by mild to moderate enlargement. By contrast, hepatomegaly was rare (10%). Our study identified increased percentage and absolute number of $CD3^+CD8^+$ T cells, meanwhile decreased $CD3^+CD4^+$ T cells, $CD3^-CD16/CD56^+$ NK, $CD19^+$ B cells and CD4/CD8 ratio (Table 1). For treatment (Table 1), cyclosporine A (CSA) in combination with methylprednisolone (MP) was administered in 6 patients, with an complete and partial remission (CR+PR) of 50.0% (3/6). A novel immunosuppressive strategy of cyclosporine (CSA), low dose methylprednisolone (MP) and danazol(DNZ), which we named CMD regimen, was administrated orally with an initial dose of CSA 3mg/kg/day, MP 0.25–0.5 mg/kg/day, and DNZ 5.0-10.0 mg/kg daily as first-line therapy for 13 patients, of which ten responded positively(76.9%). One patient received antithymocyte globulin (ATG), resulting in no response (NR). Among the three patients who failed to respond and two relapse to first-line therapy of CSA and MP, four patients received the second-line therapy of CMD regimen, with an CR+PR of 60%. Another patient received ATG, and achieved complete remission (CR). Among the three patients who failed to respond and two relapse to first-line therapy of CMD regimen, three patient responded to the second-line therapy of CMD regimen plus methotrexate (MTX). Adverse events were uncommon, one patient had impairment of liver function with transaminase values up to 110 U/L.

Table 1 Immunological profiles and response to treatment of all patients

Immunological profiles (N=20)	Min	Max	Mean	SD	Reference range	Low ,N	Normal ,N	High ,N
$CD3^+T$(%)	85.3	98.5	94.2	3.4	56-86	0	1	19
$CD3^+CD4^+T$(%)	15.3	51.0	30.3	10.7	33-58	12	8	0
$CD3^+CD8^+T$(%)	22.4	80.5	57.2	15.4	13-39	0	1	19
CD4/CD8 ratio	0.2	1.3	0.6	0.4				
$CD3^-CD16/CD56^+$ NK(%)	0	6.4	1.7	1.9	5-26	18	2	0
$CD19^+B$(%)	0.6	9.2	2.6	2.6	5-22	17	3	0

Treatment	First-line therapy, n(%)			Second-line therapy, n(%)	
	N	CR+PR(%)	Relapse	N	CR+PR(%)
CSA+MP	6	2+1 (50.0%)	2 (66.7%)		
ATG	1	0+0 (0%)		1	1+0(100.0%)
CSA+MP+DNZ	13	7+3 (76.9%)	2(20.0%)	5	2+1(60.0%)
CSA+MP+DNZ+MTX	0			5	2+1(60.0%)

CsA cyclosporine A; MP methylprednisolone; ATG antithymocyte globulin; DNZ danazol; MTX methotrexate; CR complete remission; PR partial remission; NR no response;

Summary/Conclusion: This study provides new information regarding the clinical features and therapeutic strategies for LGLL-associated PRCA, which demonstrated that the CMD regimen could be a promising strategy for patients with LGLL-associated PRCA.The multiple-center clinical trial need to initiate to validate this conclusion.

PB1493 A RETROSPECTIVE ANALYSIS OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) TREATED WITH VENETOCLAX IN THE REAL-LIFE SETTING IN SPAIN (VENARES)

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Background: Pivotal clinical trials have shown Venetoclax (Ven; BCL inhibitor) good efficacy and safety profile. Studies in real life setting are limited as Ven is commercially available in Spain since April 2018.
Aims: To evaluate the effectiveness of Ven in adult CLL pts by the overall response rate (ORR) at 9 months (mo) after the first Ven dose administration, as assessed by the treating physician.
Methods: This is a Spanish non-interventional, retrospective, national, multicenter, post-marketing, observational study. Eligible subjects were adult pts with CLL who initiated Ven at least 9 mo before inclusion. Subjects in Early Access Program from Jan 2017 were included.
Data from approximately 100 pts is planned to be collected from 30 Spanish sites. Data of pts are retrospectively reviewed until the date of last follow-up or death.
Results: 48 pts were included in the interim study: 32 pts (66.7%) were male, the median age was 74.5 years (67.5-78), pts had received a median of 4 prior lines of therapy (range 1-10 lines). 15 pts had unmutated IGHV (88%), 10 pts (33.3%) had del(17p), 10 pts (33.3%) had TP53 mut. In 42 pts, median time from CLL diagnosis to Ven initiation was 78.5 m (38-125). 81.2% of pts received Ven monotherapy, 4.2% combined with rituximab, 2% with obinutuzumab,12.5% with other agents. Objective response was evaluated in 23/39 pts treated with Ven monotherapy.
48 pts (100.0%)had dose modifications, 19 (39.6%), dose interruptions, 19 (39.6%) discontinued Ven. 26 (54.2%) had TLS greater risk before Ven initiation, 22 pts were hospitalized during ramp-up.
14pts (29.2%) presented at least 1 SAE, 10 (20.8%) presented at least 1 SAE related to Ven. 6 pts (12.5%) presented 1 AE related to Ven that led to drug withdrawal. Percentages of Specific AEs were neutropenia (43.7%), febrile neutropenia (12.5%), serious infection (18.8%), TLS in 6.3% (2 laboratory,1 clinical) and Richter transformation (RT) (6.3%). Related to Ven were 4 febrile neutropenia (8.3%) and 1 lab TLS(2.1%).

Table: Outcomes with Venetoclax monotherapy	
Patients, n	39
Overall response rate in evaluable pts (23)	
CR/Cri	8 (34.8%)
PR/nPR	9 (39.1%)
ORR	17 (73.9%)
PFS est 24 mo	75.9% (56.2-87.6)
uMRD ($<10^{-4}$) in assessed pts, (%,n)	22.2% (2/9)

Summary/Conclusion: This preliminary effectiveness data suggest overall outcomes are similar to those in the pivotal clinical trials. Safety assessment show AEs reported were consistent with the safety profile seen in prior VEN studies and did not reveal unexpected AEs.

PB1494 COMPREHENSIVE CARDIAC EVALUATION REVEALS NO INCREASE IN VENTRICULAR ARRHYTHMIAS IN PATIENTS ON CHRONIC IBRUTINIB THERAPY – A STUDY OF KROHEM, THE CROATIAN COOPERATIVE GROUP FOR HEMATOLOGIC DISEASES

M. Kolacevic Zeljkovic [1], N. Bulj [1,2], S. Basic-Kinda [3], V. Milunovic [4], D. Carzavec [5], O. Jaksic [6], M. Vodanovic [3], S. Ostojic-Kolonic [2,4], P. Gacina [5,7], D. Dujmovic [3], I. Zeljkovic [1], V. Pejsa [2,6], I. Aurer [2,3,*]

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Background: Ibrutinib is increasingly used for treatment of various B-cell malignancies. It's generally well tolerated, but has cardiovascular side-effect including hypertension and arrhythmias, most frequently atrial fibrillation (AFib). Data on the dynamics of frequency and severity of arrhythmias in patients on chronic ibrutinib treatment are lacking.
Aims: We initiated this prospective study to determine the impact of chronic ibrutinib therapy on incidence of supraventricular (SPB) and ventricular premature beats (VPB).
Methods: This was a multicentre, prospective, observational cohort study. Consecutive patients with hematologic malignancies starting ibrutinib therapy and without structural heart disease and clinically significant arrhythmias were included in the study. Cardiologic work-up included echocardiography and 24h-Holter-ECG. Diagnostic assessment was carried out before and repeated at 3, 6 and 12 months after the introduction of ibrutinib therapy. Primary endpoint was the number of VPBs on 24h-Holter-ECG; secondary endpoints were: number of SPBs on 24h-Holter-ECG, systolic left ventricular function, occurrence of AFib and newly diagnosed or worsened hypertension.
Results: 35 patients recruited from 4 hospitals were included in the study during 2019 and 2020 (Table 1). The most common indication for treatment was chronic lymphocytic leukaemia in 31 (89%) patients. Median age was 66 years (range 58-73), 54% were female. The most prevalent cardiovascular comorbidity was hypertension (45%), followed by smoking (29%). The remaining risk factors, including diabetes mellitus, stroke and coronary artery disease had a prevalence of <10%. Mean left ventricle ejection fraction was 60%, left atrial diameter 40±4 mm and volume 53±7 mL.After a median follow-up of 6 months, there was no significant increase in the number of VPBs (428±320 vs. 170±110, p=.19) or SPBs (245±104 vs. 532±305, p=.09). Hypertension was newly diagnosed or worsened in 8 patients (23%), and 2 patients developed paroxysmal AFib (6%). Ibrutinib was temporarily discontinued or its dose was adjusted in 3 patients due to non-cardiovascular side-effects.

Table 1. Baseline characteristics

	Total (N= 35)
Demographics	
Age (years)	66 (58-73)
Male sex (% (n))	46 (16)
BMI (kg/m^2)	27.3 ± 4.5
History (% (n))	
Hypertension	46 (16)
Diabetes mellitus	20 (7)
Hyperlipidaemia	23 (8)
Smoking	29 (10)
Stroke / TIA	0
Coronary artery disease	6 (2)
Chronic kidney disease	14 (5)
COPD/Asthma	6 (2)
CHA_2DS_2VASc score	2.35 ± 1.5
HAS BLED score	0.3 ± 0.45
Hemato-oncologic disease	
Chronic lymphocytic leukemia	88 (31)
Waldenstrom macroglobulinemia	6 (2)
Mantle-cell lymphoma	6 (2)
Echocardiography	
LVED diameter (mm)	47 ± 3
LA diameter (in PLAX) (mm)	40 ± 4
LA volume (mL)	53 ± 7
LVEF (%)	60 ± 3
TAPSE (mm)	21 ± 2
TAP (mmHg)	20 ± 2
Electrocardiogram	
Heart frequency	78 (72-85)
Sinus rhythm (yes/no)	100 (35)
Atrial premature beats	36 (7-141)
Ventricular premature beats	9 (2-49)

Summary/Conclusion: Prolonged treatment with ibrutinib had no significant impact on number of VPBs or SPBs. Our study suggests that ibrutinib does not significantly increase the propensity to develop dangerous cardiac arrhythmias in patients who do not have clinically important structural heart disease or arrhythmias prior to treatment start and stresses the importance of hypertension control in this group of patients.

PB1495 PROGNOSTIC VALUE OF IGHV MUTATIONAL STATE AT DIAGNOSIS FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Chronic lymphocytic leukemia (CLL) is a pathology with a variable clinical evolution; some patients remain indolent for many years while others require treatment, including shortly after diagnosis. Although molecular and genetic markers with prognostic value have been described, the current International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines only recommends their analysis prior to commencing treatment.
Aims: In this retrospective study, we analyzed the prognostic impact of molecular and genetic markers on CLL patients at diagnosis.
Methods: A consecutive series of 217 patients with CLL diagnosed in our hospital between 2008 and 2018 was analyzed. Clinical, molecular (*IGHV* and *TP53*) and cytogenetic data were collected at diagnosis.
Results: Our series confirmed the prognostic value of the CLL-IPI index for OS (p=0.003, Log-Rank test) and time to first treatment (TFT, p<0.001). In accordance with previously published results, Kaplan-Meier survival analyses identified an association between *IGHV* unmutated (p<0.022) (Figure 1**A** and **1B**) and shorter OS and TFT (p≤0.001). The variables age >65 years (p<0.001), β_2-microglobulin >3.5 mg/dL (p<0.001) and advanced Binet/Rai clinical stage (p=0.001) were also associated with shorter OS and TFT, while the presence of mutation/deletion of *TP53* (p=0.001) and deletion of 11q (p<0.001) were associated with shorter TFT. Unmutated *IGHV,* advanced clinical stage and age (albeit marginally) also showed independent prognostic value for OS as determined by multivariate analysis (**Table 1**, p=0.01, 0.033, and 0.072 respectively). For TFT, only unmutated *IGHV* and clinical stage (albeit marginally) had prognostic impact (p=0.001 and 0.081, respectively). Importantly, when only patients in the early stages were selected (RAI 0-2/ BINET A), *IGHV* mutation maintained prognostic value for both OS and TFT in the multivariate analysis (OS: OR 6.16, p=0.01/OR 5.96, p=0.009; TFT: OR 13.58, p=0.001/OR 14.08, p=0.001) and Kaplan-Meier survival analyses (OS: p=0.013, TFT: p<0.001) (Figure 1**C** and **1D**). The loss of prognostic value of β_2-microglobulin levels might be explained by the statistically significant association observed in our series between unmutated *IGHV* and β_2-microglobulin levels > 3.5 mg/dL (p = 0.002, Pearson's χ^2) as well as advanced age (p = 0.024, Pearson's χ^2). Chromosomal alterations, such as deletion/mutation of *TP53* and deletion of 11q, were not included in the multivariate analysis due to their low incidence in our series. A larger series would be required to evaluate their prognostic impact.

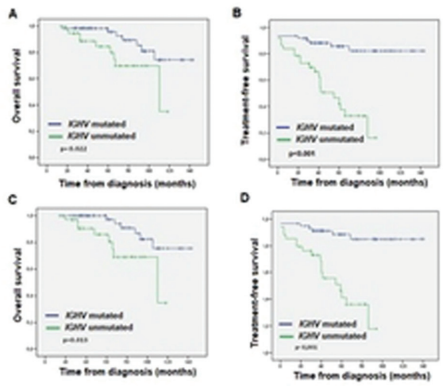


Figure 1. Kaplan-Meier survival curves according to *IGHV* mutational state. **A)** Overall survival (OS) in the whole series, **B)** Time to first treatment (TFT) in the whole series, **C)** OS in RAI stages 0-2, **D)** TFT in RAI stages 0-2.

Summary/Conclusion: *IGHV* mutational state was the only prognostic marker to have independent prognostic value for both OS and TFT, for the whole series as well as patients in the early stages. Our results indicate that the determination of *IGHV* mutational state at diagnosis informs the risk stratification of patients with CLL.

PB1496 FEATURES OF THE DIRECT ANTIGLOBULIN TEST AND THEIR ROLE IN THE DEVELOPMENT OF IMMUNE HEMOLYSIS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The course of chronic lymphocytic leukemia (CLL) is often complicated by autoimmune disorders, including autoimmune hemolytic anemia (AIHA). The direct antiglobulin test (DAT) is playing an important role in the diagnostic of autoimmune hemolysis. The modern capabilities of the DAT make it possible to detect the presence of autoantibodies and complement on the surface of red blood cells (RBC), as well as to determine the class and subclass of antibodies involved in the pathological process.
Aims: The aim of this study was to explore the frequency and features of positive DAT in patients with CLL and its possibilities to prognose AIHA.
Methods: DAT was carried out using equipment (automatic immunohematological analyzer IH-1000) and reagents from Bio-Rad (USA). DiaMed-ID-LISS/Coombs Anti-IgG + C3d cards were used for screening. Upon receiving a positive DAT, immunoglobulin classes, complement components, IgG subclasses were detected using DC-Screening I and DAT IgG1/IgG3 cards (Bio-Rad (USA)). The presence of hemolytic anemia was determined according the usual clinical and laboratory criteria. The levels of hemoglobin, RBC, reticulocytes, total and indirect bilirubin were investigated by conventional methods. DAT results were analyzed in 104 patients with CLL. The median age of the cohort was 65 years (range 53 to 85 years).
Results: Positive DAT was detected in 15.4% patients with CLL (16 out of 104 examined). The intensity of the reaction was: (+) - in 3 patients (18.8%), (++) - in 6 (37.5%), (+++) - in 5 (31.3%), (++++) - in 2 (12.5%). Positive DAT was due to fixation on RBC IgG 2/4 - in 37.5% of the examined, IgG1 — in 18.8%, IgG1 in combination with the complement component C3d — in 18.8%, IgG1 + IgG3 + IgA + C3d — in 12.5%, only C3d — in 12.5%.
Hemolysis was observed in 9 people (56.3%) among 16 patients with a positive DAT. Patients with positive DAT due to IgG2,4, showed no signs of hemolysis. The detection of C3d both independently and in combination with IgG1, IgG3, IgA, in all cases was associated with signs of hemolysis. IgG1 fixation on RBC was found in 3 patients with CLL, hemolytic anemia developed in 2 of them (66.7%).
Summary/Conclusion: Positive DAT was detected in 15.4% of patients with CLL, hemolytic anemia was found in more than half of them (56.3%). The detection of the complement component C3d on the surface of RBC, as well as the combination of C3d with IgG1, IgG1+IgG3+IgA, in 100% of cases was associated with the AIHA. Fixation of IgG1 alone led to AIHA in 66.7% of cases. The role of IgG 2,4 in the development of hemolysis has not been proven.

PB1497 COMPARATIVE ASSESSMENT OF PROGNOSTIC MODELS FOR ASYMPTOMATIC CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS IN BINET STAGE A: EVALUATION IN CHINESE HAN COHORT

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Background: Clinical course of CLL is heterogeneous and asymptomatic patients with early stage should receive active surveillance until there is evidence for progression. Several molecular, genetic and clinical prognostic markers were demonstrated to be capable of predicting the probability of treatment and various prognostic models have been proposed to predict time to first treatment (TTFT).
Aims: To explored the potency of four proposed models (IPS-E, CLL-IPI, CLL1-PM and Barcelona-Brno prognostic model) to predict TTFT using our Han cohort. All four models were initially based on western population. Considering the significant difference of CLL between Western and Asian population, the models should be validated and discussed thoroughly among all ethnics prior to its broader implementation.
Methods: From the database of Department of Hematology and Pukou CLL Center, The First Affiliated Hospital of Nanjing Medical University, a total of 110 newly diagnosed Binet stage A CLL patients without indication for treatment from Jun, 2009 and to Jan, 2020 were enrolled in our cohort. The diagnosis of CLL and stage of disease was strictly in line with the updated guidelines from iwCLL. All included patients underwent active surveillance as initial management, defined as no treatment need within the first 3 months after diagnosis and patients who didn't meet the indication for treatment were censored at date of statistical analysis. The endpoint was TTFT, which was defined as the time interval between diagnosis and start of treatment due to disease progression. We collected all parameters at diagnosis as mentioned in previous four prognostic models: (1) clinical manifestation (age, Binet and Rai stage and lymph nodes size); (2) absolute lymphocyte count (ALC) and lymphocyte doubling time (LDT); (3) b2-Microglobulin (β2-MG); (4) del [17p], del [11q] analyzed by FISH; (5) IGHV mutation status.
Results: 110 asymptomatic Binet A patients were included in our study; the median age was 58 years old (25-84). The median follow-up time was 35 months (4-189 months), 57 patients (51.8%) met the indication for treatment due to disease symptomatic progression during follow-up. Log-rank test was performed to analyze the independent risk factors associated with TTFT. Seven variables were found to be independently associated with TTFT including Rai stage, ALC > 15×10^9/L, palpable lymph node ≥ 1 cm, β2-MG > 3.5 mg/L, unmutated IGHV, TP53 disruption and 11q deletion (Figure 1). However, age older than 60 years old and LDT<12 months, as proposed in CLL1-PM model, failed to show correlation with shorter TTFT (p=0.383 and p=0.087, respectively) in our cohort. Stratification of patients according to IPS-E, CLL-IPI, CLL1-PM and Barcelona-Brno prognostic model all showed significant difference in terms of TTFT (Figure 2). The predictive power of four prognostic models was further assessed by Harrell's C-index and AIC. C-index was highest in CLL1-PM, followed by CLL-IPI, IPS-E and Barcelona-Brno prognostic model. The AIC values were lowest in CLL1-PM, followed by CLL-IPI, Barcelona-Brno and IPS-E (**Table 1**).

Figure 1. Log-rank Analysis for Time to First Treatment (TTFT).

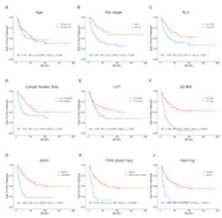


Figure 2. Kaplan-Meier Analysis Comparing TTFT According to (A) IPS-E; (B) CLL1-PM; (C) CLL-IPI; (D) Barcelona-Brno prognostic model.

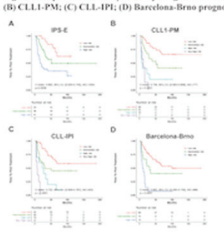


Table 1. Comparison of IPS-E, CLL-IPI, CLL1-PM and Barcelona-Brno prognostic model for prediction of time to first treatment (TTFT).

The cohort of our Binet A CLL patients (n=110)		
	C-index (95% CI)	AIC
IPS-E	0.683 (0.620-0.745)	1004
CLL-IPI	0.722 (0.656-0.787)	933
CLL1-PM	0.736 (0.663-0.808)	777
Barcelona-Brno	0.663 (0.595-0.730)	986

Abbreviations: C-index, Harrell's concordance index. AIC, Akaike information criterion

Summary/Conclusion: All four prognostic models had their efficacy in prediction of TTFT. IPS-E might be an ideal model for patients who undergo basic clinical examination so that fundamental evaluation could be conducted to guide clinical surveillance. For patients yearn for active assessment, FISH and NGS were recommended and CLL-IPI could be used to predict their prognosis more accurately and comprehensively.

PB1498 FEASIBILITY OF MEASURING ADHERENCE TO ORAL ONCOLYTICS IN ROUTINE CLINICAL PRACTICE: A PILOT STUDY IN OLDER ADULTS WITH LYMPHOID DISORDERS

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Background: Oral targeted therapies (OTT) have transformed the treatment of chronic lymphocytic leukemia (CLL). Prior studies in cancer patients (pts) have reported variable adherence rates (12-100%) to OTT with suboptimal adherence associated with inferior outcomes. Data from studies in CLL suggest that even brief treatment interruptions can lead to lower survival rates. However, defining optimal adherence and routine measurement of adherence in clinical practice is challenging. Techniques for measuring adherence include self-reporting, pill counts, electronic monitoring systems, prescription database analysis and assessment of serum/urine drug levels. We conducted a pilot study to evaluate

the performance of multiple strategies for measuring adherence in a busy oncology practice caring for older adults (OA) with CLL.
Aims: The aims of this study were three-fold:
1. To compare the utilization of self-report [brief adherence rating scale (BARS)], pill count and Medical Event Monitoring System (MEMS) Cap (an electronic bottle cap) to measure adherence to OTT in OA with CLL.
2. To determine the adherence rate and factors impacting adherence.
3. To correlate adherence rate with disease outcomes.
Methods: Pts ≥70 years (yrs) with CLL and other lymphoid disorders on OTT were followed monthly for the first 3 months (mos), then every 3 mos for 1 year. Nursing home residents were excluded. Pt, disease and treatment characteristics [including a geriatric assessment (GA)] were recorded at baseline. Adherence was measured at every visit with BARS, pill count and MEMS Cap. Data on adverse events and disease outcomes were also collected.
Results: Of the 54 pts screened, 25 were enrolled. Median age was 77 yrs (71-93 yrs), 21 pts had CLL, 3 had mantle cell lymphoma and 1 had marginal zone lymphoma. Geriatric syndromes (GS) detected at baseline included cognitive impairment (28%), depression (24%), polypharmacy (92%) and recent falls (12%); 48% pts had ≥2 GS. Most frequently used OTT were ibrutinib (n=17) and venetoclax (n=5). So far, pts have completed a total of 63 visits (30 virtual, 33 in-person) with median follow up of 3.3 mos. BARS was the most consistently used measure of adherence (63/63 visits, 100%). MEMS cap data was obtained on 13% of total visits. Pill package incompatibility (68%), refusal to use MEMS cap (8%) and clinical trial participation (4%) precluded use of MEMS cap in 80% (*n*=20) of pts. Pill counts could be performed at only 8% of visits due to increasing usage of telehealth (51%), unavailability of pill packaging (32%) or logistic issues (17%). Median adherence using both BARS and MEMS cap was 100% (range, 70%>100% for BARS; 82-100% for MEMS cap). Only 4 pts had less than 100% adherence at any visit. Patient's self-report accurately reflected MEMS cap measured adherence in these instances. Five pts (20%) required dose interruptions, mostly due to adverse events. Six pts discontinued therapy and 2 pts died of unrelated causes. Chronological age and presence GS were not associated with adherence rate or outcomes.
Summary/Conclusion: Objective measurement of adherence to oral therapies remains challenging with poor applicability of electronic pill bottle cap devices due to pill package incompatibility and increasing use of virtual/tele visits. Despite its limitations, self-report remains a feasible tool to measure adherence in routine clinical practice. Abbreviated adherence scales and other electronic monitoring technologies may be able to overcome existing challenges and warrant further study.

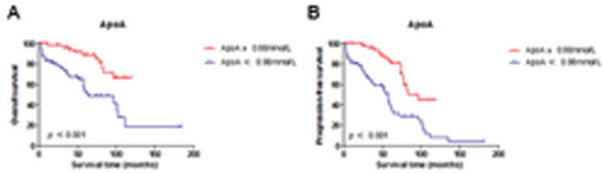
PB1499 PROGNOSTIC VALUE OF APOLIPOPROTEIN A IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The improvement of risk stratification and novel therapeutic targets of chronic lymphocytic leukemia (CLL) are urgently needed. Lipid metabolism is related to the prognosis of hematologic tumors and a potential target for novel therapies of some hematologic malignancies. Apolipoprotein A (ApoA), the major protein of high-density lipoprotein, takes effect on lipid transportation and immunity. Nevertheless, the role of ApoA in CLL has not been explored.
Aims: This study aimed to investigate the potential role of ApoA in the prognosis of CLL patients.
Methods: A total of 150 newly diagnosed CLL patients from January 2010 to December 2019 were enrolled in this study. Survival analyses were performed by Kaplan-Meier curves and univariate and multivariate Cox proportion hazard regression models. Pearson tests, Spearman tests and Chi-square tests were performed to evaluate the correlation between ApoA and other clinical and laboratory parameters.
Results: Kaplan-Meier curves revealed that increased ApoA was associated with longer overall survival (OS) (χ^2=14.985; p<0.001; shown in Figure 1A) and progression-free survival (PFS) (χ^2=16.190; p<0.001; shown in Figure 1B). Univariate and multivariate Cox regression revealed that ApoA was a significant independent prognostic factor of OS (p=0.028) and PFS (p<0.001). ApoA was related to advanced stages (p<0.001), β2-microglobulin (r=-0.447, p<0.001) and C-reactive protein (r=-0.508, p<0.001).

Figure 1



Summary/Conclusion: Our study indicates the prognostic value of ApoA in CLL patients for the first time. ApoA was a favorable prognostic biomarker of OS and PFS in CLL patients. The novel prognostic biomarker may increase prognostic accuracy of CLL.

PB1500 THE EFFICACY OF FRONT-LINE CHEMOIMMUNOTHERAPY WITH FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB (FCR) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN REAL CLINICAL PRACTICE

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Background: Treatment of chronic lymphocytic leukemia remains a significant challenge in gematology. Despite the large number of innovative targeted drugs used, the FCR program is used in many randomized trials as a reference for comparison, which indicates its importance not only for scientific tasks, but also for modern clinical practice, as it remains one of the most accessible. To date, the FCR program is included in the modern algorithm of the 1st line treatment of patients with CLL younger than 65 years with intact TP53, regardless of the mutated IGHV genes. This is based on data from randomized trials of the GCLLSG. In the CLL8 study, the standard FCR-program cycle was 28 days. There are not enough studies proving the efficacy of such treatment in patients with high comorbidity.
Aims: The aim of the study was to investigate the clinical efficacy of front-line FCR program treatment in CLL patients within a clinical model integrated into real practice.
Methods: The study included 108 previously untreated patients with CD20-positive chronic lymphocytic leukemia. The stage of the disease was assessed according to the Rai classification, the functional state was determined on the ECOG scale, and the comorbidity was assessed on the SIRS - G scale. The 17p13/TP53 deletion was calculated using the FISH method, and the IGHV-status observed through PCR. The FCR program consisting of 6 standard courses was being conducted over a longer period of time, which extended the induction period and reduced treatment density. Minimal residual disease (MRD) was assessed according to the international standardized protocol (Rawstron, 2007) by 4-color flow cytometry. Some patients were receiving maintenance treatment with Rituximab for 2 years, compared to the group of patients without maintenance therapy. The main control points of the analysis were PFS and OS. The OS was evaluated according to the intent-to-treat principle.
Results: The Me of the comorbidity index was 5(0-12). The Me of creatinine clearance was 60.4 ml / min (43-121). We have introduced the concept of treatment density (the ratio of the duration of the standard cycle to the original one) in real clinical practice. The drug doses were not reduced in our study. The Me of the FCR cycle in our study was 50 days. Accordingly, the Me duration of the induction treatment period increased to 9 months, and the treatment density decreased to 0.6. The clinical efficacy of the treatment was evaluated according to the iWCLL 2008. The overall respons rate was 92.6%, complete remission (CR) was detected in 53.9% patients. 52.8% patients had undetectable MRD (UMRD) in the peripheral blood and 39.3% patients had UMRD in the bone marrow. The Me follow-up was of 51 months (range 8-150). The Me of PFS from the beginning of FCR induction was 42 months. PFS was significantly longer in patients who achieved CR (p=0,0001), with comorbidity in patients below 5 index (p=0,02), and with achievement of UMRD (p=0,002). Reduced treatment density and maintenance therapy with Rituximab did not affect the duration of PFS. OS from the beginning of FCR-induction was 120 months in 60% of patients.
Summary/Conclusion: The study showed that the decrease in the density of the FCR program induction in real clinical practice in patients with CLL was accompanied by high efficacy and did not lead to a significant decrease in the PFS compared to patients who received the standard program.

PB1501 PATIENT PERSPECTIVES OF CHRONIC LYMPHOCYTIC LEUKEMIA & DISEASE RELATED OUTCOMES – A QUALITATIVE STUDY

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Background: Chronic lymphocytic leukemia (CLL) is a B-cell hematological malignancy of elderly population with varied presentation and multiple therapeutic options available for disease management. There are lack of studies on patient journeys in India which would provide key insights about the disease, impact the current management and quality of life of patients.
Aims: This study aims to leverage the benefits to provide the patient perspective of CLL in India which may help mitigate the current gaps and expectations regarding comprehensive care.
Methods: A focused group discussion was conducted on an online platform using a semi-structured discussion guide, with four CLL patients and two caregivers of CLL patients, of India. The duration of the meeting was 90 minutes. The discussions were focused on understanding the symptoms, diagnosis, treatment, follow up and quality of life of CLL patients. The information obtained was analyzed to identify the common trends and patterns related to the patient's health, emotional state and challenges encountered throughout the clinical course of the disease.
Results: Common symptoms observed by patients that led to primary care physician visits were unexplained weight loss, fever, fatigue, breathlessness and repetitive infections. The first point of contact were primary care physicians where patient were treated and there was a delay of 6-7 months from onset of symptoms to diagnosis of CLL and reaching specialist. Patients were anxious about the disease progression despite of completing treatment and there were psychological, emotional and financial burden associated with the disease which lead to treatment discontinuation and impact in patient morale. There is a need for psychological counselling, guidance and patient advocacy group support, peer to peer interaction, disease awareness initiatives and cost effective treatment options to improve the patient related outcomes in CLL.
Summary/Conclusion: The present study highlights the need for disease education, support to reduce diagnosis time, recurrence of disease and additionally patients support groups and counseling to improve patient's morale and adherence to treatment thus enhancing the quality of life in CLL patients.

PB1502 OUTCOMES IN PATIENTS WITH FOLLICULAR LYMPHOMA AND CHRONIC LYMPHOID LEUKEMIA RECEIVING OBINUTUZUMAB, IN THE SETTING OF COVID19 INFECTION

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Background: Obinutuzumab is a type II humanized anti-CD20 antibody of the IgG1 subclass that mediates B-cell lysis by direct cell death and by antibody-dependent cell -mediated toxicity. The treatment with GA 101 (single agent or combined) causes a potent overall B-cell depletion that may compromise the antiviral immunity and augment the tendency to severe pulmonary complications.
Aims: We conducted a one year retrospective study of all the patients hospitalized in our Service of Hematology, (Department of internal Medicine, UHC " Mother Teresa") being diagnosed with Follicular Lymphoma and Chronic Lymphoid Leukemia under treatment with Obinutuzumab to evaluate and identify all the COVID-19 positive patients and to evaluate their outcome.
Methods: We reviewed the data of all the patients >18 years old, diagnosed with Follicular Lymphoma and Chronic Lymphoid Leukemia, hospitalized in our Service of Hematology from January 2020 to January 2021 under treatment with Obinutuzumab (single agent or combined). The positivity of COVID-19 infection was demonstrated through positive PCR- based test (nasopharyngeal swab). Chest scan was performed to access the severity of pulmonary involvement from SARS-COV-2.
Results: A total number of 25 (100%) patients on Obinutuzumab treatment were identified. 20 (80%) patients were diagnosed with CLL and 5 (20%) patients were diagnosed with FL. The median age for CLL patients resulted 61,8 years (18-80 yrs) and the median age for FL resulted 50,8 years (18-80 yrs). 14 (70%) of CLL patients were classified as high- risk CLL and 6 (30%) as intermediate-risk CLL. All the FL were classified as high -risk FL. 60% of all the patients were without comorbidities at the moment of the diagnosis (11 CLL and 4 FL patients) and 40% has two or more comorbidities at diagnosis. 6 CLL patients and 4 FL patients were on 1st line Obinutuzumab, 10 CLL patients and 1 FL patient were on 2nd line Obinutuzumab, and 4 CLL patients were on 3rd line Obinutuzumab. All the patient were at the moment of starting the treatment with Obinutuzumab with ECOG 0-1. No therapy related complications were found. 32% (8) of all the patients receiving Obinutuzumab were without comorbidities and ECOG 0-1 at the moment of getting infected with SARS-COV-2 (5 high-risk CLL patients and 3 FL patients) and developed severe COVID-19 pneumonia 5 to 9 days after getting infected with rapid critically severe clinical picture evolution. The median age of the patients infected with COVID-19 resulted 55,6 years (24- 67years), and the male:female ratio resulted 1,6:1. They were all treated in the ICU and unfortunately none of them survived more than 30 days-hospitalization time. The COVID-19 mortality in this cohort was 100%.
Summary/Conclusion: The introduction of new anti-CD20 antibodies as Obinutuzumab in the treatment of CLL and Follicular Lymphoma undoubtedly is a milestone in the treatment history of Lymphoid Neoplasms, being 1,5 to 2,5 times more effective than Rituximab, prolonging the overall survival of the patients and giving a great impact on the decourse of the disease. With our study (a very small cohort study) we demonstrate that getting infected with SARS-COV-2 is not related to the treatment with Obinutuzumab or other chemotherapies, but the patients treated with Obinutuzumab (single agent or combined) develop a very severe COVID-19 clinic. If this is biologically caused or is just a casualty finding is still to be studied. Previous studies have demonstrated almost the same results but further studies are needed to evaluate this findings.

PB1503 ATYPICAL CHRONIC LYMPHOCYTIC LEUKEMIA: A COMPARATIVE MORPHOLOGICAL AND IMMUNOPHENOTYPIC STUDY

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Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, which is characterized by monomorphic clonal B-cell lymphocytosis, low expression of B-cell markers, combined with CD5 and CD23. A proportion of cases show less common laboratory features and the adjective atypical has been introduced firstly in regard to the presence of morphological heterogeneity and then – to describe forms with an uncommon phenotype. Some data suggest that the distinction between CLL and aCLL is clinically relevant, however, the concept of atypical CLL is still applied differently.
Aims: To conduct a comparative study of the morphological and immunophenotypic variants of CLL and to compare them by main clinical and laboratory parameters.
Methods: A total of 123 men and 104 women at a mean age of 65.6±11.7 years with clinical and laboratory CLL features were included in the study. Morphological assessment of the lymphocyte population and flow cytometric immunophenotyping were performed in all samples.
Results: According to WHO criteria, 35 of the patients (15.4%) were defined as "atypical CLL" with >15% atypical cells on microscopic examination, while deviations from the typical CLL immunophenotype occurred in 9.7% with high expression of CD20 (6%), CD79b (2%), CD22 (4%), and/or negative expression of CD23 (7%), defined as immunophenotypic atypical cases. The analysis revealed that the presence of atypical morphological features did not correlate significantly with immunophenotypic parameters, except the fact that 33.3% of CD23(-) CLL had atypical morphology vs 14.15% of CD23(+) (p=0.04) and 37.5% of CD38(+) cases revealed different morphological

characteristics compared to 26.6% of CD38(-) (p=0.023). On the other hand, phenotypically atypical CLL had a significantly higher incidence of CD38 (28% vs 5% in CLL with a typical immunophenotype) (p=0.002), CD49d (80% vs 23%) (p=0.001), and sIgM (33% vs 4%) (p=0.02) and lower expression of CD43 (40% vs 93% in CLL with a typical immunophenotype) (p<0.001), while CD27, CD62L, CD81 and CD200 had a similar incidence.Only 3.08% of the patients demonstrated both atypical morphology and immunophenotype, however, no significant associations with the main biological and laboratory parameters were found, except for the significantly lower relative number of Gumprecht shadows (4.5±1.8% vs 22.7-31%). There were no differences in time to treatment (TTT) and overall survival (OS) depending on morphological and/or immunophenotypic atypia.
Summary/Conclusion: In conclusion,microscopic and flow cytometric studies of leukemic cells in CLL define the disease as heterogeneous, however, the combined morphological and immunophenotypic atypia is a rare event. Further studies integrating molecular and genomic approaches are needed to shed light on the underlying causes and the potential clinical significance of atypical variants.

PB1504 PROSID STUDY: EVALUATING EFFICACY AND SAFETY OF INTRAVENOUS IMMUNOGLOBULIN (IVIG) 10% IN PRIMARY INFECTION PROPHYLAXIS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA – STUDY DESIGN

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Background: Secondary immunodeficiency (SID) occurs as a consequence of hematological malignancies (HM), most commonly in chronic lymphocytic leukemia (CLL) and multiple myeloma. About 25% of patients present with SID at diagnosis of CLL and this incidence may increase to 85% during the course of disease. Recent advances in CLL therapy also lead to cumulative immunosuppression. Infections are the main cause of morbidity and mortality in CLL patients, causing between 30% and 50% of deaths within the first year after diagnosis. Intravenous immunoglobulin (IVIg) is established as secondary prophylaxis to reduce infection rates in patients with HM with hypogammaglobulinemia. No large randomized study has established efficacy of IVIg as primary prophylaxis in CLL patients with hypogammaglobulinemia yet, although several small studies suggest an up-to 4-fold reduction of infection rates.
Aims: The primary objective is to demonstrate the benefit of IVIg 10% compared to placebo as primary infection prophylaxis in patients with CLL and SID who undergo antineoplastic therapy.
Methods: This study is planned as a prospective, double-blind, randomized, placebo controlled, multicenter, interventional phase 3 study and will be conducted in approximately 50 centers in North America and Europe (EUDRA-CT #: 2019-004375-40). A minimum of 240 adults with a diagnosis of CLL will be enrolled and allocated 1:1 to either IVIg 10% (0.4 g/kg) plus standard of care (SoC) prophylaxis or placebo plus SoC prophylaxis. Patients will receive up to 13 infusions of IVIg in 4-weekly intervals. Total duration will be up to 55 weeks consisting of up to 3 weeks for screening, 48 weeks of treatment and 4 weeks of follow-up. Main inclusion criteria are CLL diagnosis according to International Workshop on CLL (iwCLL) criteria, undergoing CLL antineoplastic treatment, and hypogammaglobulinemia with IgG levels <500 mg/dL (5 g/L). Main exclusion criteria are IgG treatment within the last 3 months, antibiotic prophylaxis and/or treatment within 7 days prior to current CLL treatment start, as well as current major infection or ˃1 major infection in the previous 6 months before baseline. The primary efficacy outcome will be the occurrence of at least one major infection defined as (□) bacterial or viral infection resulting in death, (□) microbiologically or clinically documented bacterial or viral infection requiring treatment with anti-infectives, or (□) fever of unknown origin requiring hospitalization or hospitalization prolongation. Secondary outcomes include overall infection rate, frequency of SoC prophylaxis with anti-infectives, duration of anti-infective prophylaxis. Exploratory outcomes include quality of life measured by EQ-5D, IVIg PK profiles, and resource utilization. The primary efficacy evaluation is based on the comparison of major infections in CLL patients with or without primary infection prophylaxis with IVIg. The difference between these proportions will be statistically tested in the intent-to-treat (ITT) population. The Z approximation will be used for statistical comparison of the proportions observed. One-sided 97.5% confidence interval will be provided.
Results: Interim analysis will be conducted once at least 100 patients are available for evaluation of the primary endpoint in the ITT population).
Summary/Conclusion: This study will evaluate the efficacy and safety of IVIg 10% as primary prophylaxis of infections inCLL patients with SID in a large clinical setting for the first time.

PB1505 PRETREATMENT NEUTROPENIA IN CLL PATIENTS IS ASSOCIATED WITH HIGH INFECTION RISK AND PREDICTS TREATMENT INITIATION WITHIN ONE YEAR.

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Background: CLL (Chronic Lymphocytic Leukemia) activity is frequently manifested as anemia and/or thrombocytopenia, either as a result of bone marrow infiltration or autoimmunity, but CLL-related neutropenia is not common and it's effect on disease course is rarely reported. However, the development of neutropenia, especially when considering the underlying immune dysfunction of CLL patients, might contribute to infection risk and influence treatment decisions.
Aims: To study clinical characteristics, complications and treatment outcomes of CLL patients manifesting pre-treatment CLL-related neutropenia.
Methods: Cases were retrospectively collected from members of the Israeli CLL Study Group. Patients with a diagnosis of CLL/SLL (Small lymphocytic lymphoma) and neutropenia of < 1000/μL before initiating CLL directed therapy were included. Patients who developed neutropenia while receiving CLL directed therapy or following treatment were excluded.
Results: We identified 12 treatment-naïve CLL/SLL patients with neutropenia<1000/μL (CLL n=11, SLL n=1) (Table 1). Three patients presented with neutropenia concurrently with CLL/SLL diagnosis and nine developed neutropenia during CLL follow up, with median time of 2.2 years (0.5-11.7) post CLL diagnosis. Median neutrophils count at the time of first neutropenia was 600/μL (0-900). At the time of first neutropenia, six patients had isolated neutropenia without anemia or thrombocytopenia. Bone marrow biopsy was done in 11 patients, nine patients had diffuse infiltration pattern and two non- diffuse infiltration pattern. Nine patients had splenomegaly. Direct Coombs test was positive in six patients but no patient had clinically significant AIHA (Autoimmune hemolytic anemia) or ITP (Immune thrombocytopenia). Anti-neutrophils antibody test was done in one patient and was found negative. Low IgG level (<700 mg/dL) was present in four patients, low IgA (<70 mg/dL) in two and low IgM (<40 mg/dL) in five. Six treatment naive neutropenic patients developed Grade 3 or 4 infection (50% of the study cohort). The most common infection site was the skin and soft tissues (n=3), other infection sites include the oral cavity, gastrointestinal tract, urinary tract and lungs. Among the six patients with neutropenia and significant infection, four had low IgG levels. Supportive care with GCSF was administered in eight patients. Four patients received a course of steroids, concurrently with GCSF in three. CLL directed therapy was initiated in nine patients with median time from first neutropenia to CLL directed therapy of 104 days (Range, 6-490), eight patients received CLL-directed therapy within a year (Table 2). Treatment was chemoimmunotherapy in five patients, ibrutinib in two and venetoclax-obinutuzumab in two. Data on treatment toxicity is available for seven patients, among those- two patients developed neutropenic fever following cycle one of treatment and none had neutropenic fever during cycles 2-6 of treatment. Three patients on chemoimmunotherapy needed dose reduction due to treatment toxicity. No dose reduction was reported in patients on novel agents.

Table 1

Patient Characteristics	N=12
Gender: Male/Female	7/5
Age (years) at CLL diagnosis, median (range)	63 (42–88)
Neutropenia at CLL diagnosis	3
Neutropenia developed during CLL follow up	9
Time (years) from CLL diagnosis to first neutropenia, median (range)	2.2 (0.5-11.7)
IGHV gene unmutated , n/n tested	4/6
Unfavorable FISH (11q- or 17p-), n/n tested	2/9
BINET stage A/B/C at time of first neutropenia	1/4/6
Splenomegaly	9
Bone marrow involvement, n/n tested	
Diffuse pattern	9/11
Non Diffuse pattern	2/11
Neutrophils/µL at time of first neutropenia, median (range)	600 (0-900)
Lymphocytes/µL at time of first neutropenia, median (range)	21300 (500-261000)
Hemoglobin g/dL at time of first neutropenia, median (range)	11.4 (8.4-13.3)
Platelet/µL at time of first neutropenia, median (range)	106500 (82000-279000)
Elevated LDH	2
IgG mg/dL, at time of first neutropenia, median (range)	1150 (267-2700)

Summary/Conclusion: Neutropenia in treatment naïve CLL patients is accompanied by diffuse bone marrow involvement in most patients, although anemia and/or thrombocytopenia might be absent. Neutropenia can predispose patients to significant infections. Some patients will be managed solely with GSCF and/or steroids, but most patients will need CLL-directed therapy within a year.

PB1506 SUBCUTANEOUS IMMUNOGLOBULINS USE IN IMMUNODEFICIENCY SECONDARY TO CHRONIC LYMPHOCYTIC LEUKAEMIA: MONOCENTRIC EXPERIENCE IN COVID-19 ERA

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Background: Secondary antibody deficiency (SAD) is a typical manifestation of haematological malignancies such as chronic lymphocytic leukaemia (CLL), or a side effect of their treatment. Immunological defects are observed in 25-85% of CLL patients (pts) and increases the risk of infections, with overall higher morbidity and mortality. Antibiotics administration and vaccinations are recommended as risk-reduction strategies in those pts. No real guidelines are available to recommend eligibility for prophylaxis, but many indications warrant immunoglobulins replacement therapy (IgRT) in selected pts with low IgG (<5g/l) or with more than 3 infective episodes per year despite antibiotic treatment and timely vaccination. No clear indications are available regarding the delivery method (intravenous or subcutaneous), dosage, frequency of administration and duration of IgRT.
Aims: The aim of this study is to assess the efficacy and safety of subcutaneous IgRT (SCIg) and its impact on quality of life (QoL) on CLL pts in Covid-19 era.
Methods: Ten CLL pts, have been treated with SCIg from October 2019 to December 2020. Median age and body weight were 66 years (56-88) and 68 Kg (52-86). Comorbidities were present in 5 pts (hypertension, diabetes mellitus, lung diseases). 5 pts had unmutated IgVH and 1 had 17p deletion. The median number of prior therapies was 2 (IBR, BR, Chl-antiCD20, FCR, in 5, 4, 4, 3 pts respectively). At that time, 7 pts were on therapy (IBR, Ven, Alkylating Agent in 4, 1, 2 pts respectively). None presented neutropenia. All pts underwent antibiotic prophylaxis with trimetroprin-cotimoxazole, sometimes associated with clarithromycin, and influenza vaccinations. Median baseline IgG level was 485 mg/dl (118-817), with a media of 3 infection/year (1-5; pneumonia, UTI). All pts received 10 g total dose hyaluronidase-free SCIg over a 1h double-needle subcutaneous infusion every 15 days over one year, independently from their body weight. After the first dose, administered in a hospital setting to make the patient comfortable with their personal pump, the next doses were self-administered at home. The IgG level and CD4/CD8, CD19 and CD16/56 (natural killer, NK) lymphocytes subset were recorded both at baseline and during the observation period to monitor the immunological reconstitution as the therapy went on.
Results: No patient experienced infectious events during the SCIg therapy nor Covid-19 mediated interstitial pneumonia. All patients tolerated the therapy: nobody interrupted the treatment and only one patient presented a skin rash (grade 2). Both dosage and administration schedule have been stable over time. Dealing with humoral immunity, IgG levels arose from a median of 485 mg/dl (118-817) to a stable median value >600 mg/dl from 6 months onward. About cellular immunity, T-cells including CD4 and CD8 and NK cells displayed a stable fashion until 6 months. On the other hand, the CD19 B cells values reflect both the disease status and the ongoing treatment effects. Results were in Table 1. Finally we observed advantages on both QoL and costs, since pts did not need to go to the hospital with the help of a care-giver, rather they could comfortably get their SCIg at home without any assistance.

Table 1. Results

Parameter Normal range	Baseline Median value	1° month Median value	3° months Median value	6° months Median value	9° months Median value	12° months Median value
Gamma % (10-18)	7 (2-11)	7 (4-11)	7 (6-12)	8 (7-12)	9 (8-12)	9 (7-11)
IgG mg/dl (700-1600)	485 (118-817)	491 (259-808)	471 (436-818)	615 (436-865)	621 (578-839)	602 (538-915)
IgA mg/dl (70-400)	32 (2-85)	26 (2-55)	29 (5-84)	32 (2-82)	39 (2-73)	60 (5-71)
IgM mg/dl (40-230)	17 (9-28)	16 (9-28)	15 (6-48)	18 (7-80)	25 (11-78)	10 (9-46)
CD4 x10^9/L (630-1400)	429 (292-1056)	458 (262-962)	448 (434-463)	430 (373-487)	nd	nd
CD8 x10^9/L (350-810)	854 (227-1539)	888 (218-1220)	889 (600-1179)	966 (523-1410)	nd	nd
CD19 x10^9/L (100-410)	202 (2-52488)	55 (4-2847)	43 (3-3060)	11 (8-8926)	nd	nd
CD16/56 x10^9/L (140-420)	180 (61-541)	303 (59-383)	107 (67-353)	107 (104-330)	nd	nd

Summary/Conclusion: SCIg administration in CLL pts is safe and efficacious as infectious prophylaxis, with higher median IgG levels, thanks to its pharmacokinetic advantages and improved adherence to treatment. Especially in the Covid-19 era, the subcutaneous route is preferred to the intravenous one, because of the self-administration at home and the granted availability to the drug itself.

PB1507 EVALUATION OF ADVERSE EFFECTS OF IBRUTINIB: EXPERIENCE FROM A NORTHERN HOSPITAL OF SPAIN

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Background: Ibrutinib has emerged as an effective therapeutic alternative with proven clinical benefit in several lymphoid neoplasms such as Chronic Lymphatic Leukemia (CLL), Mantle Cell Lymphoma (MCL), and Waldenström's Macroglobulinemia (WM). However, it can produce adverse effects that may limit its use.
Aims: To evaluate the clinical impact and adverse effects/toxicity of Ibrutinib in patients diagnosed with CLL, MCL and WM, who were treated with this drug between 2015 and 2020 at our hospital.
Methods: An observational study in which 41 patients diagnosed with CLL, MCL and WM and treated with Ibrutinib, were included.
Results: 41 people were enrolled: 36 CLL (88%), 4 MCL (10%) and 1 WM (2%). 63% were men and 49% were patients aged >74 years. From the total number of patients, 8 (20%) have died (5 LLC, 2 LCM and 1 WM).
Comorbidities at diagnosis were: 18 patients (44%) had arterial hypertension, 7 (17%) had diabetes mellitus, and 5 (12%) had dyslipidemia. 6 patients had cardiovascular alterations: 3 (7%) Atrial Fibrillation (AF), 2 (5%) dilated cardiomyopathy and 1 (2%) heart failure; 8 patients (19%) had respiratory disorders and 5 (12%) previous tumors (3 malignant and 2 benign).
In the subgroup of patients with CLL, 25% were Rai-Binet advanced stage and 42% had high-risk cytogenetic alterations (del17p / TP53 / del11q). 36% received Ibrutinib as the first line and 64% had relapsed CLL. The median duration of treatment in these patients was 19.5 months (range from 3 to 36 months). 5 CLL have received post-Ibrutinib treatment because of the progression of the disease.
Patients with MCL were all stage IV: 75% received Ibrutinib in the second line and 25% received it in the third line (25%). The patient with WM received Ibrutinib in the second line.
ADVERSE EFFECTS

17 patients (41%) had infectious complications (mostly relapsing CLL): 10 respiratory (3 of them were severe because of *H. influenzae*, *K. pneumoniae* and Varicella-Zoster Virus (VZV). 3 encephalitis (1 tuberculous, 1 viral because of VZV and 1 case in which the implicated microorganism was not identified), 2 urinary (E. coli), 1 digestive (Campylobacter jejuni) and 1 cutaneous (cellulitis due to S. pyogenes). In 4 CLL (24%), these infections led to the temporary suspension of the drug for an average of 13.5 days (range: 10-16 days) and in 2 CLL (12%), the infections caused the definitive suspension by the appearance of CNS involvement. 3 patients have suffered grade IV bleeding complications: 2 CLL required temporary suspension and 1 WM required definitive suspension because of subdural hematomas.
1 CLL and 1 WM developed AF, 1 CLL grade II hyponatremia and 1 CLL and 1 MCL, grade IV hyponatremia (definitive suspension). 1 LLC required a temporary suspension of Ibrutinib due to grade IV pancytopenia and edema. There was 1 CLL that developed a secondary lung neoplasm.
In conclusion, in 7 patients (17%) it was necessary to discontinue the drug (2 of them required a dose adjustment when restarting the drug) and in 5 patients (12%), Ibrutinib was permanently suspended.
8 patients died (all of them were older than 75 years and had comorbidities). 5 died due to adverse effects: 3 infectious complications (2 CLL and 1 MCL), 1 WM with grade IV hemorrhage, and 1 CLL due to secondary carcinoma.
Summary/Conclusion: In our experience, infectious complications were the most frequent and caused discontinuations and temporary suspensions of Ibrutinib in most cases. However, there was little impact of bleeding complications, hematological adverse effects and new cases of AF. Generally, Ibrutinib is a well-tolerated and effective drug.

PB1508 CD38 EXPRESSION AND CD19/CD5 CO-EXPRESSION IN CLL PATIENTS WITH DIFFERENT RESPONSES TO IMMUNOCHEMOTHERAPY

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Background: To date, great success has been achieved in the study of B-CLL oncogenetics, according to which the nature of the clinical course of the disease, the effectiveness of using various methods of therapy and predicting pathology is determined, in particular, by the features of pathogenesis, affecting certain structural components of the genome of malignant cells. Despite this, the principles of the genetic determination of B-CLL in the dynamics of the development of pathology are still largely unclear, which complicates the use of expression indicators of CD-marker molecules as diagnostic and prognostic criteria for the disease.
Aims: to monitor the expression of CD38 and the co-expression of CD19 and CD5 on lymphocytes of CLL patients with the determination of the relationship between their quantitative changes and the clinical course.
Methods: We included 11 CLL patients in the study. The median age was 57.3 years (range 44-68). The expression of CD38 markers and the co-expression of CD19 and CD5 were studied in peripheral blood before initiating therapy and during the treatment. None of the patients had a del17p13, del11q23, del13q14. Patients up to 65 years of age received FCR regimen, after 65 RB or ChlR regimes were administered. Antigen expression monitoring was carried out after the 2nd, 3th, 4th courses of therapy. Expression of CD38, co-expression of CD19/CD5 was determined by flow cytometry in the direct immunofluorescence test using monoclonal antibodies.
Results: It was noted that in 7 patients with a positive clinical and hematological effect after the second and subsequent courses of therapy, the expression of the CD38 antigen was either not observed or did not exceed 16%. Five of these patients received FCR regimen, two patients were administered RB. In 5 patients over 65 years of age and who did not receive the FCR regimen, pronounced tumor mass or hyperleukocytosis remained after the second and third courses of therapy. Three of them showed hyperexpression of CD38 + cells, amounting to (69.3 ± 7.1)%. As for the co-expression of CD19 and CD5, it did not differ in 7 patients who responded to therapy and in 5 refractory patients and was (79.5 ± 6.7)% and (80.6 ± 9.4)% after 2 courses, respectively. Similar results were observed in the dynamics of the study. Two patients, who received the RB regimen and were infected with COVID-19, unfortunately died from complications of this viral infection. They did not have any previous cardiovascular pathology or diabetes mellitus. Both patients had overexpression of the CD38 antigen, which was 69% and 74%. Perhaps, besides the negative effect of rituximab and bendamustine on the course of COVID-19, an additional negative role is played by overexpression of the CD38 molecule, which, being a marker of activation, also provides adhesion of lymphocytes to the vascular endothelium, enhances their adhesive-aggregation properties.
Summary/Conclusion: Overexpression of the CD 38 antigen is associated with resistance to immunochemotherapy, and also, possibly, has a negative effect on the course of COVID-19 in CLL patients, which requires further research. Coexpression of CD19/CD5 antigens in our study did not change in patients with different responses to immunochemotherapy.

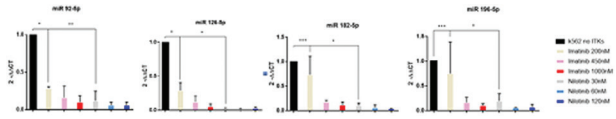
Chronic myeloid leukemia - Biology & Translational Research

PB1509 TYROSINE KINASE INHIBITORS DOWNREGULATE MIRNA EXPRESSION IN K562 CELL LINE

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Background:: Chronic myeloid leukemia is a clonal disease of the bone marrow characterized by a genetic marker: the t (9; 22) translocation. This genetic event produces an oncoprotein (BCR-ABL1) with constitutive tyrosine kinase activity which, through the phosphorylation of adapter proteins, leads to an increase in proliferation and decrease in apoptosis of hematopoietic precursors.
Although this genetic translocation was believed to be the only responsible for the pathology, nowadays, other additional molecular events are being investigated. Such events could be an alteration in the expression of microRNAs since t (9; 22) generates genomic instability and consequently additional genetic alterations to BCR-ABL1. It is well known that miRNAs are dysregulated in many types of cancer and they are being studied as potential biomarkers. Moreover, dysregulation in miRNAs expression could be independent from the activity of the BCR-ABL1.
Aims: To evaluate the dependence of miRNAs expression from BCR-ABL1 activity in vitro
Methods: mirVana miRNA Isolation Kit (Ambion®) was used for RNA extraction from K562 CML cell line which was previously incubated with either imatinib 1000nM, 450nM and 200nM or nilotinib 120nM, 60nM and 30nM according to calculated IC50 using MTT assay. To confirm inhibition of the BCR-ABL1 pathway a western blot for phospho-CRKL was performed. For qPCR a protocol that is designed to specifically amplify and quantify miRNAs using stem-loop primers was used. The following miRNAs were evaluated: hsa-miR-196a-5p, hsa-miR-92b-3p, hsa-miR-126-5p, hsa-miR-125a-5p, hsa-miR-2355-5p, hsa-miR-10a-5p, hsa-miR-132-3p, hsa-let-7a-5p and hsa-miR-182-5p. This panel was based on previous experiments from our group which assessed miRNAs expression in CML patients (leukemic stem cells vs hematopoietic stem cells) by next generation sequencing. Statistical analysis was done with GraphPad v6.0. T-Student test was used to calculate statistical significance between samples.
Results: Imatinib at a concentration of 200nM did not inhibit p-CRKL by western blot. The expression of all miRNAs aforementioned but for miR2355 was downregulated after incubation for 48hs with both TKIs. This effect was more powerful with nilotinib than imatinib. When incubated with imatinib hsa-miR-126-5p, hsa-miR-182-5p hsa-miR-92b-5p and hsa-miR-196a-5p showed a dose dependent inhibition (Figure 1).
*p< 0,01 ** p< 0,05 ***p> 0,05



Summary/Conclusion: In K562 cell line, a down regulation of miRNA expression was observed when exposed to both drugs, with a dose-dependent effect confirmed for some miRNAs incubated with imatinib. More studies should be done to evaluate if this effect is also observed in vivo. Eventually, miRNAs could be used as a biomarker of response to TKIs in CML patients.
The fact that imatinib 200nM did not inhibited BCR-ABL1 but miR92 and miR 126 where still dowregulated could be explained by off target effect of TKIs.

PB1510 PATTERN OF MINIMAL RESIDUAL DISEASE IN TUNISIAN CHRONIC MYELOID LEUKEMIA PATIENTS

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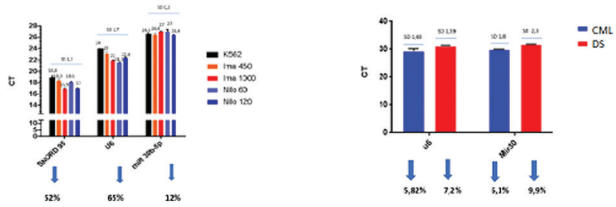
Background: The efficacy of Tyrosine Kinase inhibitors (TKI) treatment can be accurately evaluated by a molecular monitoring based on the quantification of *BCR-ABL1*.
Aims: This study was carried out to assess the minimal residual disease in Tunisian patients with chronic myeloid leukemia (CML) treated with TKI therapy in routine clinical practice in Tunisia to identify potentially eligible for treatment discontinuation, based on a molecular response (MR) on the international scale (IS).
Methods: A five-year retrospective study was carried out in the Hospital University of Sfax, south of Tunisia including all CML patients in the chronic phase at diagnosis, treated with TKI for a minimum duration of 6 months. Quantitative assessment of the BCR-ABL transcript was performed using the Cepheid Xpert BCR-ABL ultra assay. Molecular response and outcome were evaluated; according to the European Leukemia Net guidelines.
Results: A total of 162 CML patients were carried out. The median age was 50 years, the sex ratio M/F was 1.62. The rate of cumulative EMR; MMR and DMR was 80.8%; 73.8% and 55.9% respectively. According to the ELN criteria, 141 CML patients were evaluable. Optimal, sub-optimal response, and failure were noted in 81 (57.4%), 33(23.4%) and 27(19.1%) patients, respectively. Overall survival (OS) and progression-free survival (PFS) was 96.3% and 85%. Risk factors for event (death/progression) were lack of EMR, MMR and DMR (P<0.05). Among 149 patients with sustained DMR; 14 (8.6%) CML patients have discontinued TKI therapy.
Summary/Conclusion: Despite the limit of our study (duration and size), the available real-life molecular responses with TKI therapy should be considered to identify potentially CML patients eligible for discontinuation of TKI therapy.

PB1511 MI-30-B AS A HOUSEKEEPING GENE POR MIRNA QPCR QUANTIFICATION IN CHRONIC MYELOID LEUKEMIA

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Background: Quantitative polymerase chain reaction (qPCR) is a rapid and sensitive approach to identify miRNA expression. However, because of the shorter PCR products, very few reference genes have been identified for the quantitative analysis of miRNA. Different internal reference genes are needed to normalize the expression of miRNAs and mRNA genes respectively. Therefore, it is particularly important to select the suitable common reference genes for normalization of qPCR of miRNA. In CML there is not a standard control gene, both U6 and SNORD95 have been evaluated with discordant results. So, its mandatory to evaluate another housekeeping gene to use in these pathology.
Aims: To evaluate Mir-30-b as housekeeping gene in miRNA qPCR in CML cell line and patient´s samples
Methods: mirVana miRNA Isolation Kit (Ambion®) was used for RNA extraction from peripheral blood mononuclear cells (PBMCs) from 5 patients at diagnosis and 4 healthy donors' samples (DS) and K562 CML cell line previously incubated with either imatinib 1000nM and 450nM or nilotinib 120nM or 60nM according to calculated IC50 using MTT assay. For qPCR a protocol that is designed to specifically amplify and quantify miRNAs using stem-loop primers was used. SNORD95, U6 and Mir-30-b were compared.
Results: in human samples U6 and miR30-b had acceptable values to be used as control gene: standard derivation (SD) was 1,38 and 1,48 for U6 and 1,8 and 2,3 for mIR-30 in CML samples and DS respectively; while coefficient of variation (CV) was 5,8% for U6 and 6,1% for Mir-30 CML samples and 7,2% and 9,9% for DS respectively. Two-way anova comparison between CML and DS was not statistically significant neither was it comparing each ARN group individually. (p> 0,05)
In K562 cell line SD was 1,2 for SNORD95; 1,7 for U6; and 0,2 for Mir-30. CV was 52% for SNORD 95, 65% for U6, and 12% for mir-30. Tukey's multiple comparisons test of each group of RNA with different treatment showed statistical significance difference (p<0,001)



Summary/Conclusion: In conclusion, miR-30 is a suitable control gene when evaluating miRNAs expresión in K562 cell line and for human samples. To confirm this findings, a bigger cohort should be evaluated. U6 was a good control gene in human samples but not in CML cell line.

PB1512 STUDY OF TELOMERE LENGTH IN PATIENTS WITH CHRONIC MYELOLEUKOSIS

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Background: The emergence of inhibitors of atypical tyrosine kinase changed the prognosis of the course of the disease in patients with CML. This type of therapy is comparable to allogeneic hematopoietic stem cell transplantation in terms of efficiency, and radically surpasses it in terms of safety. The success of imatinib therapy may be partly due to the increase in average telomere length. Recent studies have shown a permanent decrease in telomere length in CML patients in sustained complete cytogenetic remission, virtually regardless of what therapy was used to induce remission. This finding may indicate a pre-existing shortage of telomere length in CML patients (and a potential predisposition to CML) prior to the development of BCR / ABL positive hematopoiesis.
Aims: to reseche the dependence of the length telomeric fragments of chromosome on the presence of chronic myeloid leukemia in the person.
Methods: We have studied of the length telomeric fragments of chromosome in a group of 27 patients with chronic myeloid leukemia. The group was consisted of 15 women (55.6%), average age 53.93 years and 12 men (44.4%), average age 50.54 years. The group of women was more homogeneous: 5 patients achieved a major molecular response (MMR), 3 - only a cytogenetic response (CR), MMR have not obtained, and 4 patients were newly diagnosed in the chronic phase of the disease. In the group of men, MMR was achieved in 1 patient, only CR - in 2, chronic phase, no CR was obtained in 3, primary patients in the chronic phase - 3 and progressive phase of the disease, terminal stage (blast crisis) - in 3 patients. The study of telomere length have stadied out on DNA material isolated from blood cells using quantitative PCR (qPCR) in real time based on the method of R.T. Cawthon et al. (2002) with modifications.
Results: The average level of blood telomere length (TL) was 1.185 ± 1.037 (min. 0.188 / max. 5.681, median 0.960) in the group of CML patients, and 1.388 ± 0.417 (min. 0.440 / max. 2.780, median 1.340) in the group of subjects without hemoblastosis., that is, the length of blood telomeres was shorter in patients with CML. According to the one-sample Kolmogorov-Smirnov test, the distribution did not correspond to the normal one; therefore, nonparametric tests were used for comparison. We have compared telomere lengths separately in the groups of women and men with CML and men and women from the comparison group. The length of leukocyte telomeres was significantly less in the group of women with CML, compared to the control (p <0.001; asymptotic significance (2-sided) in the Mann-Whitney test). There were no significant differences in men. In women with CML, TL 0.984 ± 0.552 (median 0.917), in the control group TL 1.442 ± 0.426) (median 1.376). In men with CML TL was 1.419 ± 1.405 (median 1.047), in the control group TL 1.317 ± 0.397 (median 1.287). The presence of an aggressive clone of lecosis cells in men with progressive stages of CML can explain the absence of significant differences and even the excess of TL (1.419 ± 1.405) compared with the control group (1.317 ± 0.397). At the same time, the median TL in men with CML is less than in the control group (1.047 and 1.287, respectively).
Summary/Conclusion: Investigation of telomere length is an important diagnostic technique in determining the predisposition to the development of CML and determining the prognosis of the deasese

Chronic myeloid leukemia – Clinical

PB1513 PULMONARY HYPERTENSION IN NEWLY DIAGNOSED AND TYROSINE KINASE INHIBITOR-TREATED PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Background: Dasatinib, a tyrosine kinase inhibitor (TKI), is known to induce pulmonary hypertension (PH) in patients with chronic myelogenous leukemia (CML). Although PH is usually reversed on discontinuation of dasatinib, this is based mainly on case reports and small case series. It remains unclear whether other TKIs, such as imatinib or nilotinib, are also linked to PH. In addition, there have been few reports on PH in newly diagnosed CML patients.
Aims: In this study, we analyzed the prevalence of PH and its clinical implications in both newly diagnosed and TKI-treated CML patients.
Methods: The medical records of newly diagnosed CML patients who underwent transthoracic echocardiographic examination (TTE) at diagnosis, and of TKI-treated patients who underwent TTE at least once during treatment at Chungnam National University Hospital from January 2003 to June 2020, were analyzed retrospectively. The TTE results were reviewed by two cardiologists and a diagnosis of PH was made when the PH probability was "high" according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.
Results: Of 189 CML patients diagnosed and/or treated during the study period, 57 (30.2%) and 112 (59.3%) underwent TTE at the time of CML diagnosis and during TKI treatment, respectively, and were therefore enrolled in the study. The majority of patients underwent TTE more recently; 40 (70.2%) of the 57 newly diagnosed patients and 92 (82.1%) of the 112 TKI-treated patients underwent TTE between January 2017 and June 2020, respectively. The majority of patients underwent TTE to screen for PH; only 7 (12.3%) of the 57 newly diagnosed patients and 11 (9.8%) of the 112 TKI-treated patients underwent TTE due to cardiopulmonary symptoms. Among the 57 newly diagnosed patients, 4 (7.0%) had PH. PH resolved in three (75.0%) of those four patients after TKI treatment (imatinib in two patients and nilotinib in one patient). PH continued for 8 years in a male patient (aged 61 years at CML diagnosis) despite changes in the TKI (from imatinib to nilotinib, and then to dasatinib); he had no specific PH-related symptoms. In TKI-treated patients, the median TKI treatment time was 40.4 months (range: 0.1–167.2 months). PH was found in 12 (10.7%) of the 112 TKI-treated patients, most frequently in the dasatinib-treated patients [i.e., in 3 (7.5%) of 40 in the imatinib-treated group, 1 (3.1%) of 32 in the nilotinib-treated group, and 8 (21.6%) of 37 in the dasatinib-treated group]. In multivariate logistic regression analyses, age > 60 years (OR, 12.3; 95% CI, 1.1–142.1, p = 0.044), dasatinib treatment (OR, 8.2; 95% CI, 1.3–50.6, p = 0.026), and positive cardiopulmonary symptoms/signs at the time of undergoing TTE (OR, 36.1; 95% CI, 5.3–247.3, p = 0.001) were statistically significant risk factors for developing PH. PH resolved in five (62.5%) of the eight dasatinib-treated patients after discontinuation of the agent. However, PH persisted in three patients, i.e., in one since CML diagnosis and in two despite discontinuing dasatinib; one of those patients had exertional dyspnea. All three imatinib-treated patients recovered from PH: one after the TKI was changed and two despite continuing imatinib. One nilotinib-treated patient also recovered from PH after the TKI was changed.
Summary/Conclusion: PH is common in CML patients treated with dasatinib; however, it is also observed in patients treated with imatinib or nilotinib, and even in newly diagnosed patients. Careful screening for PH both at the time of diagnosis and during any TKI treatment is warranted in patients with CML.

PB1514 KARYOTYPING CML PATIENTS IN TANZANIA USING DRY SPOT CARDS: A FEASIBLE AND NECESSARY DIAGNOSTIC PERFORMANCE FOR BETTER TREATMENT OUTCOME

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Background: CML is the result of the chromosome translocation t(9;22), which leads to the fusion gene between ABL1 proto-oncogen and BCR gene [1]. The resulting product is an active tyrosine kinase leading to uncontrolled proliferation of different cell lineages and eventually to leukaemia.The crude annual incidence of CML in Europe ranges between 0.7–1.0/100,000 with a median age at diagnosis of 57-60 years [2]. WHO suggests no association with race or ethnicity [3]. Due to lack of reliable data for Low-and-middle-income countries (LMIC), numbers remain an estimation, but taking existing data for extrapolation, the global annual incidence would be above 100,000 [3]. Few studies on treatment outcome in LMIC suggest a lower response rate to TKI [4,5], despite following international treatment guidelines. Assessment of additional chromosomal aberrations (ACA) is no criterion according to the ELN staging recommendation, but one criterion for accelerated phase in the WHO recommendations. However, it is not routinely assessed in LMIC due to unavailability of karyotyping diagnostics, challenges in timely transportation of samples and costs.
Aims: To assess the possibility of obtaining high quality results in karyotyping of CML patients by using dry spot cards for sample collection and storage in a resource poor setting.
Methods: 9 peripheral blood samples of newly diagnosed CML patients have been collected and stored between 1 and 5 months before analysed by array-CGH (aCGH). Storage and transportation of the samples were performed on dry spot cards. ELN and WHO criteria for CML phases were applied to all patients. aCGH analyses were carried out for all cases (4x180K microarray slides, Agilent Technologies, Santa Clara, CA). Images were analyzed using the DEVA Software v1.2.1 (Roche Nimblegen) and Nexus Copy Number 6.1 (Biodiscovery, Inc., El Segundo, CA). ACA were evaluated in each sample using BioDiscovery's Fast Adaptive States Segmentation Technique (FASST2) algorithm. Targeted NGS sequencing was performed with the TruSeq DNA library Prep (Illumina, San Diego, USA) followed by a hybridization capture workflow (IDT, Coralville, USA) for enrichment of a myeloid 34 gene panel including a CNV spike-in panel.
Results: 8 patients were in CP, 1 in AP (ELN criteria) and all 9 patients in AP (WHO criteria). All specimen for karyotyping were evaluable and 7/9 showed ACA, mainly small deletions which are cytogenetically cryptic and thus only detectable using aCGH. 2 cases showed larger chromosomal aberrations, one patient showed a trisomy 8, while another one showed a deletion 7q and gain of 8q, resulting for both in an unfavourable prognosis. Interestingly, no gene mutation was identified within the 34 analysed genes. The NGS CNV panel confirmed all larger chromosomal changes.
Summary/Conclusion: Applying ELN criteria for CML phases without karyotyping might lead to underdosing and eventually treatment failure. Our small cohort shows that 7 out of 8 patients diagnosed in CML-CP by ELN criteria, have ACA and need higher dosages of Imatinib or 2nd line TKI (CML-AP by WHO criteria). The results provide a likely explanation for the general poorer outcome of standard dose treatment in LMIC. Using dry spot cards for storage and transportation of blood samples is a simple to apply technique for clinicians and delivers DNA for standard molecular genetic diagnostics like information about chromosomal copy number changes as well as mutation analyses. These information allow further risk stratification of these patients. This approach can overcome current challenges of sample shipment and storage in LMIC.

PB1515 E13A2, E14A2 TRANSCRIPTS: DO THEY HAVE A DIFFERENT IMPACT ON OUTCOME IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA?

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Background: Most patients with Chronic Myeloid Leukemia (CML) express the *BCR-ABL* fusion gene that generates a 210 kDa/p210 tyrosine kinase protein that promotes leukemic metamorphosis. P210 is encoded by both transcripts that are created when the breakpoint in the *BCR* gene occurs in a region called M-bcr, leading to the formation of the transcripts e13a2/ "b2a2" and e14a2/ "b3a2". The difference of both e13a2 and e14a2 transcripts is the absence and presence of exon 14 of the *BCR* gene respectively. The different effect of e13a2 and

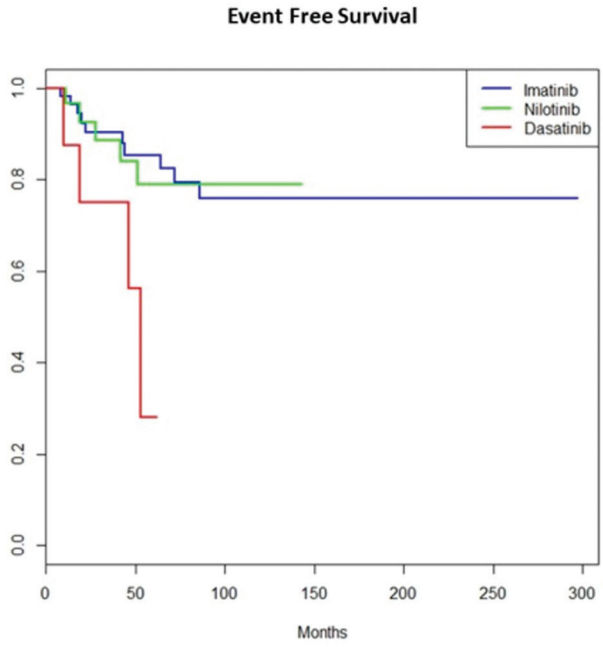
e14a2 transcripts on leukemic phenotype and disease outcome has been debated for many years.
Aims: The purpose of this retrospective study is to investigate the impact of different transcripts on the achievement of EMR, MMR and MR4.0 in patients who received Tyrosine Kinase Inhibitor (TKI) as first line treatment from 2005 to 2020 in Greece.
Methods: This study involved 261 patients with chronic phase CML treated with TKI and assessed for response to treatment according to ELN guidelines. Transcript type was identified by RT-PCR at diagnosis. RT-qPCR standardized by the EAC (Europe Against Cancer) protocol was assessed to determine *BCR-ABL* levels using *ABL* as the reference gene. All results are expressed according to International scale / IS.
Results: 168 patients with *BCR-ABL* known transcripts, either e13a2 or e14a2, were included in the analyses. Sixty-four (38.1%) carried the transcript e13a2, while 12 expressed also e1a2 transcript. A hundred and four patients (61.9%) carried e14a2 transcript, only two (1.2%) co-expressed e13a2, while 23 (22.1%) expressed also e1a2 transcript. Hematological parameters were comparable between patients with different transcripts. Regarding the achievement of EMR there are no data for 14 out of 64 (21.8%) and 22 out of 104 (24.15%) patients with e13a2 and e14a2 transcripts respectively. Out of the 50 with e13a2, 23 (46%) did not achieve EMR compared to 21 out of 82 (25.61%) of patients with e14a2 transcript. Data at the timepoint of MMR and MR4 achievement are available for 141 and 148 out of 168 patients respectively. Six out of 48 (12.5%) patients with e13a2 and 4 out of 93 (4.3%) patients with e14a2, and also 15 out of 52 (28.8%) with e13a2 and 13 out of 96 (13.5%) with e14a2 did not achieve MMR (p=0.0895) and MR4.0 (p=0.0288) respectively. Patients with e13a2 and e14a2 achieved MMR at an average time of 782.35 days (median 469) and 1021.9 days (median 275), respectively. MR4.0 was achieved in 1535.8 days on average (median 882.5) and 1505.63 days (median 609) for e13a2 and e14a2 respectively.
Summary/Conclusion: Our data suggest that a larger percentage of patients with e14a2 transcript achieve EMR compared to patients with e13a2 (74.4% *vs* 54%). More patients with e14a2 transcripts (95.7% *vs* 87.5%) achieve MMR in shorter time than patients with e13a2. Failure to achieve MR4.0 was observed in patients with e13a2 more commonly versus those with e14a2 transcript. The transcript could serve as a prognostic indicator and/or as a treatment selection criterion. At present the bibliographic data are contradictory and need further study. We plan to study their importance in a larger number of patients in combination with other features of the disease and the selected TKI.

PB1516 CHRONIC MYELOID LEUKEMIA – THE CHALLENGE OF FRONTLINE TKI SELECTION 20 YEARS AFTER IMATINIB

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Background: The introduction of Imatinib in the treatment of Chronic Myeloid Leukemia (CML) changed radically the outcome of patients, transforming a fatal disease to a disease compatible with normal lifespan. Currently, 4 tyrosine kinase inhibitors (TKIs) have been approved for the treatment of newly diagnosed CML patients in chronic phase (CP). Treatment goal is the deepest molecular response. However, the optimal time for this achievement that results in the best long-term outcome and the best chance for treatment free remission remains under discussion. Patients that do not achieve early molecular response (EMR) define a group with unfavorable prognosis. The optimal choice of TKI in terms of both effectiveness and safety remains a challenge.
Aims: In this retrospective real-world study, our goal is to investigate the role of EMR in the long-term outcome in regard to the TKI that was administered as first line treatment.
Methods: 261 patients with CML-CP that were diagnosed between 2005-2020 were included. Patients were treated with either 1st or 2nd generation TKI according to treating physician's choice and availability at the time of diagnosis. Regular evaluation of molecular response with RQ-PCR was done according to ELN guidelines. EMR (≤10% IS at 3 months) and the cumulative incidence (CI) of achievement of MMR and MR4.0 in regard to selected TKI were estimated. Event free survival (EFS) was defined as the time from treatment onset to death, disease progression, treatment failure or treatment change.
Results: Data for EMR were available for 148 patients and were included in the analysis. First line TKI was imatinib (IM) in 94, nilotinib (NIL) in 44 and dasatinib (DAS) in 10 cases. Prior to completion of three consecutive months of treatment 6 patients changed TKI due to intolerance/toxicities (IM, n=4 due to pyrexia, myalgias, edema, toxic epidermal necrolysis – NIL, n=1 due to heart failure – DAS, n=1 due to pulmonary hypertension). EMR was evaluated to the remaining 142 patients. Overall, EMR achieved 76.6%, 80.9% and 100% of patients on IM, NIL and DAS respectively (p=NS). Of 113 patients that achieved EMR 107 were on the same TKI 12 months after diagnosis. All TKI changes prior to 12 months were made due to grade ≥3 toxicities (IM, n=5 due to rash, edema, myalgias and NIL, n=1 due to gout and rash). At this timepoint, the CI of MMR was 67.7%, 70.6% and 90% for IM, NIL and DAS, respectively (p=0.06). On the same TKI remained at least for 18 consecutive months 103 patients. Three patients were switched due to toxicities (rash on IM, myocardial infarction on NIL, pleural effusion on DAS) and one patient due to not optimal treatment response on NIL according to ELN2020 (*BCR/ABL* 0.52% IS). The CI of MR4.0 at this timepoint was 45.4%, 50.9% and 73.3% on IM, NIL and DAS, respectively (p=0.16). After a median follow-up of 70.6 months the median has not been reached. At 60 months the EFS was 85.3%, 78.9% and 28.1% for IM, NIL and DAS, respectively (p=0.02). Of note, 69.9% of patients in our initial cohort achieved EMR and remained on treatment with IM for ≥18 months.



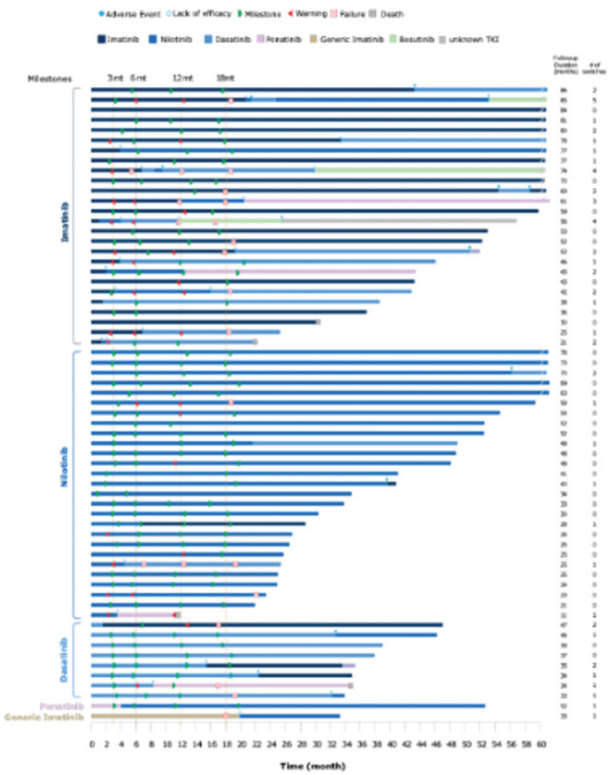
Summary/Conclusion: Long-term EFS depends on both the effectiveness and the safety profile of the TKI. In terms of effectiveness, EMR can provide guidance at an early timepoint. Although more potent TKIs are available, IM still appears to be satisfactory as frontline treatment choice taking into consideration the long term safety profile.

PB1517 A MULTICENTER REAL-WORD EVIDENCE STUDY IN THE SWISS TREATMENT LANDSCAPE OF CHRONIC MYELOID LEUKEMIA

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Background: The availability of real-world data of patients with chronic myeloid leukemia (CML) collected outside the context of clinical trials is limited.
Aims: To describe the use and choice of tyrosine kinase inhibitors (TKIs), the achievement of response per European LeukemiaNet (ELN) criteria as well as adherence to ELN recommendations in this unselected patient population in Switzerland.
Methods: This non-interventional, multicenter, retrospective chart review analyzed data from patients with newly diagnosed CML treated at six Swiss hospitals. Written informed consent was obtained from all individual participants before data collection. Included patients had received front-line TKI and were solely treated with TKIs between 2010–2015, with a minimum follow-up of 18 months. Treatment efficacy was evaluated according to ELN 2013 milestone achievements at predefined time points (3, 6, 12 and 18 months, last follow-up).
Results: Data from 63 patients treated with TKIs were collected (first-line imatinib [n = 27], nilotinib [n = 27], dasatinib [n = 8], or ponatinib [n = 1]); 56% of patients were men, and the median age at diagnosis was 55 years. A high frequency of TKI therapy switches (49 times) and treatment changes (dose adjustment, dose interruption or re-initiation; 165 times) due to intolerance or insufficient response were recorded. First-line treatment with nilotinib or dasatinib compared with imatinib consistently resulted in a higher proportion of patients achieving an ELN-defined optimal response at every timepoint, irrespective of subsequent TKI therapy. A major molecular response (BCR-ABL^{IS} ≤ 0.1%) was not reached at last visit for 18% of patients irrespective of TKI and for 24% of patients treated with imatinib as first-line therapy. A higher percentage of patients in the nilotinib and dasatinib groups versus the imatinib group reached a deep molecular response (BCR-ABL1^{IS} ≤ 0.01%) at 12 months (32% and 25%, respectively, vs. 23%) and 18 months (42% and 38%, respectively, vs 27%). Patients who received nilotinib or dasatinib as front-line TKI switched therapies less frequently compared with patients treated with first-line imatinib, irrespective of subsequent TKI therapy.



Summary/Conclusion: This study confirms that in a real-world patient population ELN guidelines are generally implemented in Switzerland. While TKI use involves all approved inhibitors, with a large proportion of patients achieving ELN milestones, an unexpectedly high number of TKI therapy switches suggests a clear difference in TKI use between registration trials and clinical practice.

PB1518 IMPACT OF LOW-DOSES TKIS IN THE RESPONSE OF CHRONIC PHASE CML PATIENTS: A 20-YEAR RETROSPECTIVE ANALYSIS.

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Background: Long-term survival in chronic myeloid leukemia (CML) has been achieved with the advent of the BCR-ABL tyrosine kinase inhibitors (TKIs), which represent the standard treatment of this disease nowadays. However, almost 20 % of LMC patients present TKIs intolerance, and finding the right dose while maintaining an optimal response, without therapy-related adverse events, is challenging.
Aims: The aim of our study was to retrospectively analyze the impact of low dose TKIs on the deep molecular response (MR) in the group of patients who required a dose reduction due to adverse effects or in order to prevent long-term toxicities, in comparison with those who maintained standard dose.
Methods: We analyzed 82 patients diagnosed with chronic phase of CML from January 2000 to December 2020, who started treatment with TKIs.
Results: Among the population of study, 47 (58,02%) were male and 35 (42,6%) female, with a median age of 50 years (range 13-87ys), at the moment of diagnosis.
Standard dose of Imatinib (400mg/day) was the first line TKI in 63 (76,8%) patients, Nilotinib (600mg/day) in 4 (4,87%) and Dasatinib (100mg/day) in 3 (3.65%). We had 5 patients with Imatinib (800/day), 1 with Bosutinib (500mg/day) and 1 with Bosutinib (400/day), all included in a clinical trial. Low-dose TKIs was started in 6 patients due to age (median age of 78.3, range 50-87); and comorbidities. 4 patients (4,94%) took Imatinib 300mg/day and 2 (2,47%), Imatinib 200mg/day. The main comorbidities for low initial dose were ischemic heart disease, atrial fibrillation, renal failure and vasculopathy. We lost follow up of 4 patients, finally analyzing the response to treatment only in 72 patients, standard dose versus patients who required adjustment the following years.
During this period, 33 (40,2%) patients, with a median age of 66.44 years, required TKIs dose reduction: 17 (51.6%) due to toxicity, and 16 of them (48.4%) in order to prevent long term toxicities once they achieved a MR ≥ 4.
Although 41 patients (50%) presented toxicities, only 17 required dose adjustment. We found mild-to-moderate events: diarrhea in 5 patients, arthromyalgia in 4, hematological toxicity in 3, cutaneous in 5, mainly skin rash, acute pulmonary edema in 1 patient and edema in another one. Ten patients from the initial population required to change first-line TKI treatment due to toxicities: 8 patients received a different TKI as a second-line treatment, whereas 2 of them changed to cytoreductive therapy.
In **table 1**, we describe the proportion of patients who lost response (MR<4): 21.21% in the group of low dose and 20.51% in the group of standard dose. When comparing TKIs dose reduction group with the group which maintained standard dose, we found no statistically differences in terms of loss of response (MR<4), using the Fisher's exact test (p 0.94).

	No. patients (N= 72)	Maintenance of response (MR≥4)	Loss of response (MR<4)	p value*
TKI standard doses	39	31 (79,49%)	8 (20,51%)	0.94
TKI dose reduction	33	26 (78,79%)	7 (21,21%)	

Table 1. Loss of response as an outcome among patients with maintenance of standard doses of TKI versus reduced dose. ***p value for Pearson's chi squared test***

Summary/Conclusion: Even if only 33 patients required a dose reduction, 26 (78.79%) maintained the depth of the molecular response (MR≥4). We can conclude that, if required, due to adverse events or in order to reduce long-term toxicities, the reduction of TKI has a clear clinical benefit and an impact on life quality, without the lost of a deep molecular response.

PB1520 RETROSPECTIVE REAL-WORLD COMPARISON OF CLINICAL AND ECONOMIC BURDEN BETWEEN FIRST-GENERATION AND SECOND-GENERATION TYROSINE KINASE INHIBITORS (TKIS) IN CHRONIC MYELOID LEUKEMIA (CML)

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Background: TKIs are the standard of care for the treatment of chronic phase CML under National Comprehensive Cancer Network (NCCN) guidelines. Imatinib is recommended as a first-generation TKI (1GTKI), and bosutinib, dasatinib, nilotinib, and ponatinib are recommended as second-generation TKIs (2GTKIs). TKIs are associated with high healthcare resource utilization (HRU) and costs, although literature is limited comparing 1GTKI and 2GTKIs in a U.S. population.
Aims: To assess clinical and economic burden of first-generation and second-generation TKIs in CML patients
Methods: Using the Veteran's Health Administration (VHA) database between April 1, 2013 and March 31, 2018, the study included patients aged ≥18 years with ≥1 medical claim for CML and ≥1 prescription claim for a TKI on or after the initial CML diagnosis date during the identification period (October 1, 2014 to September 30, 2017); the first TKI prescription claim was defined as the index date. Inverse probability of treatment weighting (IPTW) minimized potential confounding; included variables were age, race, Quan-Charlson Comorbidity Index (CCI) score, and CHA2DS2-VASc Score. Medication possession ratio (MPR) assessed adherence to index TKI; optimal adherence was defined as MPR ≥80%.
Results: 944 patients were included: 78.9% on 1GTKI and 21.1% on 2GTKI. Mean age was 62.21 years (SD:18.8); 77.2% were white. At baseline, patients on 1GTKI had a higher comorbidity burden than 2GTKIs: COPD (19.7% vs. 8%; p<0.01), anemia (17.7% vs. 11.1%; p=0.02), GI symptoms (28.5% vs. 18.6%; p<0.01), cardiac dysrhythmias (15.6% vs. 7.5%; p<0.01), coronary artery disease (26.3% vs. 13.6%; p<0.01), hypertension (55.7% vs. 43.2%; p<0.01) and CHA2DS2-VASc Score (2.2 vs 1.6; p<0.01). Optimal adherence was higher with 1GTKI (69.6% vs. 62.2%; p=0.04), although this was not statistically significant when mean MPR was compared. During follow-up, no difference between 1GTKI and 2GTKIs patients occurred with cardiac-related risk factors or CHA2DS2-VASc Score. Compared to 1GTKI, 2GTKIs had lower medical (inpatient and outpatient) costs ($3,162 vs. $3,906; p=0.04) but higher all-cause pharmacy cost ($7,214 vs. $3,895; p<0.01) due to imatinib becoming a generic drug during the study period. CML-related ($2,260 vs. $1,640, p<0.01) and cardiac-related medical costs ($1,365 vs. $665, p<0.01) were significantly higher in 1GTKI vs. 2GTKIs patients.
Summary/Conclusion: Adherence to TKI therapy was suboptimal for both 1GTKI and 2GTKIs. 2GTKIs incurred lower medical cost in comparison to 1GTKI. Differences in total all-cause cost was primarily driven by pharmacy cost of TKIs. These results show that, beyond the cost of the TKI, using a 2GTKIs in the first-line can lead to cost offsets when compared to imatinib.

PB1521 TREATMENT SELECTION IN CML: EFFECT OF ONLINE EDUCATION ON CLINICIAN KNOWLEDGE AND CONFIDENCE

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Background: Despite the improvement in patient outcomes with the implementation of TKIs, patients still relapse on or are intolerant of initial treatment and an associated impact on quality of life. Physician choice of 2nd and 3rd line treatment is currently essentially limited to the same TKIs as are available for front-line treatment, with the exception of ponatinib. Thus physician's choice of 2nd or 3rd line therapy is not only predicated on patient disease, social and clinical characteristics, but also by which TKI the patient received previously, challenging them to make choices from a decreasing pool of options.
Aims: This study determined whether online continuing medical education could improve the knowledge and confidence of clinicians in best-practice sequencing strategies for patients with CML after front line therapy with a tyrosine kinase inhibitor (TKI), using a case-based approach.
Methods: A 30-minute online video panel discussion was launched for countries outside the USA in June 2020. Data were collected to September 2020. Educational effect assessed with repeated-pairs pre-/post-activity, where individual participants served as their own control. 3 multiple-choice, knowledge questions and 1 self-efficacy, 5-point Likert scale confidence question were analyzed. Chi-squared test assessed pre- to post-activity change (5% significance level, P <.05). Magnitude of change in total number of correct responses overall, and for each question, were determined with Cramer's V (<.06=Modest, 0.06- 0.15=Noticeable, .16-.26=Considerable, >.26=Extensive).
Results: 52 hematologist/oncologists completed pre- and post-activity questions. A considerable educational effect was observed (V=.181, P<.0001) with average % of correct responses increasing from 34 to 52%. Clinicians with 3/3 answers correct increased post-activity (4 to 12%) and for 2/3 answers correct post-activity (29-46%). Improvements in % of correct responses post-activity were seen for questions on: the patient population with the best outcomes related to clinical trials data, the application of the ELN guideline recommendations for defining response to TKI treatment, and the selection of an appropriate alternative TKI for a patient case (relative improvements, 25%, 56%, and 85%). 52% of haematologist/oncologist responses were improved or reinforced post-activity. 48% of all participants stated they would modify treatment plans. 31% had a measurable increase in confidence in selecting an appropriate BCR-ABL TKI for individual patients with CML who have failed prior lines of therapy with a total average confidence shift of 9.6%.
Summary/Conclusion: This on-demand, online video panel discussion resulted in a considerable educational impact. Online medical education is valuable in improving knowledge and confidence, as well as identifying areas of continued educational need and potentially improving patient outcomes, of particular importance during the COVID-19 pandemic where in-person conference learning is inaccessible.

PB1522 CLINICAL CHARACTERISTICS, DISEASE EVOLUTION AND SURVIVAL IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA, BCR-ABL-1+ AND MUTATION T315I

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Background: Targeted inhibition of the mutant tyrosine kinase BCR-ABL-1 (Philadelphia chromosome fusion protein) is one of the brightest advances in medical science. Thanks to this fundamental discovery, patients with chronic myeloid leukemia (CML) today have a life expectancy comparable to that of people without CML. However, additional mutations in the kinase domain of the BCR-ABL-1 gene result in resistance to the effect of tyrosine kinase inhibitors (TKIs). Different TKIs cover a different spectrum of mutations, and T315I is one of the most difficult to manage.
Aims: To study the frequency of T315I mutation in patients with CML, BCR-ABL +; to analyze their clinical characteristics, disease evolution and median survival, and to compare with those of CML patients without established T315I mutation.
Methods: We studied 75 patients with CML, BCR-ABL1 + with suboptimal therapeutic response or loss of therapeutic respones. The detection and quantification of the T315I mutation was performed by digital droplet PCR (dd PCR). Molecular studies for detection and quantification of BCR - ABL 1 fusion transcripts were performed by RT-PCR and presented on the international scale, according to ELN criteria. In patients with established T315I mutation (CML, T315I +) a comparative analysis was performed by sex and age, disease phase, risk group, treatment, type and duration of molecular response and median survival compared to patients with CML without T315i mutation (CML T315i-). Statistical data were processed with descriptive analysis, correlation analysis and Independent Sample T-test for comparison of mean values, at a level of significance p <0.05. Survival analysis was performed by the Kaplan-Meier method with a log-rank test.
Results: The T315I mutation was detected in 11 (14.7%) of CML patients. The m / f ratio in the T315I (+) group was 2/3, mean age 49.27 +/- 13.5 years, with no statistical difference from the whole cohort and patients without the T315I mutation. No statistically significant difference was found in the baseline characteristics of the disease between the two groups - phase, risk group (according to Sokal and Hasford) and choice of first-line therapy. A significantly higher proportion of CML T315I + patients did not achieve a molecular response >3.5 log throughout the follow-up period, compared to patients with CML T315I-: 8 (72.7%) vs 22(34.4%), p = 0.023. The lowest mean BCR-ABL -1 expression levels reached were significantly higher in the CML T315I + group compared to the CML T315I - group: 12.1 +/- 6.0 versus 3.77 + / 1.28 (p = 0.009). In patients with CML T315I +, the mean number of treatment lines was 3.2 compared to 1.1 in the CML T315I- group. The median survival (MS) of CML T315I + patients was significantly shorter than

the MS of patients without the T315I- mutation: 73 months vs 175 months (p <0.0001).
Summary/Conclusion: Our data confirm the data from the accumulated world experience on the frequency of T315I mutation, as well as the unfavorable evolution, resistance to TKI treatment and short survival in patients with CML, T315I +. ddPCR is a highly sensitive and informative method for early detection of genetic mutations, even at low levels of expression. Timely detection of the T315I mutation, immediately after failure of first-line TKI therapy in patients with CML, gives the chance to choose effective treatment, improve their prognosis and long-term survival

PB1523 TREATMENT OF CHRONIC MYELOID LEUKEMIA IN CHILDREN WITH TYROSIN KINASE INHIBITORS

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Background: Chronic myeloid leukemia (CML) is a myeloproliferative disorder. It is very rare during childhood. Tyrosine kinase inhibitors (TKI) changed those patients' treatment approach and prognosis. The most of the authors are in consensus to TKIs should be the first line treatment in CML patients. However, in children and young adults it may be concern. Although Bone Marrow Transplantation (BMT) is a curative approach, TKIs should continue as a life- long treatment.
Aims: In this single center series we aimed to evaluate the presenting symptoms, findings, treatment approaches, responses and prognosis of children with CML under the treatment of TKIs.
Methods: Single center retrospective study was approved by Local Ethic Committee. CML patients who were diagnosed at Ege University Pediatric Hematology Department between 1997 and 2020 were evaluated.
Results: Sixteen patients were diagnosed with CML during the study period. The median age of the patients was 9,5years (range 2-16 years), nine of them were girls.
5 patients were in blastic phase, 11 patients were in chronic phase of CML.
The predominant symptoms at presentation were asthenia (31%) and fever(31%). The most predominant clinical sign was splenomegaly (80%). The fever was seen in all patients in blastic phase. The mean WBC count at presentation was 205.000/mm^3. 50% of the patients the WBC count was above 200.000/mm^3. Only one patient with normal WBC count who was investigated for the reasons of thrombocytosis (1.820.000/mm^3) was diagnosed as CML.
Hydroxyurea treatment was given before the translocation (9;22) had been detected. One patient was given ARA-C and Interferon for 4 years since imatinib was not available. Imatinib treatment was given 15 patients as initiation treatment. Complete hematological response was documented in all patients between 20 and 68 days (median33 days) of treatment. The major molecular response was achieved in 14 of the patients within 6 months. Five patients with blastic crisis received both ALLIC BFM 2002 Chemotherapy protocol and imatinib.
7 patients received only imatinib. In 7 patients imatinib was switched to dasatinib as second line therapy. In 2 Patients nilotinib was started as third line treatment.
Two patients underwent BMT. The first patient achieved MMR at 12 months, but showed molecular relapse at 14 months of follow up, and the second patient developed blastic crisis at the 19 month of imatinib treatment.
TKI treatment was discontinued in 5 patients after a median of 7 years (range 5-10.5 years) treatment. Three of the patients were in MMR for seven years and one for 10,5 years. While no molecular relapse was seen until the last follow up, the median follow up period was 70 months. One patient who was on MMR for 5 years, molecular relapse developed nine months after the discontinuation of the treatment. TKI treatment was restarted.
The median follow up of whole study group is 109 months (range 19-522 months) and overall survival is 100%. BMT is needed in 2 patients (12.5%). Additionally 3 patients (18,7%) received only TKIs and succeded to discontinue TKIs without molecular relapse for a median period of 163 months.
Summary/Conclusion: In Conclusion, CML is a very rare disease during childhood. TKIs lead very good results in survival. In some patients, it is possible to discontinue TKIs without molecular relapse.

PB1524 QTC PROLONGATION AND SUDDEN CARDIAC DEATH AS A MANIFESTATION OF CARDIOTOXICITY

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Background: There are only few descriptions available in literature about the QTc prolongation and sudden cardiac death during treatment using BCR-ABL tyrosine kinase inhibitors.
Aims: Analysis of corrected interval QT (QTc) prolongation and sudden cardiac death of patients with chronic myeloid leukemia (CML) treated with BCR-ABL tyrosine kinase inhibitors (TKI).
Methods: The study was conducted on 114 patients who received nilotinibb, dasatinib or imatinib. All the patients underwent classical ECG monitoring and 24-hour Holter ECG monitoring with measuring of QTc duration. The trial excluded patients with severe heart diseases.
Results: Conducted comparative analysis shows statistically significant greater impact of nilotinib on the duration of QTc interval compared to other tyrosine kinase inhibitors. The maximum QTc was slightly longer than in patients treated with imatinib and dazatinib already at the early and middle stages (up to 36 months), but these differences are statistically insignificant. The main differences can be seen in patients taking nilotinib over 38 months, when these differences become statistically significant: median and interquartile range in patients on nilotinib therapy were 0.46 (0.44-0.47) s, n = 17 versus 0.43 (0.42-0.44) s in the group of patients taking dazatinib or imatinib (n=23), p=0.0004. After 7 years, we found out the fate of 110 examined patients. It turned out that 4 CML patients treated with ITK died suddenly. During analysis of the obtained data, it was found that the QTc duration in the ECG of the deceased did not differ from the survivors. At the same time, the QTc in 24-hour Holter ECG monitoring of 4 patients with sudden cardiac death was statistically significant longer than in the rest: 0.48 (0.48-0.505) s (n = 4) versus 0.45 (0.43-0.46) s (n = 110) (p=0.0003). Since all of the deceased were over the age of 52, the examination results of patients of this age were studied. A similar data was found in the group of patients older than 52 years: QTc duration of patients who died from sudden cardiac death - 0.48 (0.48-0.505) s, who are currently living or died from other reasons - 0.44 (0.43-0.46) s (n=56), p=0.001. All cases of sudden cardiac death occurred on nilotinib treatment (p=0.01), and the estimation of this indicator in the group of patients older than 52 years of age shows an identical trend with lower statistical significance (p=0.05).
Summary/Conclusion: 1. We have shown that in patients with CML taking nilotinib, the QTc duration is statistically significant longer than in similar patients receiving other TKI more than 38 months.
2. Despite the small number of groups and the small number of sudden deaths, they had a statistically significant QTc prolongation in 24-hour Holter ECG monitoring compared to those currently living or died from CML progression.
3. All CML patients treating with nilotinib are indicated to receive not only classical ECG, but also regular 24-hour Holter ECG monitoring with its greater sensitivity to detection of QTc prolongation.

PB1525 THE DIAGNOSIS, TREATMENT AND MONITORING OF PATIENTS WITH CHRONIC MYELOID LEUKAEMIA: THE IMPACT OF ELN GUIDELINES ON CLINICAL PRACTICE IN A DISTRICT GENERAL HOSPITAL

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Background: Tyrosine Kinase Inhibitors (TKI) have revolutionised the treatment and outcome of patients with Chronic Myeloid Leukaemia. This treatment, however, is associated with significant toxicity, in particular cardiovascular complications, and emergence of drug resistance. In order to optimise the TKI treatment pathway, European Leukaemia Net (ELN) published a Guidelines in 2013 (Baccarani et al, Blood. 2013;122:872–84). But the recent UK TARGET CML study carried out in the United Kingdom has identified significant variations in compliance with the above guidelines (Milojkovic et al, Br Haematol. Br J Haematol. 192(1):62-74).
Aims: We conducted an audit into the treatment pathway of all patients currently treated with a TKI in our hospital
Methods: Patient demographics, clinical features at presentation, diagnostics, clinical risk assessment, prognostic evaluation, treatment choice, frequency of response monitoring and interventions at treatment failures were analysed in a cohort of 51 (31 male and 20 female) patients.
Results: The age group of this patient population is 24-88 years (mean 59.4). Good clinical records documenting relevant clinical information are

available in 40/51 (78%) cases. Cardiac co-morbidities are recorded in 21/51 (41.2%) patients. These include type II diabetes mellitus (11.8%), hypertension (11.8%), cardiac arrhythmias (5.9%), obesity (21.6%), ischaemic heart disease (5.9%) and hyperlipidaemia (1.9%). Relevant clinical signs are recorded in 86% of the cases but this information is missing in 14% of the notes studied. Splenomegaly and hepatomegaly were noted at presentation in 14 (27.4%) and 1 (1.9%) patients respectively. All patients (100%) had bone marrow evaluation and cytogenetics done at diagnosis but prognostic scores are recorded only in 10 (19.6%) cases. The first line TKI was imatinib in 44/51 (86.2%), dasatinib in 4/51 (7.8%) and nilotinib in 3/51 (5.9%). The selection of TKI was appropriate in all 14 patients (100%) with known cardiac risk factor(s). A second generation TKI was selected on the basis of risk assessment in 3 patients. The reason for the selection of a second generation TKI in the other 4 cases was not recorded. 22/51 (43.1%) patients developed treatment failure at various time points. One patient opted for palliative care. Appropriate changes to treatment were made in 18/21 (85%) patients. However, there were delays in introducing changes to treatment in the remaining 3/21 cases (15%). Second line TKI treatment was dasatinib in 10 (47.6%), nilotinib in 6 (28.6%) and imatinib in 5 (23.8%) patients. The choice of second generation TKI was based on cardiovascular risk assessment in 18/21 (85.7%). Tyrosine Kinase Domain mutation analysis was carried out prior to changing TKI in 6/21 (28.6%). The test was not performed in 15/21 (71.4%) cases. The results of the current audit were compared with the previous audit conducted in 2011, prior to the introduction of ELN Guidelines.

Summary/Conclusion: The ELN Guidelines have had a positive impact on the CML treatment pathways in our institution with significant improvements in the diagnosis, clinical risk assessment, disease monitoring and drug selection at treatment failure. However, there is still room for further improvements, in particular, in areas of prognostic evaluation, risk-adapted drug choice and TKD mutation analysis at treatment failure.

PB1526 DOSE REDUCTION OF ITKS IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA. RETROSPECTIVE STUDY OF A SINGLE CENTER EXPERIENCE: SAFETY, EFFICIENCY AND ECONOMIC IMPACT.

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Background: Discontinuation of TKIs has been gaining ground in recent years in the usual practice of CML treatment. Long-term dose reduction is another strategy shown in different publications that may in some cases contribute to improving the quality of life of patients without putting disease control at risk.

Aims: Evaluate in retrospect the clinical and analytical evolution of the cases of our service in which the doses of ITKs have been reduced in the treatment of patients with CML and make an estimate of the economic savings obtained by dose reduction.

Methods: We have reviewed the clinical and analytical course of patients with CML in follow-up in H.U. Basurto between June 2013 and April 2020. Among them we have selected 20 patients in which the dose of ITK was reduced below the standard dose and we have analyzed the evolution of its clinical course and various analytical data, including BCR-ABL/ABL (IS), blood count, glucose, cholesterol, AST, ALT and triglycerides, both before and after dose reduction of ITK. Economic savings were calculated by multiplying the monthly price of each drug by the number of months of reduction and the fraction of reduced dose.

Results: A total of 20 patients with dose reduction were identified, with a median age of 60 years (40-89). ITK distribution was 16 imatinib, 14 nilotinib, 5 dasatinib and 1 bosutinib. Twenty-six patients were under first-line treatment, 9 second-line treatment and 1 on third-line. A total of 36 dose reduction episodes were collected in the study. The average treatment time with ITK prior to reduction was 24.6 months (0-135 months). The reason for the reduction was toxicity in most cases, although in 4 cases with nilotinib it was to prevent cardiovascular toxicity and in 1 case it was by the patient's own decision. Pre- and post-reduction molecular response levels are listed in Table 1. No cases of blast crisis or accelerated phase was observed after the reduction. Of 26 reductions the molecular response worsened in 4 cases and only one loss of MMR was observed, which was subsequently rescued without increasing the dose. The improvement in toxicity symptomatology was greater than 80% with all drugs. A significant increase in Hb and cholesterol levels was observed following dose reduction of imatinib. The estimated overall economic savings from dose reduction of ITKs were 568,367€ (nilotinib 428.729 €, dasatinib: 136.153 €, bosutinib: 2.286 €, imatinib: 1.198 €).

		Post-reduction molecular response					
		N.A.	MR1	MR2	MMR	MR≥4.0	Total
Pre-reduction molecular response	N.A.	0	1	0	1	0	2
	MR2	1	0	3	1	0	5
	MMR	0	0	1	2	0	3
	MR≥4.0	1	0	0	3	22	26
	Total	2	1	4	7	22	36

Summary/Conclusion: Our series shows that dose reduction of ITKs in selected cases may reduce toxicity and improve the quality of life of patients with CML with little effect on treatment efficacy and a big impact on pharmaceutical cost.

PB1527 DISCONTINUATION OF TYROSINE KINASE INHIBITORS IN PATIENTS WITH CML WITH DEEP MOLECULAR RESPONSE IN SOUTH OF TUNISIA

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Background: The therapeutic aim of chronic myeloid leukemia (CML) has profoundly changed over this decade from obtaining normal life expectancy to discontinuing medication for treatment-free remission (TFR). TKI discontinuation becomes an option for patients who achieve a stable and prolonged deep molecular response.

Aims: We report the experience of discontinuation of TKI in CML in South of Tunisia.

Methods: Our study was prospective. We included patients with CML followed at hematologic department in the south of Tunisia from October 2015 to December 2020. The criteria of inclusion suitable patients for discontinuation of TKI therapy were an age ≥18 years, a chronic phase CML with no prior history of accelerated or blast phase CML, non-high sokal-score at diagnosis, typical b2a2- or b3a2-bcr–abl1 transcripts, TKI therapy for at least 5 years, no history of resistant or progressive disease and stable deep molecular response (DMR) (*bcr-abl1* ≤0.0032% IS) for at least 2 years. After TKI discontinuation, hematological monitoring including a complete blood count and bcr-abl1 messenger RNA quantification by RT-PCR were done monthly during the first 6 months, every 2 months from 7 to 12 months, quarterly the second year and then every 3 to 6 months. Molecular relapse after TKI discontinuation was defined by loss of major molecular response (MMR) (bcr-abl1 >0.1% IS) and was an indicator for a resumption of TKI.

Results: Eleven patients out of 160 patients with CML (7%) were enrolled in our study. Seven patients were women and 4 were men. Median age at TKI discontinuation was 52 years (range 48-77 years). Sokal-score at diagnosis was low in 8 cases and intermediate in 3 cases. All patients were treated with Imatinib. Median period of TKI therapy was 117 months (range 60- 180 months). The average of length of DMR before TKI discontinuation was 45 months (range 24-72 months). The median period of follow-up after TKI discontinuation was 26 months (15-50 months). Molecular relapse occurred in 4 patients (36% of patients) in the first 3 months of discontinuation therapy. After the reintroduction of TKI, all of these patients obtained DMR again with 3.2 months (3 patients at 3 months and 1 at 4 months). The remaining 7 patients (63%) achieved a TFR.

Summary/Conclusion: In our study, the rate of TFR is 63% which is similar to literature results (40-60%). We conclude that TKI can be safely discontinued in our CML population fulfilling criteria of eligibility. To make more concrete conclusion, we must enlarge patient population and much longer follow up are needed.

PB1528 PARAPROTEINEMIA PREVALENCE AND CHARACTERISTICS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Background: Chronic myeloid leukemia (CML) is a clonal disorder of myeloid origin. Paraproteinemias are a group of disorders arising from the clonal proliferation of a lymphoid origin leading to the production of a monoclonal (M-) protein. Though originating from different cell origins, there have been several reports describing patients with coexistence of CML and multiple myeloma (MM) or other paraproteinemias, mostly in patients treated with tyrosine kinase inhibitors (TKIs).
Aims: To determine whether the prevalence of paraproteinemia in a large cohort of CML patients is higher than in the general population in a tertiary medical center.
Methods: This is a cross sectional study among chronic phase CML patients treated in the Institute of Hematology at the Rabin Medical Center, a university affiliated tertiary medical center in Israel. Between February 2019 and Februray 2021 consecutive patients with a diagnosis of chronic phase CML, who gave their consent to the study, performed the following serum samples: protein electrophoresis & immunofixation (SPEP, IFIX), serum free light chains (FLC) and quantitative immunoglobulin (Ig) levels. The study's primary outcome was the prevalence of paraproteinemia among this cohort of CML patients. Secondary outcomes evaluated the correlations between paraproteinemia and various patient, disease and treatment-related variables. The study was approved by the Institutional Review Board.
Results: A total of 96 patients were recruited. Data for the analysis were available for 90 of them. Patients' characteristics are presented in Table 1. On SPEP - 18 patients (20%) had hypergammaglobulinemia, 14 patients (15.5%) had hypogammaglobulinemia and 58 patients (64.5%) had normal gammaglobulin fraction.
M-protein was detected on SPEP and IFIX in 6 patients (6.6%) with a median age of 71.5 years (range 46-74). Among them, two patients had also an abnormal FLC and elevated IgG or IgA levels with corresponding immunoparesis of the uninvolved Ig heavy chain. These patients underwent a bone marrow biopsy and skeletal imaging and were diagnosed with IgG-kappa and IgA-kappa smoldering multiple myeloma (SMM). The other four patients had normal FLCs and their characteristics were compatible with the diagnosis of low risk monoclonal gammopathy of undetermined significance (MGUS). None of the patients in our cohort was diagnosed with active MM.
All six patients with an M-protein are currently under observation for their newly-diagnosed paraproteinemia.
At enrollment, five of the six patients with a detectable M-protein were treated with a TKI [imatinib (n=2), dasatinib (n=2), bosutinib (n=1)] and one had been in TFR for two months, after 6 years of imatinib therapy.

Table 1 – cohort characteristics (n=90)

Variables	
Median age, year (range)	
At CML diagnosis	54.6 (23.9-90.4)
At enrollment & testing	64.3 (26-92)
Median time from CML diagnosis to enrollment & testing, year (range)	6.8 (0.1-23.5)
Gender, n (%)	
Male	44 (49)
CML treatment at enrollment, n (%)	
1st line TKI	48 (53.3)
2nd line TKI	37 (41.1)
3rd line TKI	2 (2.2)
Treatment free remission	3 (3.3)

Summary/Conclusion: To the best of our knowledge this is the largest study to describe the prevalence of paraproteinemia among CML patients. We found the prevalence of MGUS in chronic phase CML patients (4.4%) to be similar to that of the general population above the age of 50 years. Nonetheless, we found a non-negligible prevalence of SMM (2.2%), a relatively uncommon clinical entity. Based on these data, we recommend to consider screening for paraproteinemia coexistence in patients with CML, since this might have a clinical impact. Further studies, including extended follow up of the present cohort should elucidate the true clinical significance of our findings.

PB1530 CHRONIC MYELOID LEUKEMIA WITH THREE-WAY TRANSLOCATION T(4;9;22) AND MULTIPLE MYELOMA – A RARE CASE OF COMORBIDITY

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Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells, that is genetically characterized by Philadelphia (Ph') chromosome in 90% of cases, consisting of reciprocal t(9;22)(q34;q11) translocation. About 5-10% of CML patients develop variant translocations involving one or more chromosomes beside 9 and 22. Multiple myeloma (MM) is a monoclonal disorder of plasma cells which have differentiated from lymphoid B cells. Since different cell lines give rise to CML and MM, the occurrence of both MM and CML in the same patient is extremely rare.
Aims: We describe a rare case of a patient with CML with t(4;9;22)(q21;q34;q11) three-way translocation and MM diagnosed and treated in our Clinic.
Methods: Case report. Data was collected form medical history and clinical charts. Relevant literature was reviewed.
Results: We present a case of 71-year-old man with leukocytosis, mild anemia and splenomegaly, who was initially diagnosed with CML, chronic phase. The bone marrow aspirate was typical of CML with granulocyte hyperplasia and 1% myeloblasts. The cytogenetic analysis revealed the presence of an uncommon three-way translocation 46,XY,t(4;9;22)(q21;q34;q11) in all metaphases obtained from the bone marrow, confirmed with positive dual fusion FISH probe for t(9;22)BCR/ABL. The qRT-PCR detected BCR/ABL1 transcripts. Treatment with tyrosine kinase inhibitor (TKI), nilotinib (300mg bid), was started and the patient achieved a complete hematologic response and at 3 months – complete cytogenetic response with normal bone marrow karyotype and early molecular response.
Six months after initial therapy with TKI, mild anemia with a rise of total serum protein were detected and serum protein electrophoresis revealed a monoclonal IgG lambda M-spike of 27g/L. Bone marrow biopsy at that time showed 35-40% CD138+/CD56+ plasma cells infiltration, and no increased blast cells. FISH analysis for BCR/ABL of bone marrow was negative, but quantitative RT-PCR detected M-BCR/ABL with a level of expression of 0.63%. MM was diagnosed, in addition to CML. The revision of the bone marrow at initial CML diagnosis was negative for plasma cells. Chemotherapy with weekly bortezomib, cyclophosphamide and dexamethasone was preferred considering the risk of drug interactions and pancytopenia when combined with nilotinib for CML. The patient achieved complete response with 6 courses of chemotherapy for MM, deep molecular response (DMR) of CML at the first year of TKI therapy; therapy was well tolerated. One year later he developed myeloma relapse with anemia, while DMR of CML remained stable with nilotinib. The patient was treated for relapsed myeloma, but he experienced a complicated COVID-19 infection with pneumonia and renal failure, and had fatal outcome in few weeks.
Summary/Conclusion: While other than 9 and 22 chromosomes are frequently involved in three-way translocations, chromosome 4 is a very rare event in CML complex variant, with only seven cases with breakpoint 4q21 reported in cytogenetic databases. The coexistence of CML and MM is another extremely uncommon event with only ten patients described in medical literature diagnosed first as having CML, and then MM. This is for the first time that CML patient with three-way translocation t(4;9;22)(q21;q34;q11) is diagnosed with MM. Due to the rarity of coexistence of two hematological malignancy in the same patient, we have scarce data on treatment approach. Our case demonstrates that nilotinib combined with certain myeloma therapy can be considered safe and efficient in a case of CML and MM comorbidity.

PB1531 CHRONIC MYELOID LEUKEMIA AS A SECONDARY MALIGNANCY IN A PATIENT WITH SPLENIC MARGINAL ZONE LYMPHOMA: A CASE REPORT

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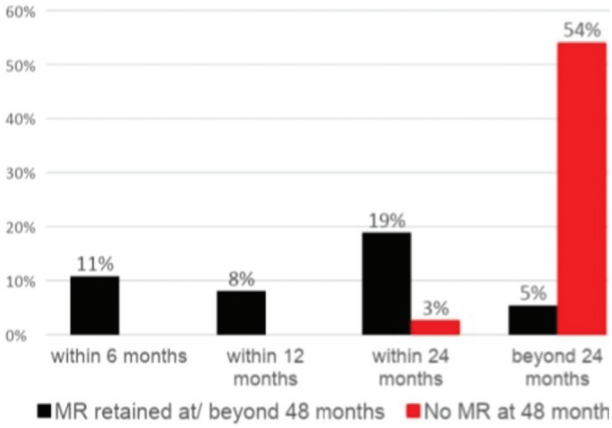
Background: Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) occurring as a secondary malignancy is a rare clinical scenario, the publications on treatment-related CML (tr-CML) in lymphoma patients is limited by a few case reports.
Aims: To describe a unique case of an elderly patient who developed CML subsequent to splenic marginal zone lymphoma (SMZL). To our knowledge, CML as a secondary malignancy in a SMZL patient is hitherto unreported worldwide.
Methods: A case study.
Results: Male, 61-year-old, diagnosed with SMZL in February 2009. He had white blood cell count (WBC) of $33.1x10^9$/L, 86% lymphocytes in peripheral blood, immunophenotype with positive for HLA-DR, CD19, CD20, cCD79α, κ, negative for CD10, CD5, BCL-2, CD103, CD23, normal karyotype and splenomegaly. The patient was asymptomatic, so a watch-and-wait approach was used. Follow-up observation showed stable disease till 2012. From Jun 2012, chlorambucil was applied intermittently, due to thrombocytopenia and progressive enlargement of the spleen. Thereafter the disease was generally stable. In Aug 2014, the patient presented with an elevated WBC of $87.98x10^9$/L. Peripheral blood smear revealed increased immature granulocytes, with 4% promyelocyte, 12% myelocyte, 3% metamyelocyte. The BM smear identified the cellular hyperplasia and increased myeloid to erythroid ratio, with 61.5% marrow myelocytes and 31% marrow mature lymphocytes. Cytogenetic analysis revealed t (9;22) and RT-PCR analysis demonstrated *BCR/ABL* fusion transcript. Over six years after the initial diagnosis of SMZL, a diagnosis of CML in chronic phase was made. He started on imatinib (400mg daily), and was simultaneously treated with cyclophosphamide for the SMZL because he refused the anti-lymphoma immuno-targeting therapy. Imatinib treatment was switched to nilotinib (300mg, twice per day) after seven months due to recurrent skin rash and refractory mucous membrane ulcer, which were probably attributed to imatinib. As of Dec 2020, the patient is in sustained complete molecular response from CML, and the disease state of SMZL is stable.
Summary/Conclusion: In conclusion, we report a rare tr-CML case of an elderly patient treating with an alkylating agent for SMZL. Tr-CML is an infrequent complication after chemotherapy and/or radiotherapy, which may increase the risk of secondary malignancies by inducing genetic damage. Nilotinib, the second generation TKI, could show a favorable response in Ph+ tr-CML, similar to that in *de novo* CML.

PB1532 FISH VERSUS REAL-TIME QUANTITATIVE PCR FOR MONITORING OF MINIMAL RESIDUAL DISEASE IN CHRONIC MYELOID LEUKAEMIA PATIENTS ON TYROSINE KINASE INHIBITOR THERAPY

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Background: BCR-ABL fusion gene, the oncogenic driver of CML, results from a translocation between short arms of chromosome 9 and 22. Monitoring of CML patients during treatment is essential, not only for tailoring the treatment but also to detect early relapse to enable timely intervention. Commonly used methods for detection of residual disease are conventional karyotyping, FISH and molecular methods. In this study, we compared FISH with QRT-PCR for detection of residual disease in CML.
Aims: To demonstrate correlation between FISH and Quantitative PCR for BCR ABL1
Methods: CML patients on tyrosine kinase inhibitor (TKI) therapy and on regular follow up at University Kebangsaan Malaysia Medical Center (UKMMC) were selected. A comparative study was conducted between FISH and QRT-PCR for BCR-ABL transcripts at diagnosis and during follow-up.
Results: There was good correlation between FISH and QRT-PCR for BCR-ABL. At 6th month of follow-up post diagnosis, FISH had a sensitivity of 83.3% and specificity of 65.2% (k >0.339, p<0.033). At 12th month, the sensitivity of FISH was 83% and the specificity was 59.1% (k >0.286, p <0.065). Similarly, at the 24th month, FISH had a sensitivity of 100% and specificity of 68.8% (k >0.642, p<0.000).



Summary/Conclusion: QRT-PCR was the most reliable and therefore the current gold-standard method to monitor residual disease in CML patients. In our study FISH analysis was demonstrated to be a reliable investigation that should be considered with QRT-PCR for BCR-ABL. It was also demonstrated that time to achievement of molecular and cytogenetic targets i.e. MMR and CCyR respectively, were reliable indicators to detect the long-term outcome of the disease.

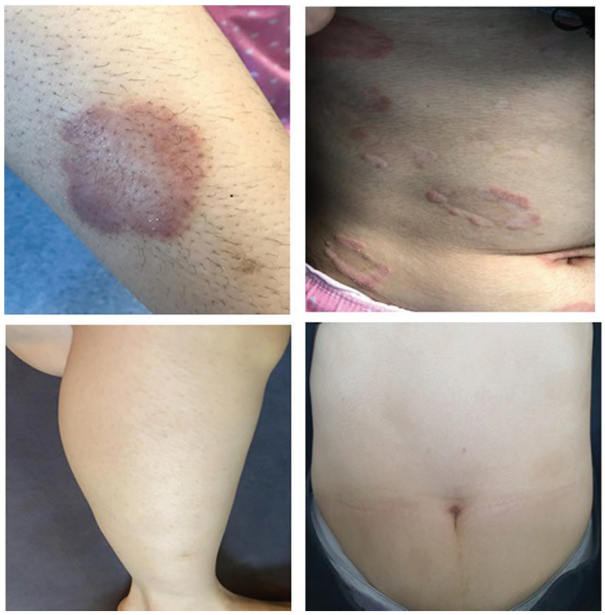
PB1533 COMPLETE REMISSION OF PSORIASIS IN CML LADY TREATED WITH DASATINIB: JOYFUL EXPERIENCE

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Background: Discovery of tyrosine Kinase inhibitors (TKIs) was a watershed moment in Chronic Myeloid Leukemia (CML) treatment. Adverse cutaneous reactions (ACRs) represent the most common non-hematological adverse reactions with TKIs. More with 1st generation TKIs (Imatinib), tend to be less severe with second-generation. Development of psoriasis during Imatinib and Nilotinib was reported in few cases. One reported case showed that Dasatinib causing worsening of Psoriasis vulgaris. To our knowledge, this is the first case showed complete remission of psoriasis after Treatment with Dasatinib.
Aims: To document a rare beneficial effect of dasatinib which is accidently discovered during treating female patient of CML.
Methods: Case Report: 27 years old Saudi Female, medically free before, presented in Jul 2019 to ED with abdominal pain mainly in epigastric region associated with heart burn and vomiting, this condition started 3 days ago. Preceded by fever mainly during night, night sweating and weight loss for 1 month. She also suffered from recurrent nose bleeds with headache. Clinical examination showed Huge splenomegaly reaching Umbilicus. Skin examination showed multiple ecchymotic patches with multiple skin lesions scattered all over the abdomen, back and lower limbs which were red in Colour with scaly patches.
Initial laboratory tests showed anemia (Hb 7.8 gm/dL), leukocytosis (WBC 537.00 x 109/L), with platelet count 327.00 x 109/L. The Peripheral blood smear showed picture of Chronic Myeloid Leukemia –chronic phase. The pelvi-abdominal ultrasound showed markedly enlarged splenomegaly 20 cm in size. Coagulation profile was with normal range. High LDH level [820 U/L]. ESR 1st hour was 100. PCR was positive for the BCR-ABL1 fusion transcript p210(85% IS score). July

2019 Back skin, Punch biopsy showed hyperkeratosis, parakeratosis, Munro's micro abscess, acanthosis, diminished granular layer, and tortuous dilated papillary capillaries which Consistent with annular non-pustular psoriasis.
Sockal score was calculated to be Intermediate. She had plan for marriage after 1 year from diagnosis. So, we started Dasatinib 100 mg once daily with optimum response at 3 months (BCR-ABL 1% IS score). But the amazing thing is that psoriatic lesions started to improve gradually without using any medications for psoriasis. During her last visit to Hematology Clinic on Feb 2021, she was very happy that psoriasis disappeared completely and got married with gentleman accompanied her to the clinic. She agreed to take photos for abdomen and Lower Limb.
Results: -



Summary/Conclusion: It is well known that tyrosine kinase inhibitors made a revolution in CML, but it can be hope for other difficult treating conditions as psoriasis.

PB1534 CHRONIC MYELOID LEUKEMIA: ATYPICAL PRESENTATION WITH ISOLATED EXTREME THROMBOCITOSIS

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Background: Chronic myeloid leukemia (CML) represents a common condition in the spectrum of myeloproliferative disorders. It classically exhibits leukocytosis, but rarely presents with isolated thrombocytosis. Severe thrombocytosis, with a platelet count of more than 1,000×109/L, is exceptionally rare to be found upon initial laboratory workup in newly diagnosed patients with CML. A systematic review done by Dawood Findakly et al only found 20 cases in PubMed, MEDLINE®, ScienceDirect, and Scopus for English-language articles for the period 2000-2020.
Aims: To describe a case of a patient with isolated thrombocytosis as initial manifestation of CML.
Methods: A 33 yo woman was admitted for spontaneous hematomas and extreme thrombocytosis. Laboratory was as follows: Hg 13gr/dl WBC 8400 (normal blood smear) Platelet 2 million/mm3. Factor VIII 61% V. Willebrand (VW) 70%, Ristocetin ccofactor 40%. Abdominal ultrasound showed no visceromegalies. A bone marrow biopsy was done: cellularity was 70% CD34+ cells 4% with marked hyperplasia. Hydroxyurea was initiated at an initial dose of 500mg BID and she was discharged. Essential thrombocytemia was the initial suspected diagnosis. 1 week after she was admitted again with headache and dizziness. Platelet count has risen to 3 million/mm3 despite an increase in hydroxyurea to 1gr every 8hs. Since she had neurological symptoms, she initiated platelet apheresis for 3 sessions achieving symptomatic relief and was discharged with a platelet count of 500000/mm3. Cytogenetic results were 46XX, t (9;22) and BCRABL p210 transcript by qPCR was positive. JAK2V16F was negative. CALR and MPL mutations were also negative
Results: With diagnosis of CML she iniated imatinib 400mg/daily achieving at month 6 mayor molecular response, normalization of platelet and VW factor. We present this case because of the rare incidence isolated thrombocytosis as manifestation of CML
Summary/Conclusion: This atypical CML presentation with an isolated thrombocytosis is a rare entity. Isolated thrombocytosis could lead to a misdiagnosis of essential thrombocythemia.

PB1535 COMPLEX CYTOGENETIC ABNORMALITIES IN CHRONIC MYELOID LEUKEMIA RESULTING IN EARLY PROGRESSION TO BLAST CRISIS: A CASE REPORT

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Background: BCR-ABL1, resulting from t(9;22), is the oncogenic driver of chronic myeloid leukemia and the therapeutic target of the disease. Molecular studies have been the gold standard modality for patient assessment since the advent of tyrosine kinase inhibitor therapy. In spite of that, there are cytogenetic abnormalities that can render the disease unresponsive to conventional therapy, thus making cytogenetics an important component of patient management guidelines.
Aims: To present a novel karyotype in CML with impact on clinical outcome of the patient.
Methods: Conventional Karyotyping using Giemsa Banding
Results: We present a case of a Tajik, Afghan patient with chronic myeloid leukemia with del(6)(q23.3q27), t(9;22)(q34;q11.2), monosomy 11, monosomy 12, and marker chromosome who, despite having typical clinical and hematological disease with initial response to therapy, progressed to blast crisis very early and thus required special interventions.



Summary/Conclusion: Cytogenetic monitoring is an important pillar in the management of patients with chronic myeloidleukemia that cannot be ignored. It should therefore be a part of patient management not only during diagnosisbut also during management. We present an unusual cytogenetic abnormality in a patient with chronic myeloidleukemia that resulted in early disease progression.

Enzymopathies, membranopathies and other anemias

PB1536 NEXT-GENERATION OSMOTIC GRADIENT EKTACYTOMETRY: AN ESSENTIAL STEP FOR THE DIAGNOSIS OF RED BLOOD CELL MEMBRANE DISORDERS

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Background: During the last decade, next-generation osmotic gradient ektacytometry, which analyses the red blood cell (RBC) deformability under an osmotic gradient, has become a very useful tool for the

diagnosis of RBC membrane disorders, especially for hereditary spherocytosis (HS). The LHUB-ULB is currently the National Reference Center for RBC membrane disorders and ektacytometer is one of its tools.
Aims: The aim of this study was to improve our diagnosis of HS by using ektacytometry.
Methods: Between 2017 and 2020, a total of 124 consecutive EDTA samples from patients with chronic haemolytic anaemia were obtained from our routine workload. They were analyzed prospectively using the osmoscan module of an osmotic gradient ektacytometer. According to our diagnostic algorithm, 66 cases of HS, three hereditary elliptocytosis, one hereditary stomatocytosis, one congenital dyserythropoietic anemia type II and one Southeast Asian ovalocytosis were diagnosed. Finally, 52 patients were classified as "membranopathies excluded". Osmoscan parameters were expressed as percentage of change compared to the control sample of the day. Cut-off values for the most robust parameters for the diagnosis of HS were established using receiver operating characteristic (ROC) curve analysis.
Results: The best criteria for the diagnosis of HS were the combination of a decreased area under the curve (AUC) of more than 17.9% and an increased minimal osmolality point (Omin) of more than 18.3% compared to the control. Using these established cut-offs, osmotic gradient ektacytometry reported a sensitivity of 93.9 % and a specificity of 91.4% for the diagnosis of HS.
Summary/Conclusion: After more than three years of routine use in our laboratory, by using dedicated cut-offs for several parameters obtained by osmotic gradient ektacytometry, the next-generation ektacytometer confirmed its place as a powerful diagnostic tool for the diagnosis of RBC membrane disorders.

PB1537 DIAGNOSTIC IMPORTANCE OF BONE MARROW ASPIRATION IN CHILDREN WITH ANEMIA OF UNKNOWN ETIOLOGY

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Background: Anemia of unknown etiology is a major problem for hematologists and requires a wide range of studies. One of the main investigations at this time is bone marrow examination.
Aims: This study was designed to determine the diagnostic importance of bone marrow aspiration in children with anemia of unknown etiology during 5 years (2016-2020).Study place: Children's clinic, hematology department, Tbilisi, Georgia.
Methods: A total of 50 children, aged 2 month to 16 years presenting with anemia, whose cause cannot be established on detailed history, physical and routine laboratory examinations, were referred for bone marrow aspiration during the study period. Patients having malignancies, blast cells on peripheral blood film and other causes associated marrow suppression were excluded from the study.
Results: Out of 50 cases presenting with unexplained anemia, about 7 (14%) made up rare anemias: congenital form of vitamin B12 deficiency anemia-2 (1-Imerslund-Grasbeck syndrome), congenital dyserithropoietic anemia type II-1, pure red cell aplasia (Diamond-Blackfan syndrome)-2, congenital sideroblastic anemia-1, iron refractory iron deficiency anemia 1. It was also revealed bone marrow megaloblastic changes caused by a acquired forms of B12 deficiency-8 (16%), folic acid deficiency-2 (4%).13 cases were iron deficiency anemia (26%),6 cases were of anemia of chronic disease (12%),4 cases as hemolytic anemia unknown etiology (8%).About 5 cases as aplastic anemia (10%). 5 Cases of anemia remain undiagnosed (10%).
Summary/Conclusion: Research data analysis demonstrate that the bone marrow aspiration is essential and necessary and should be performed as soon as possible in all cases of unexplained anemia. This examination successfully provide diagnostic evolution and confirmation of anemia where cause cannot be found by routine laboratory investigations in most cases (90%).It gives us precise direction to conduct additional studies to confirm the diagnosis. Accurate examination of bone marrow is crucial in diagnosis of very rare anemias. The final morphological interpretation of bone marrow aspirate smears reveals specific abnormalities of various anemias and helps hematologists choose the right direction in disease management.

PB1538 CLINICAL MANIFESTATIONS AND COMPLICATIONS IN PEOPLE WITH HEMOGLOBIN C DISEASE

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Background: Hemoglobin C disease is a type of hemolytic anemia, like sickle cell disease, caused by a structural change on the beta globin gene, which provokes a tendency to hemoglobin cristalization.The disease manifests itself when the two genes in beta globin are altered (HbCC). It usually develops with mild to moderate hemolytic anemia, splenomegaly (most frequent symptom), target cells, HbC crystallization, reticulocytosis and low mean corpuscular volume (CMV).HbC has an affinity slightly reduced by oxygen and tends to crystallize in its oxygenated form, there are more dehydrated, dense, viscous and less deformable erythrocytes, which, however, does not lead to vaso-occlusive crises as occurs in the presence of HbS.There are few reports in the literature about its prevalence in the population and its clinical behavior.
Aims: Describe the clinical manifestations and complications in people with hemoglobin C disease assited in a sickle cell disease reference center in Feira de Santana (BA), Brazil and promote a critical reflection of the multidisciplinary team.
Methods: Descriptive observational study of a case series with 13 children with hemoglobin C disease diagnosed by electrophoresis. Interviews were conducted alongside medical record review to analyse the participants social and clinical variables, as well as laboratorial behavior through hemoglobin levels (Hb).
Results: The studied population consisted of children aged 2-18 years, with the majority of people being in the age group 5-7 years (46.2%).11 particpants were female with an average of 6.6±2.1 years old and 9 identified themselves as black or brown. Regarding the use of medications, 12 people reported use of folic acid, 3 used profilatic penicilin, 4 used painkillers because of painful episodes and 3 reported use of other medications. Concerning clinical manifestations, 1 person had splenomegaly; 5 reported mild to moderate painful episodes in the last 12 months; 7 reported acute chest syndrome (ATS) as complication; no one had any target-organ damage or had gone through blood transfusion in the last 12 months. The hemoglobin levels varied between 8.6-12.6g/dL with an average of 11.3±0.9 g/dL, 4 patients didn't have anemia, 3 had mild anemia and 3 others had moderate anemia.

Clinical and Sociodemographic Characteristics		N (13)	%
Sex			
	Female	11	84,6
	Male	2	15,4
Race			
	Brown	5	38,5
	Balck	4	30,8
Pain Crises*		5	38,5
Medical Emergencies*		4	30,8
N° hospital admissions*			
1		1	0,1
Clinical Complications			
	Acute Chest Syndrome	7	53,8

In the last 12 months.

Summary/Conclusion: This study showed that people with hemoglobin C disease had mild clinical manifestations. Studies are needed to better understand it's pathophysiology as well as coohort studies to evaluate the clinical evolution of the disease and it's clinical manisfestions.That way, people with hemoglobina C disease will be able to receive a better defined and beneficial treatment, one that isn't based only on what is known and established for sickle cell anemia.

PB1539 PROSPECTIVE ANALYSIS OF NEWLY DIAGNOSED AUTOIMMUNE HEMOLYTIC ANEMIA: A SINGLE CENTER STUDY

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Background: Autoimmune hemolytic anemia (AIHA) is an autoimmune-mediated disease in which erythrocytes are destroyed through (auto)antibodies against their surface antigens, resulting in premature lysis. It is a rare disorder and data about characteristics of AIHA from clinical practice are rare, especially if collected prospectively.
Aims: This prospective study was conducted in order to analyze characteristics of patients with newly diagnosed AIHA.
Methods: A single-center prospective study was performed at the University Hospital Center Zagreb (UHC), a tertiary center and the largest Croatian hospital, which included all consecutive patients with a newly diagnosed direct antiglobulin test positive AIHA from 1st Jan 2019 to 31th Dec 2020. Study was approved by UHC Ethical Committee. Descriptive statistics were performed and results are reported as frequencies (percentage) for categorical and as means (±standard deviation) or medians (minimum-maximum), as appropriate, for continuous values.
Results: Data includes 17 patients (41% men), median age at diagnosis 52 (5-76) years. Majority of patients had secondary AIHA (14/17, 82%), mostly due to underlying lymphoproliferative malignant disease (7/14 patients, 50%). 4 had underlying autoimmune disorders, 1 solid cancer, 1 developed AIHA after allogeneic bone marrow transplantation, and 1 after *M. pneumoniae* infection. Median hemoglobin (Hb) at diagnosis was 74 (39-124) g/L; 12 (71%) patients required hospital care with admission Hb of 58 (39-124) g/L, and 10 (59%) received erythrocyte transfusion. 15 (88%) patients required therapy with corticosteroids, and 6 (35%) received rituximab (as the first line therapy in 3/6 (50%) of patients). Patients were followed with a median time of 474 (22-648) days during which 13 (76%) achieved complete remission (CR) without signs of hemolysis or anemia, 1 showed improvement but failed to achieve normal Hb levels, 1 was refractory to therapy, and 2 were lost to follow-up. Median time from diagnosis to best response was 137 (43-606) days. Of 13 patients in CR, 2 (15%) relapsed which was observed 260 and 363 days after remission. During follow up 2 patients suffered from COVID-19 infection, but neither showed signs of AIHA relapse. 2 patients died during follow-up due to AIHA-unrelated causes.
Summary/Conclusion: Although with relatively small number of patients, this prospective study of newly diagnosed AIHA patients showed increased percentage of rituximab administration (from 17.6% to 35%) comparing to our previous retrospective single-center analysis from 2014 to 2018 (EHA library: Pulanic D, et al. 2019;PB 1963.). This is probably due to the increase of rituximab availability due to lower costs and more experience with this treatment modality.

PB1540 EPIDEMIOLOGICAL CHARACTERS OF ADULT EGYPTIAN AUTO IMMUNE HEAMOLYTIC ANEMIA PATIENTS: A SINGLE CENTER EXPERIENCE

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Background: Auto immune Heamolytic anemia (AIHA) is a widely used title for a variety of anemia types which are mostly diagnosed by exclusion and comprises a lot of symptoms and signs with a myriad of complications. No age is immune with majority being middle-aged with a significant female predominance over male patients. It could be primary or secondary to many factors but mostly other immune disorders. The treatment may include a watch and wait strategy with regular tonics or the major used line corticosteroids and if the patient fails this immunosuppressive drugs might be added or replace corticosteroids with the increased use of monoclonal antibodies especially rituximab and splenectomy still remains an option for resistant cases with certain types of chemotherapeutic agents. The burden of such medications and their associated toxicities affect the patient adherence to therapy itself and follow up dates which requires meticulous and tailored treatment choices for each patient to decrease disease complications and treatment related adverse events and ensure the patient compliance.
Aims: The Aim of this study is to outline the Demographic characters of Egyptian AIHA patients on regular follow up at an adult academic hematology center in Egypt and the characters of their disease
Methods: This is a descriptive study regarding Adult (above the age of18) AIHA patients on follow up with the clinical hematology unit Oncology center Mansoura University, Dakahlia, Egypt who had recorded follow up visits on our System in the period between 2005 and 2021 regarding their age at diagnosis, sex, baseline criteria, presence of crisis or not method of diagnosis and their follow up regimen.
Results: By reviewing the data on our system over the period of 1-1-2005 and 1-1-2021 we found that we have 228 AIHA anemia patients with 25 males (10.8 %) and 203 females (89.2 %), The average age at diagnosis at our center was 45 years with the range of 16 – 72 years, The median follow up of our patients was 61 months (180 – 6).All patients with follow up under 6 months were excluded from final analysis. 77.9 % of our patients were primary AIHA while the remaining 22.1% were secondary from which 41.6% were secondary to Viral hepatitis, 16.6% to both of Myelodysplastic syndrome and Systemic lupus erythrmatosis and 8.3% to pregnancy, rheumatoid arthritis and Antiphospholipid syndrome.The average hemoglobin at diagnosis was 7 gm/dl with the range (3 – 12), average White blood cell count was 8 $x10^3$/ ml (3 - 67) and platelets average was 205 $x10^3$/ ml (5 - 387). 15.2% of our patients had immune thrombocytopenia and were considered to be having Evan's syndrome while the other 84.8 had normal platelets count. As regard direct coomb's test 91.5 % were positive while the remaining 8.5 % were negative while the indirect coomb's test was positive in 71.2 % and negative in 28.2 %. 75% of our patients required packed red blood cells transfusion during their course of the disease while the rest were not transfused.
Summary/Conclusion: Patients with AIHA need more care and psychological support with increasing the awarence regarding their disease characters and complications with an increased need for further progress in the treatments avaibale for them to ensure longer and more stable remissions

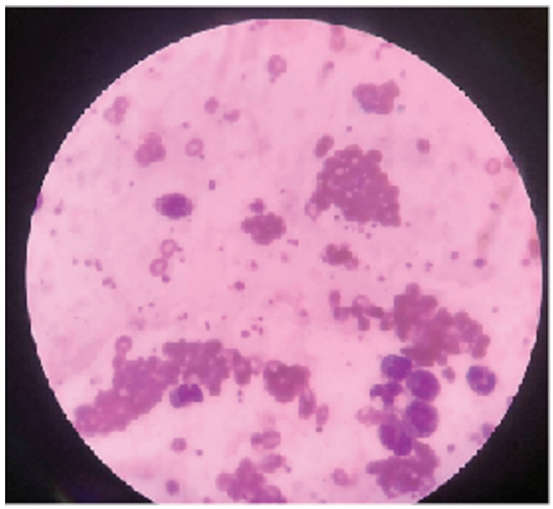
PB1541 HEMOLYTIC ANAEMIA COMPLICATING PREGNANCY

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Background: Hemolytic anaemia and pneumonia are uncommon complications of pregnancy.Most common aetiological agents of pneumonia in pregnancy are typical bacterial pathogens,like Streptococcus pneumoniae,Haemophilus influenzae and atypical bacterial pathogens,like Mycoplasma pneumoniae,Chlamydia pneumoniae and Legionella pneumophilia.
Aims: Unfortunately,the incidence of Mycoplasma pneumonia in pregnant women and the probability of spontaneous abortion is unknown. Also,the association between risk for abortion in patients complicated by secondary autoimmune hemolytic anaemia is yet to be established.
Methods: A 31 year old woman,with no known comorbidities in the past,$G_2P_1L_1A_0$,at 12 weeks period of gestation,presented with fever,cough and breathlessness for 2 weeks.Upon physical examination,patient appeared ill,dyspnoeic,with significant pallor and icterus,had bilateral basal crepitations and 12-14 weeks relaxed uterus.Initial investigation reports revealed anaemia,indirect hyperbilirubinemia,elevated LDH and reticulocyte count,and,single live intrauterine gestation 11 weeks 4 days on USG abdomen.
Results: Positive direct coombs test,high cold agglutinin titer with anti-I specificity and peripheral smear examination (figure 1) showing agglutination of RBCs with normal platelets,increased number of WBCs without immature cells,pointed towards immune hemolytic anaemia,suggestive of cold agglutinin disease.Bone marrow biopsy was not indicative of any hematological malignancy.Though steroids,blood transfusion(O negative)and antibiotics were initiated,she developed bleeding per vagina and products of conception expelled with fetus.Acute hemolysis complicating Mycoplasma pneumoniae infection seemed the most likely diagnosis,which was confirmed serologically with positive

antimycoplasma IgM and high antibody titer by complement fixation. Chest X-ray showed high-density area in right lower lobe.Azithromycin was given along with steroids.Patient improved and she remains clinically well,with no recurrence of jaundice



Summary/Conclusion: We report a unique case of Mycoplasma pneumonia complicating pregnancy,resulting in spontaneous abortion and secondary autoimmune hemolytic anaemia.Though pneumonia in pregnancy can cause severe maternal morbidity and mortality,Mycoplasma pneumonia causing spontaneous abortion isn't a common clinical scenario.Moreover,our patient had severe hemolytic anaemia to such extent that cross matching for blood transfusion was not possible due to autoagglutination.There have been many instances where autoimmune hemolytic anaemias are not evaluated for any secondary causes.This could leave an asymptomatic infection or hematologic malignancy undetected unless progressed to an advanced stage.The infrequency with which it is encountered makes it a formidable diagnostic challenge.We emphasize the need for further studies on association,if any,between the risk of spontaneous abortion in Mycoplasma pneumoniae complicated by secondary autoimmune hemolytic anaemia.

Gene therapy, cellular immunotherapy and vaccination - Biology & Translational Research

PB1542 GENETICALLY ENGINEERED IPSC-DERIVED NK CELLS AS A PROMISING CLINICAL DRUG CANDIDATE FOR THE TREATMENT OF B CELL MALIGNANT LYMPHOMA

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Background: Chimeric antigen receptors (CARs) are synthetic transmembrane receptors designed to target tumor-associated antigen to treat human malignancies. CARs have been used to redirect the specificity of T cells and NK cells against several hematologic cancers with notable clinical responses. Despite their antitumor activity, autologous CAR-modified T cells have many limitations including clinical safety and manufacturing difficulties. NK cells that have been engineered to express a CAR are candidate effectors for cancer treatment. Unlike T cells, allogeneic NK cells do not cause GvHD and can be safely administered without the need of full HLA matching based on previous clinical trials. This eliminates the need to produce a unique, patient-specific CAR product for each patient. A major advantage of NK cells is that they are naturally "off-the-shelf" and can be manufactured centrally so that product is available on-demand and ready-to-use.
Aims: iPSCs, with their ease to be genetically engineered, indefinite expansion capacity in vitro and feasibility to be differentiated into NK cells, are attractive starting cell resources to produce therapeutic NK products.
Methods: Extensive genetic modifications on iPSCs can be achieved by engineering a population of iPSCs, followed by single-cell-derived clone expansion and screening. The resulting iPSC clones carrying homogeneous genetic composition can be used as the MCB for downstream manufacturing.
Results: Here we report some characteristics of NK019 cells, a genetically engineered iPSC-derived NK cell therapy candidate. NK019 cells were differentiated from a modified human iPSC single-cell clone carrying 3 transgenes, including a Chimeric Antigen Receptor (CAR) targeting CD19, a modified CD16 and an IL15 molecule. The 3 transgenes maintain stable expression before and after differentiation from iPSC into NK cells. In addition, NK019 cells display typical NK cell characteristics, with CD19 target-specific cytotoxicity, enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and constitutively activated IL15 signaling. Furthermore, NK019 cells also show promising in vivo antitumor activity in a Raji NCG mouse model.
Here we report some characteristics of NK019 cells, a genetically engineered iPSC-derived NK cell therapy candidate. NK019 cells were differentiated from a modified human iPSC single-cell clone carrying 3 transgenes, including a Chimeric Antigen Receptor (CAR) targeting CD19, a modified CD16 and an IL15 molecule. The 3 transgenes maintain stable expression before and after differentiation from iPSC into NK cells. In addition, NK019 cells display typical NK cell characteristics, with CD19 target-specific cytotoxicity, enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and constitutively activated IL15 signaling. Furthermore, NK019 cells also show promising *in vivo* anti-tumor activity in a Raji NCG mouse model. In summary, we have engineered iPSC-derived NK cells as a promising clinical drug candidate for the treatment of B cell malignant lymphoma.
Summary/Conclusion: In summary, we have engineered iPSC-derived NK cells as a promising clinical drug candidate for the treatment of B cell malignant lymphoma.

PB1543 LIR-1 EDUCATES EXPANDED HUMAN NK CELLS AND DEFINES A UNIQUE NK CELL SUBSET WITH POTENT ADCC CAPACITY ATTRACTIVE FOR CANCER IMMUNOTHERAPY ACROSS HLA BARRIERS

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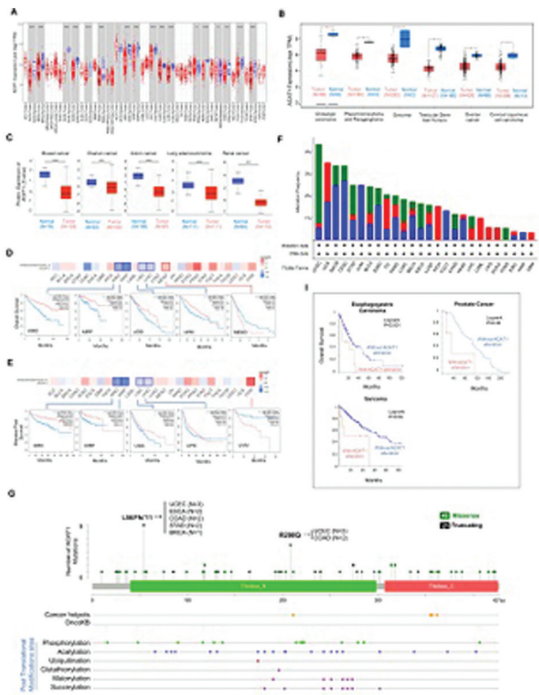
Background: NK cells are educated to stay responsive to cells with diminished HLA class I expression as a consequence of viral- or tumor-transformation. Inhibitory KIR and NKG2A receptors are known to educate human NK cells upon interaction with cells expressing their cognate HLA class I ligands.
Aims: To addressed if the inhibitory receptor LIR-1 (LILRB1/ILT2/CD85j) that is widely expressed on human NK cells and mediates inhibition via similar mechanisms as KIR and NKG2A, can mediate education and contribute to anti-tumor functions of NK cells.
Methods: NK cells were obtained from healthy donors and used resting, cytokine-activated or following ex vivo expansion. NK cell phenotype and activation were addressed using flow cytometry, while tumor cytotoxicity was assessed using ^{51}Cr-release assays with flow cytometry cell sorted NK cell subsets. Antibody-dependent cellular cytotoxicity was asses using the monoclonal antibody rituximab.
Results: LIR-1 can mediate NK cell education. This novel finding was exclusive to expanded NK cells and associated with high expression of granzyme B and DNAM-1, which both have been linked to NK cell education. Corroborating the rheostat education model, LIR-1 co-expression with an educating KIR further increased the responsiveness of expanded NK cells. Inversely, antibody masking of LIR-1 decreased the responsiveness. Using rituximab and a panel of CD20$^+$ target cells, LIR-1$^+$ expanded NK cells displayed high intrinsic ADCC that, in contrast to KIR and NKG2A, was not inhibited by HLA class I.
Summary/Conclusion: Overall, these findings define a unique NK cell subset attractive for adoptive cell therapy to treat cancer. Given that LIR-1 binds most HLA class I molecules, this subset may be utilized in both autologous and allogeneic settings to innately reject HLA class I$^-$ tumor cells as well as HLA class I$^+$ target cells when combined with anti-tumor antibodies. Further studies are warranted to explore the potential of this subset in clinical therapy.

PB1544 A PAN-CANCER ANALYSIS OF THE SUPPRESSOR ROLE OF ACETYL-COA ACETYLTRANSFERASE 1 IN TUMORS

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Background: Acetyl-CoA acetyltransferase 1 (ACAT1) is an enzyme to catalyze the condensation of two acetyl-CoAs to make acetoacetyl-CoA as well as the reverse reaction. Recently, the abnormal ACAT1 enzyme activity in diverse cancer cell lines was recently reported. Yet, the roles of ACAT1 in malignant progression have been incompletely understood so far.
Aims: The aim of this study was to investigate the function and significance of ACAT1 in tumors.
Methods: In the present study, gene expression analysis is completed through the TIMER2 and GEPIA2 web, based on the combination of the HPA, GTEx, and FANTOM5 datasets. The data of protein expression is acquired from the CPTAC dataset. The statistical significance of survival prognosis is analyzed by log-rank test. Genetic alteration analysis is accomplished by cBioPortal web.
Results: Aberrantly alleviated expression of ACAT1 was detected in multiple tumors at mRNA level compared with normal cells, such as bladder urothelial carcinoma (BLCA), head and neck squamous cell carcinoma (HNSC) *et al* (Figure 1A). After including the normal tissue of the GTEx dataset as controls, we further evaluated the expression difference of ACAT1 between the normal tissues and tumor tissues of PCPG, SARC, TGCT, *et al*. ACAT1 expression levels were significantly downregulated (tumor versus normal) in above types of tumor (Figure 1B, P<0.05). Similarly, the outcome of decreased protein level of ACAT1 (tumor versus normal) could be obtained (Figure 1C, P<0.001). Next, we investigated the correlation of ACAT1 expression with the prognosis of patients with different tumors. Stratified $ACAT1^{low}$ patients were observed with significantly shorter overall survival (OS) versus the $ACAT1^{high}$ group in kidney renal clear cell carcinoma (KIRC, P<0.001), kidney renal papillary cell carcinoma (KIRP, P<0.001), brain lower grade glioma (LGG, P=0.019) and liver hepatocellular carcinoma (LIHC, P=0.004) (Figure 1D). Likewise, the shorter disease-free survival (DFS) was shown in $ACAT1^{low}$ patients (Figure 1E). Intriguingly, $ACAT1^{low}$ group showed a better OS and DFS than $ACAT1^{high}$ group in mesothelioma (MESA, P=0.02) and uveal melanoma (UVM, P=0.017), respectively. Then, we observed the genetic alteration status of ACAT1 in different tumor samples of the TCGA cohorts. As shown in Figure 1F, the highest alteration frequency of ACAT1 (>7%) appears for patients with uterine tumors. The types, sites, and case number of the ACAT1 genetic alteration are further presented in Figure 1G. We found that missense mutation of ACAT1 was the main type of genetic alteration (N=48). Additionally, we explored the potential association between genetic alteration of ACAT1 and the clinical survival prognosis of cases with different types of cancer. The data of Figure 1H indicated a better overall survival in cases without altered ACAT1 compared with cases with ACAT1 alteration in variety of malignant, such as esophagogastric carcinoma (P<0.001), prostate cancer (P=0.03) and sarcoma (P=0.04).



Summary/Conclusion: Taken together, the present study was the first pan-cancer analysis on the role of ACAT1 in tumors. ACAT1 was down-regulated and conferred independent prognostic significance, highlighting the effectiveness and potential of ACAT1 as a potential target for future therapeutic strategies.

PB1545 THE IMPLEMENTATION OF BLOOD CANCER BIOBANKING IN GALWAY UNIVERSITY HOSPITAL

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Background: Galway University Hospital (GUH) is the designated cancer centre for the west of Ireland. It has strong links with the National University of Ireland, Galway (NUIG) for training and research. The Blood Cancer Network Ireland (BCNI) established a biobank in NUIG in 2017. With the collaboration of GUH and NUIG, biobanking of peripheral blood and bone marrow aspirate commenced in Galway that same year. Bone marrow procedures are carried out daily in GUH for the diagnosis of haematological disorders. After obtaining informed patient consent, additional bone marrow aspirate and peripheral blood samples for BCNI biobanking are collected at the patient bedside. These samples are transported to NUIG, then processed and stored in the BCNI biobank for future research.
Aims: To establish a blood cancer biobank for use in early phase clinical trials. To optimise sample collection and transport to ensure the integrity of the biobanked sample.
Methods: Implementation involved multidisciplinary collaborations including researchers, consultant haematologists, haematology registrars, advanced nurse practitioner and medical scientists at the BCNI, Galway and the Department of Haematology, GUH. Staff educational sessions were provided by the BCNI. Bone marrow procedures were performed by haematology registrars or the advanced nurse practitioner at GUH. Patient consent for biobanking was obtained prior to the bone marrow proceedure and informational leaflets provided to each patient. The medical scientist ensured that the bone marrow aspirate sample was adequate for the evaluation of the patient's haematological condition and then collected additional samples for biobanking. On return to the Haematology Laboratory the medical scientist arranged transport to the BCNI laboratory in a timely manner, to ensure sample integrity. Samples were processed and stored in the BCNI biobank at NUIG.
Results: Currently, 448 samples have been collected and stored in biobanks at BCNI sites across Ireland. Of these, 62 samples have been provided through the Department of Haematology, GUH. The majority of samples collected have been from patients with Acute Myeloid Leukaemia (AML).
Summary/Conclusion: The implementation of biobanking in GUH has been successful to date. Biobanking has now expanded to include the collection of samples from patients with Monoclonal Gammopathy of Undetermined Significance (MGUS). Additional educational sessions are required to increase awareness of biobanking to all relevant staff in GUH, in order to optimise the collection of samples. Improvement of quality control measures to ensure optimal transport and storage of cells from GUH to NUIG is also required.

Gene therapy, cellular immunotherapy and vaccination – Clinical

PB1546 REAL-WORLD DRUG USE AND COMPLEMENTARY AND ALTERNATIVE MEDICINES PRACTICE IN LYMPHOMA PATIENTS TREATED WITH CAR T CELLS IN A FRENCH UNIVERSITY HOSPITAL

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[1]Clinical Oncology Pharmacy Unit, [2]Hematology, [3]Public Health Department, Hospices Civils de Lyon, PIERRE BENITE Cedex, France

Background: Genetically engineered CAR T cells represent a breakthrough therapeutic innovation for lymphoma patients in second or more relapse. Despite clinical trials, there is a lack of data, especially about drug use and Complementary and Alternative Medicines (CAM). Such data are necessary to optimize patient care and safety and to improve knowledge about this recent population.
Aims: We performed a prospective real-world study to evaluate drug use and CAM practice in lymphoma patients treated with axi-cel, tisa-cel and brexu-cel.
Methods: Data from patients who received CAR T cells between May and November 2020, outside of clinical trials, were prospectively collected and analyzed. Drug use and CAM were collected during an interview between a hospital pharmacist and the patient the day before lymphodepletion chemotherapy and at month 3 after CAR T cell infusion.
Results: 25 successive patients were infused among them 17 patients with DLBCL and one with mantle cell lymphoma were analysed. Patients were treated by axi-cel (11), tisa-cel (7) and brexu-cel (1). Six of the 18 patients were excluded from the study in the first 3 months (1 death, 3 progressions, 2 refusals).
The male/female sex ratio was 1.25 (10/18), and mean age at infusion 59 years [range, 20-77 years], with 100% of the patients with ECOG performance status ≤ 1. Median number of prior therapies was 2 [range, 2-4]. Median Charlson score was 2 [range, 0-5]. Half of the patients were unemployed or retired (n=9) at diagnosis. Some patients were polymedicated (n=9), using ≥ 5 daily prescribed drugs; the most frequent classes were anti-infectious (n=13), anti-ulcer drugs (n=10), cardiovascular drugs (n=4) as well as thromboprophylaxis agents (n=3). 16 patients used analgesics (prescription or self-medication). Psychotropic drugs were taken by 5 patients (28%) to manage stress, anxiety, sleep disorders or depression; 16/18 patients used at least one CAM with a mean of 3.3 [range, 1-12] (Table). No changes of drug use and CAM were observed through the first 3 months following the infusion of CAR T.

Type of CAM	Nb of patients using at least 1 CAM
Natural products	**16**
Herbal medicine	7
Essential oils	7
Vitamins and minerals	7
Other dietary supplements	6
Homeopathy	**4**
Mind and body practice	**5**
Massage therapy	4
Osteopathic manipulation	3
Acupuncture	2
Traditional healers	**4**
Magnetizer	4
Uthotherapy	2
Reason for using CAM	**Nb of patients using at least 1 CAM**
To manage symptoms and side effects	**11**
Pain	6
side effects of chemotherapy	5
asthenia	5
stress and anxiety	3
To improve health and treatment	**7**
to improve health status	5
to improve well being	4
to boost immunity	5
to drain organs	3

Summary/Conclusion: This study provides one of the first datasets on drug use and CAM in lymphoma patients treated by CAR T cells in real-life. Despite CAR T cells bring an innovative and expensive strategy, lymphoma patients continue using CAM to manage health disorders and to boost immunity as other cancer patients treated with chemotherapy. Such results should led us to investigate patients' representations about innovative anticancer drugs.

Hematopoiesis, stem cells and microenvironment

PB1547 SECONDARY HYPERPARATHYROIDISM AND ERYTHROPOETIN-STIMULATING-AGENT REFRACTORY ANEMIA: A CASE OF REVERSIBLE TRANSFUSION DEPENDENCE

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Background: Anemia is a universal complication of End Stage Renal Disease (ESRD). Erythropoiesis-stimulating agents (ESAs) have fundamentally changed the treatment of anemia of ESRD, greatly decreasing transfusion dependence. However, ESA-resistant anemia is not well studied and a difficult condition to manage. Among the most frequent causes of ESA-resistant anemia is secondary hyperparathyroidism (SHP), which is associated with bone marrow remodeling and bone marrow fibrosis. Treatment goals of SHP are centered on goal calcium, phosphorus and parathyroid hormone (PTH) levels determined largely by consensus, and not pathophysiology including hematologic effects.
Aims: Here we describe a patient with ESRD, SHP with reversible bone marrow changes and transfusion-dependent anemia, as well as descriptive findings of bone marrow changes in patients with anemia and ESRD in our center.
Methods: Using the EMR, the patient's data including demographics, progress notes, laboratoy values, and bone marrow findings were extracted. Subsequently, the EMR was interrogated to reveal all patients with anemia and ESRD, who had a bone marrow biopsy at out center. Data including demographics, laboratory values, bone marrow findings, and medications were extracted. Data was presented descriptively.
Results: A 67-year-old male with ESRD secondary to hypertension and type 2 diabetes was referred to our Hematology clinic for anemia of ESRD. He was receiving epoeitin 20,000 three times weekly. He was transfusion-dependent to maintain a hemoglobin of 6.3 g/dL, with a concomitant PTH of 400.5 pg/mL. Calcium and phosphorus were normal. Bone marrow biopsy revealed focal areas of bone marrow remodeling and reticulin fibrosis. Fluorescence in situ hybridization studies for myelodysplastic syndrome were negative, as were thyroid studies, serum protein electrophoresis (SPEP), and free light chain ratio. In conjunction with his Nephrologist, treatment of his SHP was optimized. His initial regimen was calcitriol 0.25 mcg once daily and calcium acetate 667 mg three times daily. Subsequently, cinacalcet 30 mg twice daily was added and calcium acetate was replaced with sevelamer 1600 mg three times daily. Following these changes, his hemoglobin remained stable in the range of 8-9 g/dL. He became transfusion independent, despite only a modest reduction in PTH to 311.2 pg/mL. Repeat bone marrow biopsy revealed no bone marrow remodeling or reticulin fibrosis.
Bone marrow findings for all patients in our center with ESRD and anemia are summarized in Table 1. The range of PTH for patients with bony remodeling was 183-16161.9 pg/mL versus 90.8-3283 pg/mL for those without bony remodeling. The range of PTH for patients with fibrotic changes was 183-2487 pg/mL versus 90.8-16161.9 pg/mL for those without fibrotic changes.

Table 1: Descriptive Bone Marrow Findings of Patients with ESRD and Anemia Versus PTH Levels

Age	Sex	Race	Ethnicity	Hemoglobin (g/dL)	PTH (pg/mL)	Bone Marrow Fibrosis	Bone Marrow Remodeling
32	F	Black	Non-Hispanic	7.2	2763	Marked Fibrosis	Yes
53	F	Other	Hispanic or Latino	8.6	207.8	None	No
20	F	Black	Non-Hispanic	8.2	246.7	None	No
47	F	White	Hispanic or Latino	8.1	156.4	None	No
74	M	White	Non-Hispanic	9.2	121	None	No
52	M	Black	Non-Hispanic	8.9	116.8	None	No
33	F	White	Hispanic or Latino	8.3	183.2	None	No
63	M	Black	Non-Hispanic	8.3	1043	None	Yes
29	F	Other	Hispanic or Latino	7.5	90.8	None	No
70	F	Black	Non-Hispanic	9.4	777.7	None	No
37	M	Black	Non-Hispanic	8.6	340.4	None	No
67	F	Black	Non-Hispanic	9.6	437.6	None	No
54	M	Asian	Non-Hispanic	8.1	329.5	None	No
67	M	Black	Non-Hispanic	6.7	400.5	Reticulin Fibrosis	No
13	F	Black	Non-Hispanic	6.6	16161.9	None	Yes
13	F	Black	Non-Hispanic	7	2487	Marked Fibrosis	Yes
45	M	White	Hispanic or Latino	6.8	452.4	None	No
36	M	Unknown	Unknown	8.4	183	Reticulin Fibrosis	Yes
57	F	Black	Non-Hispanic	8	127.3	None	No
82	M	White	Hispanic or Latino	8.3	162.8	none	No
64	M	Black	Non-Hispanic	6.6	228.3	None	Yes
56	M	White	Non-Hispanic	7.3	76.8	None	No
56	M	White	Non-Hispanic	8.4	504.7	None	No
20	M	White	Hispanic or Latino	8.6	3283	None	Yes
54	F	White	Hispanic or Latino	6.7	171.9	None	No

Summary/Conclusion: SHP is an increasingly defined cause of ESA-resistant anemia in ESRD. Here we describe a patient with modestly elevated PTH and reversibility of his transfusion-dependent anemia and bone marrow changes following optimized management of his SHP. The degree of reversible ESA-resistant anemia and transfusion dependence in the setting of a PTH elevation to 400.5 in this case is surprising. The great variability in PTH levels of both affected and unaffected patients (i.e. bone marrow changes) presented here indicates the relationship between SHP and anemia is complex. A single level for the whole dialysis population is not appropriate. It may be reasonable to attempt a trial of more aggressive management of SHP in patients with difficult to manage ESA-resistant anemia and only mild-moderate PTH elevation.

PB1548 A POSSIBLE NEW MUTATION IN DNMT3A AS A MARKER OF CLONAL HEMATOPOIESIS

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Background: DNMT3A is one of the most frequently mutated genes in adult hematological neoplasms, including myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and myeloproliferative neoplasms (MPN). Probably, the effect of mutations in this gene on disease progression is to destabilize the tetrameric form of DNMT3A and reduce the enzyme activity. Here we report the unexpected discovery of a new mutation in DNMT3A at the Fsp4HI restriction site (2:25234469 - 2:25234473), which was also located in the DNA sequence we examined during the development of a test to identify the most common R882H mutation in DNMT3A using the Fsp4HI restrictase.
Aims: This study was aimed to investigate the possibility of creating a simple restriction test system to diagnose the R882H mutation and determine the possible clinical significance of the new mutation.
Methods: From September 2019 to December 2020 we consecutively recruited 81 patients (43 male and 38 female) with the median age is 57 years (18-87) diagnosed at the Clinic of Rostov State Medical University and City hospital No 7 (Rostov-on-Don), with the following diagnoses: MDS = 31, OML = 30, MPN = 19 (chronic myeloid leukemia (CML) = 17, primary myelofibrosis (PM) = 2). We developed a specific restriction test using Fsp4HI restrictase and original primers. The sequence after PCR contained two Fsp4HI-recognition sites - the target site for R882H and the non-target site in positions (2:25234469 - 2:25234473).
Results: Despite the expected high frequency of R882H (12 to 14% according to different sources), we did not find this mutation in our study. But we did find 5 patients with a mutation in a non-targeted restrictase recognition site, which caused a length-specific unique bend on electrophoresis. We did not find mutations in this region by searching databases (e.g., COSMIC, GenBank), so we tend to believe that the DNMT3A region (2:25234469 - 2:25234473) contains a new mutation, which we plan to confirm by sequencing in the next stage of the study. We found this mutation in 5 (6,17%) patients from our sample (AML = 1, MDS = 1, CML = 2, PM = 1) with clonal hematopoiesis together with other mutations in JAK2 (V716F), BCR-ABL and FLT3/TKD, but not MPL (W515L, W515K).
Summary/Conclusion: During the development of a test system to detect the R882H mutation, we discovered a possible new mutation in the region (2:25234469 - 2:25234473) DNMT3A, which is a common marker for clonal hematopoiesis and is associated with other mutations and requires to determine the exact location and further research as a possible clinical marker.

PB1549 SPONTANEOUS APOPTOSIS IN THE CULTURE OF BONE MARROW`S MESENCHYMAL STROMAL CELLS

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Background: Mesenchymal stromal cells (MSC) are one of the cell lines for potential use in the treatment of a number of hematological and non-hematological diseases. The basis of successful cultivation is the study of factors influencing the activity of culture's growth. It is known that apoptosis processes can affect the growth parameters of MSC. Apoptosis is programmed cell death resulting from the implementation of its genetic program in response to external signals. One of the universal methods for detecting apoptotic cells is the analysis of the lipid composition of their membrane. Phosphatidylserine molecules are found in large quantities on the surface of the cell membrane at the stage of apoptosis. It can be detected by flow cytometry. Currently, the method of studying programmed cell death by staining cells with annexin 5 conjugated with fluorescein isothiocyanate (AnxV-FITC) and vital DNA dyes (7-aminoactinomycin D (7-AAD) is widely used.
Aims: To assess the relationship between the growth activity of MSC cultures and the number of cells at the stage of apoptosis.
Methods: MSC were obtained from the donors bone marrow (n = 15), whose age ranged from 24 to 46 (median, 26.5) years. Cultivation of MSC was carried out on the surface of plastic flasks under conditions of 5% carbon dioxide at a temperature of 37 ° C. When confluent growth of cultures was achieved, the cells were detached from the plastic using a solution of trypsin. The growth activity of cell cultures was determined by the time the cells of primary seeding (PO) reached the confluent monolayer and the period of cell doubling at passage 1 (P1). Apoptotic cells were distinguished from necrotic cells by spontaneous binding to AnxV-FITC and lack of 7-AAD staining (AnxV-FITC+ 7-AAD-) by laser flow cytometry using a BD FACS Canto II analyzer.
Results: The relative number of MSC with the AnxV-FITC+ 7-AAD- characteristic in the primary culture ranged from 1.3 to 7.9 (median 2.3)% of the total number of MSC, P1 - from 1.7 to 6.0 (median 3.8)%. The period of reaching of confluent monolayer for the primary culture varied from 336 to 528 (median - 456) h, the time of cell doubling on P1 - from 53.4 to 63.3 (median - 58.9) h. A direct relationship between the number of AnxV-FITC+ 7 -AAD- MSC and the time the cells reached the confluent monolayer was found (Pearson's coefficient, r = 0.73). Also a direct correlation between the number of MSC with the characteristic AnxV-FITC+ 7-AAD- and the cell doubling time at P1 was determined (r = 0.83). With increasing of number cells with markers of apoptosis, the longer it takes to achieve confluent growth.
Summary/Conclusion: The number of apoptotic MSC spontaneously binding to AnxV-FITC and unstained with 7-AAD has a direct effect on the activity of culture growth.

Hodgkin lymphoma - Clinical

PB1550 LATE TOXICITIES IN CLASSICAL HODGKIN LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA SURVIVORS AND LONG-TERM MONITORING: A SERIES OF SYSTEMATIC REVIEWS OF THE FONDAZIONE ITALIANA LINFOMI

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Background: In the current years it is estimated that cancer survivors are more than 16 million and it is predicted to reach 22 million by 2030.The prevalence of long-term lymphoma survivors is steadily increasing, and includes mainly histotypes for which biological knowledge and treatments obtained better results. Up today there is a paucity of data on late toxicities affecting lymphoma survivors, thus we still need more data from literature to follow late sequelae of these patients and to set up an organized and evidence based follow-up strategy.
Aims: Researchers belonging to the Fondazione Italiana Linfomi drawn a series of systematic reviews with the aim to:i) evaluate available data and develop homogeneous indications for lymphoma survivors' monitoring using a systematic approach; ii) find a balance between the unmet medical need and the sustainability of healthcare system.
Methods: The research work was carried out by a multi-disciplinary team of 16 researchers of the Fondazione Italiana Linfomi under the methodological supervision of 3 Researchers of the Istituto di Ricerche Farmacologiche "Mario Negri", in Milan. The systematic reviews focused on six topics: cardiotoxicity, secondary cancers, endocrine-metabolic sequelae, fertility and neurological/ cognitive toxicities, healthy lifestyles. The following specific questions were analyzed, considering the population of classical Hodgkin lymphoma (cHL) and Diffuse large

B-cell lymphoma (DLBCL) survivors treated at adult age (≥ 18 years old): i) incidence of the long-term toxicity; ii) comparison with more recent therapies (e.i. modern radiation therapy); iii) best monitoringof long-term sequelae. The search was conducted on 3 bibliographic databases (PubMed, Embase and the Cochrane Library) with also hand searching up to December, 2020. Selection process and data extraction were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines.
Results: Six independent systematic reviews were conducted according to the topics of research. A global number of 170 full text papers resulted eligible for data extraction and were included in the final sample. They concerned: cardiotoxicity (n=22), secondary cancers (n=21), endocrine-metabolic sequelae (n=9), fertility (n=46), neurologic and cognitive toxicity (n=62), healthy lifestyles (n=10). The incidence for cardiovascular disease, endocrine-metabolic sequelae, secondary cancers, neurological and anxiety and depression, infertility were calculated and related to risk factors. The optimal detection and monitoring was found out for: i) early left ventricular ejection fraction dysfunction, coronary artery disease, valvular heart disease; ii) secondary acute myeloid leukemias/myelodisplastic syndromes and solid tumors; iii) metabolic syndrome, thyroid, gonadal, and mineral bone disorders; iv) peripheral neuropathy, fatigue, cognitive impairment, anxiety and depression. Fertility preservation and correction of unhealthy lifestyles were also examined. The possible use of Survivorship Care Plans was introduced.
Summary/Conclusion: The final documents could be a reasonable bridge from evidence to decision in order to improve the clinical practice and customize the general follow-up approach of cHL and DLBCL survivors. Data emerged will suggest also direction of future research.

PB1551 RISK FACTORS FOR THE OCCURRENCE OF BLEOMYCIN-INDUCED LUNG TOXICITY IN THE ERA OF POSITRON EMISSION TOMOGRAPHY.

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Background: Bleomycin is a major antimitotic agent in the first-line treatment for Hodgkin's lymphoma. The main limitation of its use is its pulmonary toxicity.
Aims: The objectives of this study are to find out the risk factors for the occurrence of bleomycin-induced lung toxicity in patients with Hodgkin's lymphoma, on the other hand to determine if positron emission tomography scan is a reliable means of early detection of this toxicity.
Methods: This is a retrospective study conducted in the clinical haematology department of Mohammed V Military Instruction Hospital of Rabat in Morocco. All patients with Hodgkin's lymphoma and treated with a bleomycin based chemotherapy were included.
Results: Among 124 patients included in the study, 18 (14.5%) patients experienced bleomycin-induced lung toxicity. On multivariate analysis, smoking (p: 0.038) and the use of the ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) compared to the escalated BEACOPPe (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) regimen (p: 0.018) were statistically significant risk factors.
After 2 and 4 courses of therapy, the positron emission tomography was able to predict the occurrence of bleomycin-induced lung toxicity before the appearance of clinical symptoms in 43.7 % and 12.5% of patients, respectively.
Summary/Conclusion: Researches to identify risk factors for the development of bleomycin-induced lung toxicity are crucial to reduce toxicity in the treatment of Hodgkin's lymphoma. However, 2- and 4-cycles positron emission tomography scans cannot be considered as a reliable means of early detection of this toxicity.

PB1552 PROGNOSTIC FACTORS OF WORSE SURVIVAL IN NEWLY DIAGNOSED ADVANCED-STAGE HODGKIN LYMPHOMA IN TAIWAN: A NATIONWIDE RETROSPECTIVE STUDY

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Background: While the majority of Hodgkin lymphoma (HL) patients are curable, some patients with advanced disease still relapse and have poor prognosis. Although the International Prognostic Score (IPS) or a modified IPS were developed to predict prognosis, therapeutic and imaging modalities of HL have improved over time and their impact among different risk groups has diminished nowadays. It is crucial to identify and assess new prognostic factors in advanced HL patients.
Aims: To identify and assess the prognostic factors for newly-diagnosed HL (NDHL) patients with stage III/IV in Taiwan.
Methods: This study used Taiwan's National Health Insurance Research Database and the Taiwan Cancer Registry. All NDHL patients with stage III/IV who underwent front-line therapy with ABVD or ABVD-like regimens (the standard of care) between 2009 and 2016 enrolled. We randomly split these patients into the development and validation samples by a ratio of 80:20. Cox proportional hazards models were used to identify prognostic factors for overall survival (OS) and time to next treatment (TTNT, as a surrogate for progression-free survival, PFS). Factors with a p-value <0.25 in the univariable model were included in the multivariable model. In the multivariable model, factors with a p-value <0.05 were considered significant, and adjusted hazard ratios (aHRs) with 95% confidence interval (CI) were estimated. Additionally, we used the time-dependent area under the receiver operating characteristic curve (AUC) to assess the model performance.
Results: A total of 459 NDHL patients with stage III/IV were included. At a median follow-up of 4.7 years, the OS was 76%. The median TTNT was 5.1 years. There were 359 and 100 patients in the development and validation samples, respectively. Age (45-59 years: aHR 2.4 [95% CI 1.2-4.7], 60 years or older: aHR 9.9 [5.9-16.8]; both compared to age <45) and extra-nodal disease (aHR 1.8 [1.1-2.9]) were significant factors associated with a shorter OS in the final model. The mean time-dependent AUC was 0.82 in the development sample and 0.81 in the validation sample. With regard to disease progression, patients with older age (45-59 years: aHR =1.2 [0.8-1.9], 60 years or older: aHR 2.3 [1.6-3.3]) and extra-nodal disease (aHR 1.5 [1.1-2.1]) also had significantly shorter TTNT. The mean time-dependent AUC was 0.61 in the development sample and 0.65 in the validation sample.
Summary/Conclusion: In NDHL patients with stage III/IV, older age and extra-nodal disease were important prognostic factors for both shorter OS and shorter TTNT. Furthermore, the discrimination ability of the OS model was excellent. Since laboratory data were not available in the present study, further studies that evaluate all HL-related clinical factors may be required to validate the findings and provide a more comprehensive evaluation.

PB1553 BRENTUXIMAB VEDOTIN IN COMBINATION WITH NIVOLUMAB, DOXORUBICIN, AND DACARBAZINE IN NEWLY DIAGNOSED PATIENTS WITH ADVANCED HODGKIN LYMPHOMA (SGN35-027, TRIAL IN PROGRESS)

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Background: Brentuximab vedotin (BV, ADCETRIS®) is approved for the treatment of adults with treatment-naïve Stage III or IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) (Connors 2017). Nivolumab is approved for treatment of adults with relapsed/refractory cHL. Both agents have been well tolerated with promising activity when combined with multiagent chemotherapy. The combination of BV plus nivolumab was evaluated as a frontline treatment option for patients (pts) with cHL who are over 60 years and ineligible for or declined conventional combination chemotherapy (Yasenchak 2020). The ongoing study reported an overall response rate (ORR) of 82% in 11 pts and appears well tolerated in this population. In another trial in 93 pts in the first salvage setting, the combination produced a 67% complete response (CR) rate (Herrera 2018, Moskowitz 2019) and the majority of pts were able to undergo subsequent stem cell transplant. It is reasonable to expect that the combination of BV, nivolumab, A, and D (AN+AD) will result in high response rates and be well tolerated, with potentially less toxicity relative to A+AVD.

Aims: Part A will evaluate the efficacy and safety of A+AVD when administered with growth factor prophylaxis in pts with Stage III/IV cHL. Part B will evaluate the combination of AN+AD in pts with Stage I or II cHL with bulky mediastinal disease or Stage III or IV cHL. Part C will evaluate the efficacy and tolerability of AN+AD in pts with Stage I or II cHL without bulky disease. The primary objective of Parts B and C is to estimate the CR rate at end of treatment (EOT) in pts with treatment-naïve cHL.
Methods: SGN35-027 (EudraCT 2020-004027-17) is an open-label, multiple part, multicenter, phase 2 clinical trial. Approximately 240 pts will be enrolled in this study: approximately 40 in Part A, 50 in Part B, and 150 in Part C. Part A has completed enrollment, and Part B is fully enrolled. Pts in Parts B and C will be treated with BV 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m^2, and dacarbazine 375 mg/m^2, administered separately by IV infusion on Days 1 and 15 of each 28-day cycle. Pts in Part B will receive up to 6 cycles of treatment; pts in Part C will receive 4 cycles. Efficacy will be assessed by PET/CT scans at Cycle 2 and EOT; disease response and progression for Parts B and C will be assessed using the LYRIC modification of the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2016). Pts will be followed for disease progression and overall survival for 5 years. Enrollment is ongoing in the US, with plans for rest-of-world expansion for Part C.
Results: N/A
Summary/Conclusion: N/A

PB1554 OUTCOMES AFTER INITIAL REFUSAL OF CURATIVE TREATMENT IN PATIENTS WITH HODGKIN LYMPHOMA IN BRITISH COLUMBIA

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Background: Classical Hodgkin lymphoma (cHL) is considered a highly curable cancer. With standard combination chemotherapy regimens, long-term survival exceeds 95% for limited-stage and 85% for advanced-stage patients. Despite these excellent outcomes some patients delay or decline conventional treatment for cHL. We retrospectively assessed the impact of initial treatment refusal on outcomes of patients with cHL in British Columbia (BC).
Aims: We retrospectively assessed the impact of initial treatment refusal on outcomes of patients with cHL in British Columbia (BC).
Methods: Using the BC Cancer Lymphoid Cancer Database, we identified all patients aged 18-70 diagnosed between 1st Jan 1999- 31st Dec 2020 that had documented treatment refusal at initial presentation ('refusers' defined as not receiving or delaying treatment > 16 weeks). We identified a control cohort (min. 3 controls/refuser) treated within 8 weeks of diagnosis, matched for age, stage, diagnosis date within 3 years, and blinded for outcome. All patients had centrally reviewed biopsies and were treated with ABVD or ABVD-like regimens +/- radiotherapy if appropriate. Patient and disease characteristics at baseline and at time of treatment were analyzed with Chi-squared test and one-way ANOVA test. The Kaplan-Meier method was used to assess progression-free survival (PFS) and overall survival (OS), and statistical significance between groups was determined using the log-rank test.
Results: We identified a cohort of 15 patients who initially refused treatment and 47 matched controls. The control cohort was well-matched, with no statistically significant differences in baseline characteristics (age, sex, Ann Arbor stage, B symptoms, International Prognostic Score (IPS) score, ECOG PS, and disease bulk) between groups. The most common reason for initial treatment refusal was to pursue alternative therapy (73%). 13 of 15 refusers eventually accepted treatment (mean time to treatment 76 weeks [range 26-214] vs. 5 weeks [range 1-8] for controls, $p < 0.001$). At time of treatment, the proportion of refusers with advanced-stage disease increased from 20% to 62% ($p = 0.03$) and had an associated alteration of treatment plan, and 62% of patients developed higher risk disease with increased IPS score ($p = 0.02$). At median follow-up of 5 years (0.4-21 years) for all living patients, estimated 5-year PFS was 65% vs 84%, and 5-year OS was 93% vs 98% for refusers and controls respectively. With extended follow up, 13% of refusers (1 late death at 8 years) compared to only 4% of controls died of cHL specifically.
Summary/Conclusion: This study highlights the impact of treatment refusal in this highly curable malignancy. Initial refusal of treatment is associated with progression of stage, worsening prognostic score, escalation to more prolonged treatment than required at diagnosis, and increased risk of death from cHL. This analysis may help to provide guidance to counselling physicians, as well as inform patients who may be considering alternatives to standard of care for cHL.

PB1555 RETROSPECTIVE STUDY TO DESCRIBE TREATMENT PATHWAYS, OUTCOMES, AND RESOURCE USE IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA (B-HOLISTIC): RESULTS FROM THE SUBGROUP ANALYSIS OF PATIENTS FROM CHINA

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Background: Classical Hodgkin Lymphoma (cHL) constitutes 95% of all reported cases of HL and is often cured with chemotherapy. Approximately 10% to 20% of the patients progress to relapsed/refractory cHL (RRHL), requiring intense treatment with chemotherapy and hematopoietic stem cell transplantation (SCT). Differences in clinicopathological characteristics based on geographical and socioeconomic status are reported previously.
Aims: In this subgroup analysis of the B-CD30+ HOdgkin Lymphoma International Multicenter Retrospective Study of Treatment PractIces and OutComes (B-HOLISTIC) (NCT03327571) study, we report the treatment pathways and outcomes in patients from China with cHL and RRHL.
Methods: This retrospective, multicenter, observational study retrieved data from the medical records of patients (≥18 years) with a diagnosis of stage IIb-IV cHL between January 1, 2010 and December 31, 2013 who have received frontline treatment with chemotherapy with or without radiotherapy (Group 1) and of patients with a diagnosis of RRHL (Group 2). Patients who progressed from cHL to RRHL during the study period were included in both the groups. The primary end point was progression-free survival (PFS) in patients with RRHL and the secondary end points were overall survival (OS), best clinical response, and incidences of adverse events (AEs). Survival analysis (OS and PFS) was performed using Kaplan Meier method, and the differences in baseline factors were adjusted with multivariable analysis.
Results: In all, 93 and 34 Chinese patients were enrolled in the cHL and RRHL groups, respectively (27 patients in the cHL group progressed to RRHL and were included in both the groups). The median age (range) of patients at diagnosis in the cHL group was 33 (18-88) years, and 62/93 (66.7%) patients were males. The distribution of clinical stage (Ann Arbor staging) at cHL diagnosis was as follows: stage II, 18/93 (19.4%); stage III, 43/93 (46.2%); stage IV, 32/93 (34.4%). All patients in the cHL group received first-line chemotherapy, with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD; 78/93 [83.9%]) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone (BEACOPP; 17/93 [18.3%]) being the most prevalent chemotherapeutic regimen. A total of 12/93 (12.9%) patients in the cHL group also received consolidation radiotherapy. The median age (range) at diagnosis for patients in the RRHL group was 34 (20-73) years, and 20/34 (58.8%) were males. At RRHL diagnosis, intensive second-line chemotherapy was used in 31/34 (91.2%) patients: the common regimens used in second line were BEACOPP (5/34 [16.1%]), cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (5/34 [16.1%]), and ABVD (4/34 [12.9%]). Of the 34 patients with RRHL, 28 (82.4%) were eligible for hematopoietic SCT at relapse/refractory diagnosis; Among the 34 patients, 13 patients (38.2%) patients underwent autologous SCT and 1 patient underwent allogenic SCT. Median PFS (95% confidence interval) for the RRHL group was 9.53 (3.84-20.43) months, with estimated 1-, 3-, and 5-year PFS rates of 43%, 29.8%, and 29.8%, respectively (Table 1). Median OS was not reached for both the groups. AEs were reported by 67/93 (72%) patients with cHL and 31/34 (91.2%) patients with RRHL.

Table 1. Clinical Outcomes for Chinese Patients

	cHL (n=93)[a]	RRHL (n=34)
Best clinical response, n (%)[b]		
Complete remission	50 (53.8)	6 (17.6)
Partial remission	27 (29)	16(47.1)
Unconfirmed complete remission	3 (3.2)	0
Stable disease	6 (6.5)	3 (8.8)
Progressive disease	6 (6.5)	8 (23.5)
Unknown[c]	4 (4.3)	1 (2.9)
PFS % (95% CI)		
1-year	81.6 (71.7, 88.3)	43 (25.6,59.3)
3-year	61.8 (49.9, 71.7)	29.8 (15, 46.1)
5-year	55.1 (42.3, 65.8)	29.8 (15, 46.1)
OS, % (95% CI)		
1-year	98.8 (91.5, 99.8)	96.9[d] (79.8, 99.6)
3-year	87.4 (77.1, 93.3)	77.9[d] (59.1, 88.8)
5-year	80.5 (68.6, 88.3)	66.5[d] (46.4, 80.5)

Abbreviations: cHL, classical Hodgkin lymphoma; CI, confidence interval; OS, overall survival; PFS, progression-free survival; RRHL, relapsed/refractory cHL.
[a] 27 patients with an initial diagnosis of cHL progressed to RRHL during the study period and were included in both the groups. [b] Best clinical response after completion of first-line treatment. [c] Unknown: there is no entry in the medical record or patient chart relating to an item as confirmed by the site. [d] OS from diagnosis of cHL.

Summary/Conclusion: Subgroup analyses of Chinese patients from the B-HOLISTIC study reveal that the PFS remains low in patients with RRHL in real-world clinical practice in China. This emphasizes the unmet need for novel targeted therapies to improve survival in patients with RRHL.

PB1556 THE PARTICULARITY OF MANAGEMENT OF PEDIATRIC HODGKIN LYMPHOMA IN TUNISIA: MONOCENTRIC STUDY

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Background: The pediatric Hodgkin lymphoma (PHL) treatment particularity is to guarantee the efficacy with toxicity reduction. This was the objective of the first European protocol of PHL treatment: Euronet-PHL-C1. It consisted of the early FDG-PET response assessment. The indication for radiotherapy is based on early response evaluation by TEP scan. In Tunisia, the Euronet-PHL-C1 protocol has been used since 2012 with some modification because of the difficulty of the FDG-PET access. So, the early response assessment was based on whole body CT scan and the radiotherapy was maintained.
Aims: The objectives of the study were to analyze the characteristics of PHL and the therapeutic response.
Methods: A retrospective study was involving 49 patients, with PHL, treated with Euronet-PHL-C1 protocol modified, in the clinical hematology department of Aziza Othmana Hospital of Tunis, between 2013 and 2019.
Results: The median age was 13 years with a sex ratio of 1.59. Twenty-two children had less than 2 lymph nodes regions affected. Thirty-two patients didn't have B symptoms. Ten had a large mediastinum in the chest x-ray. Thirty- two had an ESR≥ 30mm. Localized stages represented the majority (67%). Twenty-two had a CHIPS score between 1 and 4 (i.e. 24%). Nine patients belonged to therapeutic groups TG1 group, 24 to TG2 group and 16 to TG3 group. All the three TG received two OEPA cycles. The TG2 and TG3 received after the both OEPA courses, 2 and 4 COPDAC courses, respectively. The radiotherapy of in-volved fields (IF) is done for all TG. The assessment is based on whole body CT scan. The overall response rate (ORR) after 2 OEPA courses was 100%. The ORR after 2 COPDAC regimens was 95%. The ORR after 4 COPDAC regimens was 100%. Forty among the 49 patients received a radiotherapy of involved fields. Four patients (8%) had a pro-gressive disease: two during the chemotherapy and two before the radiotherapy. These patients belonged to the high risk relapse group of the Euronet-PHL-C1 protocol (RG3) and were in indication for treatment intensification. The Overall survival rate (OS), the event free survival (EFS) and the relapse free survival (RFS) were respectively, 95%, 80% and 99%.
Summary/Conclusion: PHL had a good prognosis. To maintain these excellent results and to limit the long-term consequences by using the FDG-PET to omit the radiotherapy.

PB1557 LONG-TERM OUTCOME OF HODGKIN'S LYMPHOMA CASES IN A POPULATION-BASED CANCER CENTER

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Background: Background: Hodgkin's lymphoma (HL) is a common malignancy among a young population with a reported improved outcome. There has been major changes in the mamagement stratgies of HL over the past two decades; less chemotherapy and smaller RT filed and dosing. In the current study, we report the long-term outcome in a population-based cancer center after adotping the changes in management in our HL cases.
Aims: The aim of the study is to monitor the long-term outcomes of treatment strategies adopted from international studies thar were implemented in a community-based cancer senetr
Methods: Data from consecutive sets of patients diagnosed with HL between 2000-2016 were collected by ERIC and subjected to detailed statistical analysis. Collected variables included: demographics, stage at diagnosis, treatment, treatment response, and death. Early favorable-early stage HL cases were generally treated with abbreviated ABVD courses (2 cycles) followed by involved-field radiotherapy (IFRT). Unfavorable-early stage HL cases were treated with four courses of ABVD and IFRT (20 Gry). 6 courses treated advanced stage HL cases of ABVD.
Results: 186 cases are included in this analysis. The majority were males, representing 57.5% of the cases. The majority are adolescents and young adults, between 20-40 years, with a median age of 31. The most common histology is Nodular sclerosis, representing 59% of all diagnosed cases. The median progression-free survival (PFS) among the entire group is 159 (CI:144-175) months. The median survival among the early stages HL is 160(CI:8-144) months compared to 150 (12_125) months in the unfavorable early stages(P value=0.5). The advanced favorable HL PFS is 99 (CI:85-114), compared to 150 (12-125) months among the unfavorable group (p=0.06)

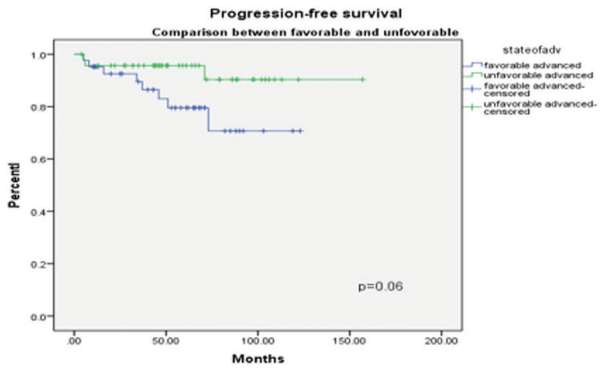


Figure 1: PFS among the advanced cases, comparing favorable vs. unfavorable.

Summary/Conclusion: We report the long-term survival among the local HL cohort from Kuwait. The cohort achieved long-term survival compared to the historical data. There is no difference between the favorable and the unfavorable early stages HL cases. The outcome represents a non-inferiority in the early favorable patients treated with short courses of ABVD and limited RT. There is no difference in survival among advanced stages HL; favorable vs. unfavorable. However, there a trend of lower survival among the favorable group. This finding warrants longer follow-up.
Key-words: Hodgkins lymphoma' outcome, lon-term

PB1558 HODGKIN'S LYMPHOMA IN ADOLESCENTS TREATED WITH ABVD

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Background: The standard treatment for adolescent patients with Hodgkin lymphoma (HL) is not well defined, especially in the choice between pediatric and adult protocols.
Aims: To compare the risk factors and the therapeutic results of adolescents and young adults with HL treated with ABVD.
Methods: 98 patients treated in our department between 2000 and 2015 were analyzed: 33 adolescents aged between 15 and 21 years, and 65 young adults aged between 22 and 39 years. All patients received the

ABVD protocol as initial chemotherapy, followed in 65 (66.3%) by radiotherapy. We compared the characteristics of patients of the two populations using Fisher's exact test. Survival was estimated using the Kaplan and Meier method, and compared by the log rank test. A Cox proportional hazards model regression was used to assess prognostic factors in adolescent patients.
Results: Histologic type 2 as well as hypoalbuminaemia were more common in adolescent patients (P = 0.05, P = 0.02 respectively). The incidence of other risk factors is not significantly different between the two populations. With a median follow-up of 67 months, overall survival (OS) and 5-year event-free survival (EFS) rates are of 79% and 72% for all the patients. The overall complete remission rate (CR) is 87.8%, 84.8% for adolescents and 89% for young adults (P = 0.53). The log rank test showed no significant difference between the two age groups in OS (P = 0.31) or EFS (P = 0.51). At 5 years, the estimate of OS and EFS are of 77% and 74% for young adults, 73% and 68% for adolescents, respectively. After Cox model analysis, two factors were important for the prognosis of adolescent patients: massive tumor involvement (P = 0.008) and extranodal involvement (P = 0.04).
Summary/Conclusion: The prognosis and risk factors of adolescent and young adult patients with HL, treated with ABVD are comparable. These data suggest that adult treatment protocols are safe and an effective option for adolescent patients.

PB1559 EARLY DISEASE PROGRESSION PREDICTS SHORTER SURVIVAL IN PATIENTS TREATED FOR HODGKIN LYMPHOMA.

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Background: Early disease progression within two years of diagnosis (POD24) is linked to poor overall survival (OS) in follicular lymphoma but its prognostic role is less clear in Hodgkin lymphoma (HL).
Aims: In this study, we wanted to identify the prognostic factors associated with early progression of HL and to determine its impact on patient survival and outcome.
Methods: We analyzed the impact of POD 24 of patients followed for HL in our department, and who received initially ABVD, with or without radiotherapy. This study involved 96 patients followed between 2002 and 2012. We excluded from the analysis patients who, within 24 months of starting treatment, died without progression or were lost of follow-up without prior progression. OS was calculated from progression (for patients with early progression), and from 24 months after initiation of treatment for those without progression.
Results: Early progression was observed in 28 (29%) patients. The 10-year OS of patients with POD24 was 18%, while that of patients without early progression was 80% (p <0.0001). POD24 was correlated with the existence of an extranodal localization (p = 0.0008), an extended stage of the disease (p = 0.02), B symptoms (p = 0.02), as well as hypoalbuminemia (p = 0.04). The rate of relapses was higher in patients with POD24 (32%), compared to patients without POD (10%, p = 0.02). In multivariate analysis, two factors were predictive for the long-term survival of the patients: extranodal localization (p = 0.03), and POD24 (p <0.0001).
Summary/Conclusion: In patients with HL who have received first-line treatment, early disease progression is associated with poorer survival, and POD24 may represent a useful endpoint in future prospective clinical trials or assessments of responses. to treatment.

PB1560 INTERIM PET BASED OMISSION OF RADIOTHERAPY OR INTENSIFICATION OF CHEMOTHERAPY IN YOUNGER PATIENTS WITH LOCALIZED STAGE CLASSICAL HODGKIN LYMPHOMA: PRELIMINARY EXPERIENCE FROM A SINGLE REFERRAL CENTER

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Background: Combined modality therapy including ABVD and radiotherapy (RT) has been traditionally the treatment of choice for limited-stage Hodgkin lymphoma (HL) (I/II). The long-term side effects of RT are still notable and consist the main reason for the attempt to exclude it from the treatment algorithm in a group of patients that are mostly young and, thus, vulnerable to late-onset neoplastic and cardiovascular complications. Recently, in 2017, the EORTC H10 study demonstrated that RT can be safely omitted in case of a strictly negative interim PET (iPET) [roughly corresponding to Deauville-5-point scale score (D5PSS) 1-2], with a statistically significant but numerically negligible loss in disease control of about 2-3%, especially in patients with early unfavorable disease. On the contrary, in patients who remain iPET-positive, RT is preserved and chemotherapy can be intensified with excellent results.
Aims: The aim of this study was the initial evaluation of the results of the above strategy, which was adopted in our Center in 2018, as most of the relapses occur within the first 2 years from diagnosis and therefore, a preliminary assessment of the safety of RT omission in regard to disease control can be performed in a real-life setting.
Methods: 52 patients <50 years old with a median follow-up of 18 months were retrospectively evaluated. Since the beginning of 2018 we used the aforementioned therapeutic strategy in patients with favorable or unfavorable limited-stage disease with mediastinal involvement. On the other hand, RT was maintained in patients without mediastinal involvement, those with iPET D5PSS 3 as well as those with D5PSS 4-5, who received BEACOPP-escalated and RT, and in patients >50 years old, who are potentially less susceptible to long-term complications.
Results: *Patients <50 years with mediastinal involvement:* Among 41 patients included, 31 had early unfavorable and 10 early favorable HL according to EORTC. Among 24 patients who achieved D5PSS-1/2 (59%) only 3 received RT. The 2-year Progression-Free Survival (PFS) was 96% with only one event of primary refractory disease upon restaging that could not have been avoided with RT. Among 11 patients (27%) who achieved D5PSS 7 received RT with no relapses observed in this group so far. iPET remained positive with D5PSS-4/5 in 6 patients (15%), 5 of whom were switched to BEACOPP-esc and RT. The 1-year PFS was 50%. *Patients<50 years without mediastinal involvement:* Among 11 patients included, 10 had early favorable and 1 early unfavorable HL according to EORTC. Among 9 patients (82%) who achieved D5PSS-1/2/3, 8 received RT. No relapses were observed. iPET was positive with D5PSS-4/5 in 2 patients that were treated with BEACOPP-esc and RT without any relapse so far.
Summary/Conclusion: These initial results demonstrate that when RT is omitted following a strictly negative iPET, the relapse rate remains low and absolutely acceptable in the short-term, which is the highest-risk time period. In fact, in this situation the only observed failure event could not have been avoided with RT. However, the question whether RT remains necessary for patients with D5PSS-3 still exists. No safe conclusions can be made so far in regard to the intensification of therapy with BEACOPP-esc in the small subgroup with clearly positive iPET. These results encourage the continuation of this therapeutic strategy based on H10 study, in order to eliminate the long-term side effects of radiotherapy. Further observation and recruitment of much more patients in this real-life setting is scheduled.

PB1561 ACUTE NEUROLOGIC DETERIORATION FOLLOWING THREE DOSES OF BRENTUXIMAB-VEDOTIN IN A PATIENT WITH CHARCOT-MARIE-TOOTH DISEASE

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Background: Charcot-Marie-Tooth (CMT) disease represents a heterogeneous group of disorders of peripheral nerve, that is characterized by progressive weakness and atrophy of distal muscles, loss of tendon reflexes, mild sensory impairment and foot deformity.
Two major types of CMT can be differentiated: type I (IA chromosome 17p11.2 gen PMP22, IB chromosome 1q22-23 gen P0, IC unknown gen) more frequently (60%) and type II. Both types are inherited in an autosomal dominant pattern and generally show a benign and chronic clinical course.
Aims: To show severe and life-threatening neuropathic events in patients with hereditary neuropathies receiving Brentuximab-Vedotin (BV).
Methods: We report an unusual case of acute deterioration of CMT disease IA following three doses of BV.
Results: A 27-year-old male was diagnosed with Hodgkin's lymphoma in June 2020. He presented cervical lymphadenopathies. Definite histological diagnosis was made after lymph node removal. Further diagnostic studies revealed splenic and bone infiltration and he was staged IVA (Ann Arbor Classification). BV+AVD-chemotherapy (Adriamycin, Bleomycin, Vinblastine) was the chosen treatment; 120 mg was the BV dose administered in each cycle (1,2 mg/kg). At that point, the neurological status and clinical examination results showed no alterations. No family or personal history was notified.
He received two doses of BV without problems. The third dose was given on 11 September. Three days later, the patient started with neurological symptoms such as muscular weakness, both in the upper and lower limbs (power grade III), fingertips' paresthesia, bilateral sensory impairment of feet and lower legs. Symptoms worsened significantly resulting in dependency of a wheelchair. Finally, he was assessed by a neurologist and diagnostic studies were performed. He continued with the treatment for his lymphoma without BV and with a provisional diagnosis of severe BV-induced neuropathy. At this moment, his father revealed that he had a Charcot-Marie-Tooth disease.
Electrophysiological studies showed sensory-motor polyneuropathy with predominantly demyelinating. We searched his medical history from children's hospital and it was observed that he presented 17p11.2 duplication typical for CMT disease IA. While continuing chemotherapy without the use of BV, the patient's neurological symptoms slowly recovered with rehabilitation for four months.
Summary/Conclusion: Peripheral neuropathy induced by BV is a characteristic effect of cumulative exposure to this drug and it is reversible in most cases. As shown in our patient the coincidence of BV use and underlying CMT IA can lead to severe neurological impairment. If these symptoms are unusual or do not recover before the next dose of BV, diagnostic work-up for underlying hereditary neuropathy including nerve conduction velocity studies and sometimes molecular genetic analysis should be performed. No further use of BV or at least adequate dose reduction have also to be considered. However, we have not found cases like ours on bibliography. Only a few cases have been reported with the use of vincristine. We conclude that a detailed family history and careful clinical examination should be obtained before exposing patients to any kind of neurotoxic agents. Otherwise, consequences can be deleterious for the quality of patient's life.

PB1562 BULKY MEDIASTINAL DISEASE IN HODGKIN LYMPHOMA: THERAPEUTIC OUTCOMES OF ABVD VERSUS BEACOPP ESCALATED REGIMEN IN A SINGLE TUNISIAN CENTER

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Background: Bulky mediastinal disease (BMD) is one of the prognostic factors in Hodgkin lymphoma (HL) usually associated with a poor prognosis. In order to improve treatment results for patients with BMD, the Tunisian group changed the national protocol based on ABVD (MDH2002)to BEACOPP escalated regimen(MDH2008 in 2008,then MDH2015 in 2015).
Aims: Our study aims to evaluate and compare the therapeutic results of these protocols in these patients.
Methods: Our study is retrospective interesting 71 newly diagnosed HL adults (<60 years old) with BMD (MTI ≥0.35) treated between January 2002 and June 2020 at the hematology department of Hedi Chaker hospital in Sfax, Tunisia with different versions of national protocols. A total of 20 patients were enrolled from January 2002 to December 2007 with the MDH2002. It is based on the use of the ABVD regimen: 6 cycles for unfavorable early stagesfollowed by involved field radiation therapy (IFRT), and 8 cycles for advanced stages followed by consolidative radiation therapy if there is a residual mass. The MDH2008 and MDH2015 protocol sare rather based on staging these patients in advanced stages and treating themwith intensive chemotherapy: the BEACOPP escalated regimen. Early assessment of response based on scanography is recommended after two cycles and de-escalation to ABVD is favored if the response is ≥75%(according to Cheson's criteria).MDH2015 differs from MDH2008 by reducing the number of cycles to six instead of eight in order to decrease toxicity. Our review determines therapeutic responses, the overall survival (OS), event-free survival (EFS), and factors forecast which influenced these survivals. It aims to compare these survivals using the ABVD regimen (MDH2002=P1) and BEACOPP regimen (MDH2008 and 2015 = P2).
Results: Median age at presentation was 24 years (range 16-51 years). The study included 44 females and 27 males. Forty-four percent(44 %) of patients presented with advanced disease. B-symptoms, more than three sites of involvement, and Bulky tumor were respectively recorded in 75%, 39.4%, and 43.7% of cases.The CR/CRu rate was 69% at the end of treatment (55% with P1 versus 74.5% with P2). PR was 11.3%(5% vs 13.7%). 19.7% of patients did not respond to treatment (40% vs 11.7%) either by a stable disease, progressive disease,or death before the end of chemotherapy.The difference in response between P1 and P2 was significant (p=0.023).With a median follow-up of 72months (range 1-232 months),3- year and 6-year OS rates were respectively 79.6% (65% vs 85.4%) and77.9% (60% vs 85%) with a statistically significant difference between the two groups (p=0.039). Median EFS was 40months. Three-year EFS was 59.7% (45% vs 65.6%), (p=0.01).
Summary/Conclusion: Our results show that the BEACOPP regimen is superior to ABVD for initial disease control and prolonged time to relapse in the treatment of patientswith BMD as described in the literature. However, it noted that BMD stills a poor prognosis factor for OS and EFS comparing to other cases of HL without BMD.

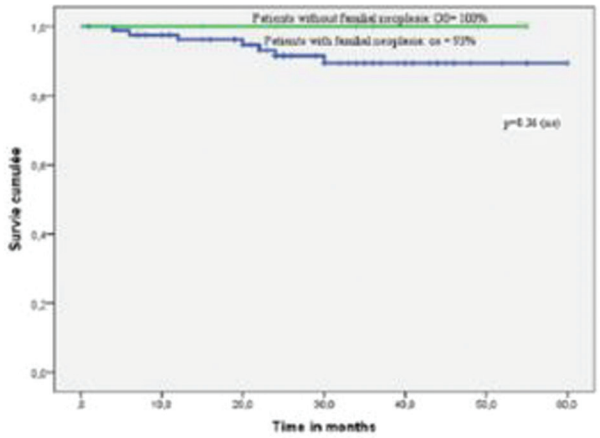
PB1563 IS THERE ANY CORRELATION BETWEEN THE HISTORY OF FAMILIAL NEOPLASIA AND THE DESCRIPTIVE AND PROGRESSIVE PROFILE OF HODGKIN LYMPHOMAS? 4-YEAR COHORT STUDY

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Background: malignant lymphoid hemopathies represent a heterogeneous group, many authors have reported a history of familial neoplasia in these patients, in particular, in case of Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma. The pathophysiology involves genetic factors since a close link with certain HLA groups is found. The data in the literature are contradictory, however, many studies indicate that these clinical forms have certain peculiarities: an older age at diagnosis compared to the sporadic forms, a predominance of the male sex, of the scleronodular type and Poppema and Lennert's paragranuloma, extensive stages and extra nodal involvement.
Aims: to analyze the clinical and progressive characteristics of patients with Hodgkin lymphoma and with a history of familial neoplasia (hematological or extra-hematological) and to seek a correlation between the observed data and this parameter over a period of 4 years.

Methods: we conducted a retrospective, single-center and descriptive study on 98 patients with Hodgkin lymphoma enrolled in the Hematology department of Centra Hospital during the period (2016-2019), a history of familial neoplasia is found. in 08 cases (8%).
Results: in 8/98 patients with HL with a history of familial neoplasia, we found a history of Hodgkin lymphoma in 1 case (in the brother), digestive cancer in 4 cases (cousins), breast cancer in 1 case (2 sisters), uterine neoplasia in 1 case and lung carcinoma in 1 case (father). The mean age at diagnosis is 35 years in the sporadic forms and 37.5 years in the forms with a history of familial neoplasia, p = 0.12 (ns). Three out of 5 patients are male in the group with familial neoplasia vs 53/90 in the sporadic group, p = 0.22 (ns).The scleronodular type is found in the 8 cases of LH with familial neoplasia vs 74/90 (in the sporadic forms), p = 0.09 (ns), only one patient in our cohort presents a Poppema and Lennert paragranuloma, it belongs to in the 1st group (with familial neoplasia), p = 0.0004 (s). Four out of 8 patients are classified as localized stages (I-II) versus 30/90 in the sporadic forms, p = 0.38 (ns), a bulky mass (diameter greater than 7cm and / or IMT> 0.35) is found in 6 out of 8 cases versus 34/90 in the 2nd group, p = 0.02 (s). Extra nodal location (contiguous to a lymph node involvement) is noted in 3 out of 8 cases in the forms with familial neoplasia vs. 18/90 in the sporadic forms, p = 0.12 (ns)
By applying the prognostic classification of the EORTC (European Organization for Research and Treatment of Cancer) in the localized stages and the IPS (international Prognostic Score) in the extended stages, all patients with HL with familial neoplasia are classified in the unfavorable group vs 58/90 in sporadic forms: p = 0.01 (s).We recorded, over a period of 4 years, 8 deaths in the sporadic forms (no deaths were noted in the group with familial neoplasia), p = 0.21 (ns). The 5-year overall survival (January 2016 to January 2021) is estimated at 91% all forms combined, this factor is not influenced by the family history of the patients (p = 0.32)



Summary/Conclusion: our results agree with the data in the literature: the family history of neoplasia gives patients with HL certain clinical characteristics, however, the impact of this factor on the evolution of patients is not confirmed in our study series.

PB1564 THERAPEUTIC RESULTS OF A TUNISIAN PROSPECTIVE NON-RANDOMIZED ADULT HODGKIN LYMPHOMA STUDY: SINGLE-INSTITUTION EXPERIENCE ABOUT 73 ADULT PATIENTS

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Background: Hodgkin lymphoma (HL) is a hematologic malignancy with a high rate of curability. Several national and international groups have established management protocols for this disease. Since 1999, The Tunisian group has adopted four versions of the HL national protocol(MDH99, MDH2002, MDH2008, and MDH2015).
Aims: Our study aims to evaluate the therapeutic results of the fourth-protocol: MDH2015.
Methods: Our study is retrospectiveabout73newly diagnosed HL adult patients (<60 years old) treated between December 2015 and June 2020at the hematology department of HediChaker hospital Sfax, Tunisia, according to the MDH2015 protocol. The MDH2015recommends an early assessment of response based on scanography after 2 cycles of chemotherapy in each group. For favorable early stages (G1), ABVD regimen was used:two to three cycles followed by involved field radiation therapy (IFRT). For unfavorable early stages (G2), four cycles of ABVD were usedfollowed byIFRT. An escalation to BEACOPP escalated regimenwas recommended if the response was ≤75% (according to Cheson's criteria).For the advanced stages and localized stages with bulky mediastinal mass (BMM)(G3), treatment is based on six cycles of BEACOPP escalated regimen. De-escalation to four ABVD cycles is used if the response is ≥ 75%after two cycles.The date of point is in February 2021. Our study determines therapeutic responses, the overall survival (OS), event-free survival (EFS), and factorsthat affect the survivals.
Results: Median age at presentation was 33 years (range 16-57 years). There were 27 females and 46 males (M/F: 1.7). Fifty-three percent (53 %) of patients presented with advanced disease. Distribution by group was: G1(n=4), G2(n=20), and G3(n=49).B-symptoms, more than three sites of involvement, BMM, and peripheral bulky tumor were respectively recorded in 74%, 35.6%, 28.8%, and 45.2% of cases. The CR/CRu rate was 82.2% at the end of treatment. PR was 9.6%. The rest of the patients (8.2%) had stable disease. No progressive disease was noted. With a median follow-up of 37 months, one year and 3-year OS and EFS were respectively 97%, 83% and 81.5%, 74.2%. Therapeutic response at the end of treatment was a predictive adverse prognostic factor for OS (p=0.014) and EFS (p=0.0001) in multivariate analysis.
Summary/Conclusion: Our results with the MDH2015 protocol in both localized and advanced stages of the disease are encouraging either in initial therapeutic response or in OS and EFSwhich correlates favorably with previous findings of BEACOPP regimen results in the literature: more than 90% of survival in the first year, and more than 80% in three years.

Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

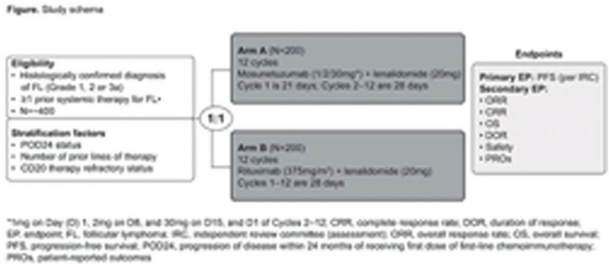
PB1565 A PHASE III TRIAL (GO42909) EVALUATING MOSUNETUZUMAB IN COMBINATION WITH LENALIDOMIDE (M-LEN) VERSUS RITUXIMAB-LENALIDOMIDE (R-LEN) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

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Background: Despite currently available therapies, FL is characterized by recurrent relapses, with increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Mosunetuzumab is a full length, IgG1 CD20xCD3 bispecific antibody that redirects T cells to engage and eliminate malignant B cells. Mosunetuzumab monotherapy elicited high and consistent complete response (CR) and overall response rates (ORR) across high-risk FL subsets in an ongoing Phase I/Ib study (N=62; CR rate: 51.6%; ORR: 67.7%; NCT02500407; Assouline, et al. ASH 2020). Lenalidomide is a potent immunomodulatory agent that has been shown to enhance T-cell and natural killer-cell activity. As such, mosunetuzumab and lenalidomide have potential to exhibit synergistic activity. The combination of M-Len may afford further clinical benefit, providing a new treatment option for patients with R/R FL. Here we present details of a trial in progress assessing M-Len.
Aims: To evaluate the efficacy and safety of M-Len versus R-Len in patients with R/R FL.
Methods: GO42909 (NCT04712097) is a Phase III, open-label, multicenter, randomized controlled trial in patients with R/R FL. Eligible patients must have CD20-positive FL (excluding grade 3b and transformed FL) with an Eastern Cooperative Oncology Group Performance status ≤2, patients must also have received at least one prior systemic therapy, and require treatment according to Groupe d'Etude des Lymphomes

Folliculaires (GELF) criteria (Solal-Céligny, et al. J Clin Oncol 1998). Patients are randomized 1:1 to receive either M-Len or R-Len; randomization is stratified by progression of disease within 24 months of receiving the first dose of first-line immunochemotherapy, number of prior therapies, and CD20-refractoriness. Patients in the M-Len cohort receive mosunetuzumab intravenously (IV) as step-up doses in Cycle 1 (21-day cycle): 1mg on Day (D)1, 2mg on D8, and 30mg on D15, and D1 of Cycles 2–12 (28-day cycles). Lenalidomide (20mg) is administered orally, once daily on D1–21 of Cycles 2–12. Patients in the R-Len cohort receive 375mg/m^2 rituximab (IV) on D1, 8, 15 and 22 of Cycle 1, and on D1 of Cycles 3, 5, 7, 9 and 11 (28-day cycles); lenalidomide is administered once a day on D1–21 of Cycles 1–12 (Figure). The primary efficacy endpoint is progression-free survival as determined by an independent review committee using the 2014 Lugano response criteria (Cheson, et al. J Clin Oncol 2014). Key secondary efficacy endpoints include ORR, CR rate, and overall survival. Safety endpoints comprise incidence and severity of adverse events (NCI CTCAE v5.0) including cytokine release syndrome (ASTCT criteria; Lee, et al. Biol Blood Marrow Transplant 2019), change from baseline in targeted vital signs and clinical laboratory test results, and tolerability; an independent data monitoring committee will evaluate safety data periodically during the study. In addition, pharmacokinetic and biomarker endpoints will be explored.
Results: The study start date is planned for 2021, with an anticipated enrollment of around 400 patients from approximately 16 countries and at least 150 sites globally.



Summary/Conclusion: GO42909 is an ongoing study of M-Len versus R-Len in patients with R/R FL. Further study details will be presented.

PB1566 TRIAL IN PROGRESS: A PHASE 2, SINGLE-ARM, OPEN-LABEL, MULTICENTER STUDY OF TAZEMETOSTAT IN COMBINATION WITH RITUXIMAB FOR THE TREATMENT OF RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA

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Background: Patients with follicular lymphoma (FL) who do not achieve a response after 2 or more prior lines of systemic therapy have a poor prognosis when treated with salvage chemotherapy alone or phosphoinositide 3-kinase (PI3K) inhibitors. Tazemetostat, a first-in-class, oral, selective enhancer of zeste homolog 2 (EZH2) inhibitor, has demonstrated single-agent antitumor activity and a favorable safety profile in patients with wild-type (WT) and mutant (MT) *EZH2* relapsed/refractory (R/R) FL who had received ≥2 prior lines of therapy. Rituximab, as a single agent or in combination, is often used in the second line or later in patients with FL. In preclinical studies, tazemetostat has shown synergistic activity when combined with rituximab. This, in addition to clinical study experience with the combination of tazemetostat and rituximab in patients with diffuse large B-cell lymphoma, support the evaluation of tazemetostat in combination with rituximab in patients with R/R FL.
Aims: To determine the efficacy and safety of tazemetostat in combination with rituximab for the treatment of R/R FL.
Methods: This trial (NCT04762160) is a phase 2, single-arm, open-label, multicenter study of tazemetostat in combination with rituximab in patients with R/R FL who have received ≥2 prior lines of systemic therapy, including an anti-CD20–based regimen. Patients eligible for inclusion are aged ≥18 years with grade 1 to 3A FL who have met Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria to receive treatment, have an Eastern Cooperative Oncology Group (ECOG) performance score ≤2, and have not received any prior treatment with EZH2 inhibitors. Patients with transformed FL, a history of clinically significant gastrointestinal conditions, or any uncontrolled illness are excluded from this study. *EZH2* mutation testing will be performed during patient screening; however, the presence of an *EZH2* mutation is not required to be eligible for the study. Patients will receive tazemetostat 800 mg orally twice daily beginning on cycle 1 day 1 for continuous 28-day cycles until the end of cycle 24, for a total of 24 months of therapy. Patients will also receive rituximab 375 mg/m^2 intravenously (IV) on cycle 1 day 1, then 375 mg/m^2 IV or 1400 mg subcutaneously on days 8, 15, and 22 of cycle 1, and on day 1 of cycles 3, 4, 5, and 6, for a total of 8 doses of rituximab. The primary endpoint is the objective response rate (ORR; the proportion of patients with complete or partial response) in patients with WT *EZH2*. Key secondary endpoints include median progression free survival (PFS) in patients with WT *EZH2*; median PFS in all patients, regardless of mutational status; ORR in patients with MT *EZH2*; efficacy outcomes in rituximab-refractory patients; and incidence of adverse events. Efficacy and safety analyses will be performed on all patients who receive ≥1 dose of study drug. The evaluation of ORR will be based on Lugano 2014 response criteria and will be presented with corresponding 2-sided Clopper-Pearson 95% confidence intervals. The Kaplan-Meier method will be used to estimate PFS. Survival follow-up will be done following the study treatment period every 6 months for 2 years or until disease progression or death for all patients who complete the 24 months of tazemetostat therapy. As of February 2021, 1 site is recruiting patients in the United States, with 2 patients enrolled.
Results: N/A
Summary/Conclusion: N/A

PB1567 THE PROGNOSTIC NUTRITIONAL INDEX (PNI) IS AN INDEPENDENT PREDICTOR OF OVERALL SURVIVAL IN OLDER PATIENTS WITH FOLLICULAR LYMPHOMA

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Background: Although outcomes in follicular lymphoma (FL) are generally good, some patients experience early relapse or histological transformation (HT), which compromise their life expectancy. The Prognostic Nutritional Index (PNI), a parameter combining the serum albumin concentration and the absolute lymphocyte count, was initially designed to estimate the prognosis of patients undergoing gastrointestinal surgery, but it has then been successfully applied to a wide range of solid and hematological cancer types. This index, a putative combined measure of the nutritional and inflammatory status and host's anti-tumor response, has not been well characterized in FL.
Aims: To evaluate the role of the PNI in a large single-center series of FL patients.
Methods: We studied 351 grade 1-3A FL patients (190 F / 160 M; median age, 61 years) diagnosed at a single institution between 2000 and 2018. The PNI (a unitless parameter) was calculated using the original formula (Buzby *et al*, Am J Surg, 1980): PNI = albumin (g/L) + [5 x absolute lymphocyte count (x10^9/L)]. Clinical characteristics, treatment modalities, response, progression-free (PFS) and overall survival (OS), risk of HT, and of second primary malignancies (SPM) were assessed and compared between patients with a PNI below and above 45, the most widespread cut-off.
Results: Forty-one patients (12%) had a PNI ≤45 (Table), who were older and showed adverse baseline features (poor ECOG PS, B symptoms, high LDH and/or β_2-microglobulin levels, anemia, and high-risk FLIPI score). Median follow-up was 5 years (range, 0.8–16.2 years). Frontline treatment and responses were comparable among groups. Globally, PFS did not significantly differ based on the PNI. When a subgroup analysis was performed, a PNI ≤45 was predictive of a lower PFS in patients >60 years, but not in those ≤60 years. Using competing risks of death, the 10-year cumulative incidence of lymphoma-related death (progressive FL or treatment-related complications) was significantly higher for patients with a PNI ≤45 (29 vs. 11% at 10 years, P = 0.0006, Figure A). A low PNI was associated with a shorter OS in the global series (10-year OS, 52% versus 74%, P = 0.0001, Figure B). In a 6-element multivariate model also including the presence of B symptoms and of a bulky mass, ECOG PS, FLIPI score, and β_2-microglobulin, the prognostic impact of the PNI on OS was confirmed for patients >60 years (HR = 3, P = 0.006). Finally, the PNI did not predict the risk of HT or SPM.

	Prognostic Nutritional Index		
	≤45	>45	P
Number of patients, n (%)	41 (12)	310 (88)	–
Age (median, range)	71 (33-91)	60 (26-86)	<0.001
Female sex, n (%)	25 (61)	166 (54)	NS
Charlson Comorbidity Index ≥2, n (%)	11 (27)	70 (23)	NS
Histological grade 1-2, n (%)	30 (75)	255 (84)	NS
ECOG PS ≥2, n (%)	10 (24)	14 (5)	<0.001
B symptoms, n (%)	11 (27)	30 (10)	0.001
Ann-Arbor stage III/IV, n (%)	33 (81)	231 (75)	NS
Secondary extranodal involvement, n (%)	30 (73)	193 (62)	NS
Bulky mass, n (%)	11 (27)	65 (21)	NS
Elevated serum LDH, n (%)	15 (37)	53 (17)	0.003
Elevated β2-microglobulin, n (%)	27 (73)	122 (40)	<0.001
Hemoglobin <120 g/L, n (%)	23 (56)	42 (14)	<0.001
High-risk FLIPI score, n (%)	20 (49)	69 (22)	<0.001
Frontline treatment with R-CHOP, n (%)	21 (55)	144 (54)	NS
CR rate, n (%)	27 (71)	201 (75)	NS
PFS, % at 10 y (95% CI)	46 (30-70)	53 (45-62)	NS
OS, % at 10 y (95% CI)	52 (35-78)	74 (68-82)	0.0001
Cumulative incidence of lymphoma-related death, % at 10 y (95% CI)	29 (14-45)	11 (7-16)	0.0006

Table. Baseline features of the 351 patients, globally and according to the PNI.
PNI, Prognostic Nutritional Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index; ULN, upper limit of normal; NS, not statistically significant; CR, complete response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; HT, histological transformation; FL, follicular lymphoma; NS, not statistically significant; PFS, progression-free survival; OS, overall survival; SM, second malignancies.

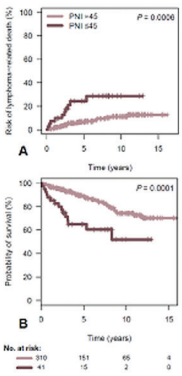


Figure. A. Cumulative incidence of lymphoma-related death according to the PNI. **B.** Overall survival according to the PNI.

Summary/Conclusion: The PNI is a readily accessible piece of information that can identify a small subset of FL patients with shorter survival, especially among the older age subgroup. Upon validation in other series, it could be a valuable tool to anticipate outcomes and identify patients who could have their nutritional status optimized before treatment initiation.

PB1568 PROGNOSTIC PERFORMANCE OF CLINICAL RISK SCORES IN FOLLICULAR LYMPHOMA: EVALUATION IN A SINGLE-CENTER SERIES

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Background: Most follicular lymphoma (FL) patients have prolonged survival. However, early progression (POD24) and histological transformation (HT) compromise their life expectancy. With the intention of identifying such individuals, different risk scores (RS) have been developed. Although FLIPI has gained the widest acceptance, none of the previous (IPI, ILI) or more recent indexes (FLIPI2, PRIMA-PI) has been clearly shown to outperform the others.
Aims: To evaluate the utility of the IPI, ILI, FLIPI, FLIPI2, and PRIMA-PI in a single-center series of FL patients.
Methods: We studied 414 grade 1-3A FL patients [230 F/184 M; median age, 60 years (range, 26–91)] who had available information about at least one of the five clinical RS (IPI, ILI, FLIPI, FLIPI2, PRIMA-PI), diagnosed at our institution between 2002 and 2018. Three hundred and ten patients (75%) had advanced-stage disease, and 250 (69%) received frontline treatment with R-CHOP or R-CVP. With a median follow-up of 5.9 years, 10-year overall survival (OS) was 71%.
Prognostic performance of each RS was evaluated in terms of calibration (Hosmer-Lemeshow goodness of fit), discrimination [Harrell's c-index, Akaike's information criterion (AIC), and Gönen & Heller's concordance probability estimate (CPE)], reclassification [net reclassification index (NRI)], and clinical utility [prediction of time to first treatment (TTFT), response, progression-free survival (PFS), OS, risk of lymphoma related death (LRD), and of HT].
Results: Performance metrics of the five RS are detailed in *Table 1*. Goodness of fit, Harrell's c-index, AIC, and CPE were similar across indexes. NRI did not show improvement of any RS in comparison with the existing ones. The proportion of patients allocated to the high-risk category by each RS was as follows: 7% (IPI), 27% (ILI), 28% (FLIPI), 30% (FLIPI2), and 27% (PRIMA-PI). Pairwise concordance (patients allocated to the same risk category by two RS, *Table 2*) was lowest between IPI-FLIPI2, ILI-FLIPI2, and ILI-PRIMA-PI (51%), and highest between IPI-FLIPI (67%). All five RS predicted TTFT (P <0.01). Using logistic regression, all five RS predicted for the absence of complete response, as well as for POD24.
All five RS were predictive of PFS (P <0.0001), OS (P <0.0001, Figure), and LRD (P <0.001). Ten-year OS estimates for each high-risk group were as follows: 16% (IPI), 46% (ILI), 46% (FLIPI), 48% (FLIPI2), 43% (PRIMA-PI). Although PRIMA-PI identified a high-risk group (B2M >3 mg/L), no significant differences in OS were found according to bone marrow infiltration (pairwise P = 0.7). FLIPI was the only RS to predict HT, with 10-y cumulative incidences of 3%, 8% and 10% for low-, intermediate-, and high-risk patients, respectively (P = 0.04).

Figure. Kaplan-Meier curves of overall survival according to the five risk scores.

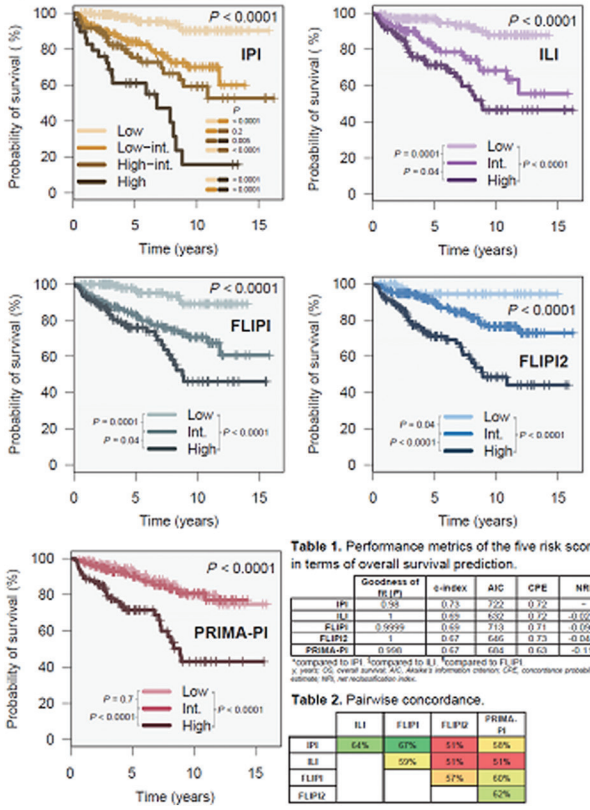


Table 1. Performance metrics of the five risk scores in terms of overall survival prediction.

	Goodness of fit (LR)	c-index	AIC	CPE	NRI
IPI	0.98	0.73	7222	0.72	–
ILI	1	0.69	6992	0.72	-0.022*
FLIPI	0.9999	0.69	713	0.71	-0.096†
FLIPI2	1	0.67	686	0.73	-0.044‡
PRIMA-PI	0.998	0.67	684	0.63	-0.11§

*compared to IPI. †compared to ILI. ‡compared to FLIPI.
y, years; OS, overall survival; AIC, Akaike's information criterion; CPE, concordance probability estimate; NRI, net reclassification index.

Table 2. Pairwise concordance.

	ILI	FLIPI	FLIPI2	PRIMA-PI
IPI	64%	67%	51%	58%
ILI		59%	51%	51%
FLIPI			57%	60%
FLIPI2				62%

Summary/Conclusion: The five RS exhibit very subtle differences in their performance metrics. All of them predict TTFT, response, POD24, PFS, OS, and the risk of LRD. IPI identifies a small subset of patients with dismal outcomes. Bone marrow involvement did not impact OS, questioning the prognostic discrimination of the low- and intermediate-risk PRIMA-PI categories. In our series, FLIPI was the only RS to predict HT. In summary, all available RS are similarly valid for prognostication. Their potential to aid in the decision of initiating treatment should be explored.

PB1569 COASTAL: A PHASE 3 STUDY OF THE PI3KΔ INHIBITOR ZANDELISIB WITH RITUXIMAB (R) VERSUS IMMUNOCHEMOTHERAPY IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA (INHL)

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Background: Patients (pts) with iNHL treated with front-line immunochemotherapy may benefit from an alternative, chemotherapy-free regimen at relapse. Zandelisib, a potent, selective, and structurally differentiated oral PI3Kδ inhibitor, achieved an 87% response rate, with median duration of response not reached in iNHL when given as a monotherapy or in combination with R. A low rate (<10%) of Grade ≥ 3 immune-mediated adverse events of special interest associated with PI3kδ inhibitors is observed in patients administered zandelisib on an intermittent schedule (IS) (JCO 2020 38:15_suppl, 8016). An open-label, phase 2 study (TIDAL, NCT03768505) of zandelisib as monotherapy is ongoing in pts with relapsed/refractory follicular lymphoma (FL) and marginal zone lymphoma (MZL).
Aims: The COASTAL study is a randomized, open-label, controlled multicenter phase 3 trial to investigate the safety and efficacy of zandelisib in combination with R versus standard immunochemotherapy in pts with iNHL.
Methods: Key eligibility criteria: adults with relapsed or refractory FL or MZL who received ≥1 prior lines of therapy which must have included an anti-CD20 antibody in combination with chemotherapy or lenalidomide

(L); at least one bi-dimensionally measured lesion >1.5 cm; adequate bone marrow, renal and hepatic function; ECOG performance status score of 0 to 1. Key exclusion criteria: histologically confirmed diagnosis of FL grade 3b or transformed disease; administration of 2 prior immunochemotherapy regimens; prior PI3K inhibitor therapy; known lymphomatous involvement of the central nervous system. Subjects will be randomized 1:1 to receive R-zandelisib or immunochemotherapy (R-CHOP or R-B) and stratified by type and number of prior treatment regimens, histology, and duration of treatment-free interval after last therapy. Zandelisib will be given in a 28-day cycle comprising of daily dosing for 2 cycles followed by IS dosing on days 1-7 or each 28-day subsequent cycle for a duration of 2 years. Rituximab or immunochemotherapy will be given for a total of 6 cycles. Disease response will be assessed by an Independent Response Review Committee according to the modified Lugano Classification. Radiographic tumor assessment will be performed approximately every 12 weeks for the first 9 months, every 16 weeks for the next 12 months, and every 24 weeks thereafter. The primary efficacy endpoint is progression-free survival. The major secondary endpoints include ORR, complete response rate, overall survival, and safety.
Results: The trial will enroll approximately 534 pts in ~200 sites globally and will begin enrollment in mid-2021.
Summary/Conclusion: NCT04745832

PB1570 A PHASE 2 RANDOMIZED STUDY OF LONCASTUXIMAB TESIRINE VERSUS IDELALISIB IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA (LOTIS-6)

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Background: Although many patients (pts) with follicular lymphoma (FL) respond to first-line therapy, most pts have a history of successive relapses and response duration shortens after each relapse; therefore, FL is considered incurable and an area of considerable unmet need. Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer (PBD) toxin. Single-agent Lonca demonstrated antitumor activity and a manageable safety profile in pts with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma, including FL, in a Phase 1 clinical trial (ADCT-402-101), and in heavily pretreated pts with R/R diffuse large B-cell lymphoma in a Phase 2 trial (ADCT-402-201). Idelalisib is an inhibitor of phosphatidylinositol 3-kinase, approved for pts with relapsed FL who had ≥2 prior systemic therapies.
Aims: The primary objective of this trial (NCT04699461) is to evaluate the efficacy of single-agent Lonca compared with idelalisib in R/R FL.
Methods: This is a prospective, randomized, two-arm, multicenter, open-label, Phase 2 study of Lonca versus idelalisib in pts with R/R FL. Key inclusion and exclusion criteria for the study are presented in **Table 1**. Informed consent will be obtained. Eligible pts will be randomized 2:1 to Lonca (intravenous infusion; 150 µg/kg every 3 weeks [Q3W] for 2 cycles then 75 µg/kg Q3W for subsequent cycles) or idelalisib (oral; 150 mg twice daily). Randomization will be stratified based on the time since last systemic therapy (ie, ≤2 years versus >2 years). The follow-up period will be up to 3 years after the end of treatment. Pts can continue treatment until disease progression, unacceptable toxicity, or other discontinuation criteria.
The primary endpoint is complete response rate (CRR) according to the 2014 Lugano Classification as determined by central review. CRR will be tested for the intent-to-treat population between the two treatment arms using the Cochran–Mantel–Haenszel method adjusted for stratification factors from the randomization list. The study is 99% powered for the primary efficacy endpoint, assuming a 55% CRR to Lonca and a 15% CRR to idelalisib, and the sample size for enrollment (approximately 150 pts) allows for a robust safety data set. Secondary endpoints include overall response rate (key secondary endpoint); progression-free survival; overall survival; duration of response; incidence and severity of adverse events (AEs) and serious AEs; change from baseline in laboratory values, vital signs, 12-lead electrocardiogram, and Eastern Cooperative Oncology Group performance status; concentration and pharmacokinetic parameters of Lonca total antibody, PBD-conjugated antibody, and unconjugated warhead (SG3199); anti-drug antibody titers; and patient-reported outcome (PRO) measures. PRO measures will include change from baseline in PROs, as measured by EuroQol–5 Dimensions–5 Levels and Functional Assessment of Cancer Therapy-Lymphoma, and the occurrence, severity, and interference of specific symptomatic AEs selected from the PROs version of the Common Terminology Criteria for AEs.
The trial is anticipated to open for recruitment in Quarter 1, 2021.
This study is sponsored by ADC Therapeutics SA.
Results: N/A

Table 1 : Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Patients aged ≥18 years with a pathologic diagnosis of FL (Grade 1, 2, 3A) • Patients with R/R FL following ≥2 lines of therapy, at least 1 of which contained an anti-CD20 therapy • Patients who received prior CD19-directed therapy must have a biopsy showing CD19 expression after the CD19-directed therapy is completed • Presence of measurable disease as defined by the 2014 Lugano Classification • Eastern Cooperative Oncology Group performance status 0–2 • Adequate organ function	• Prior treatment with loncastuximab tesirine or idelalisib • Patients with FL that has transformed to diffuse large B-cell lymphoma or other aggressive lymphomas • Patients needing treatment or prophylaxis with a strong cytochrome P450 3A inhibitor, inducer, or sensitive substrate • Active or prior drug-induced pneumonitis or inflammatory bowel disease • A condition that could interfere with absorption/metabolism of idelalisib • Autologous or allogeneic stem cell transplant within 30 or 60 days, respectively, before the start of study treatment • Clinically significant third space fluid accumulation (ie, ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath) • Active Grade ≥3 infection requiring IV antibiotics, antiviral, or antifungal treatment

Summary/Conclusion: N/A

PB1571 CLINICAL OUTCOMES IN PATIENTS RELAPSED/REFRACTORY AFTER ≥ 2 PRIOR LINES OF THERAPY FOR FOLLICULAR LYMPHOMA: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Background: Patients with follicular lymphoma (FL) can have high response rates to early lines of treatment. However, among FL patients relapsed/refractory (r/r) after ≥2 prior lines of therapies (LOT), remission tends to be shorter. Moreover, there is limited guidance for treatment options among these patients.
Aims: This study sought to evaluate the clinical outcomes for r/r FL after ≥2 prior LOT using currently available treatment options.
Methods: Electronic databases were searched on 2nd June 2020. Eligible studies were comparative or non-comparative interventional or observational studies of systemic therapies among adults with FL r/r after ≥2 prior LOT. Prior LOT must have included anti-CD20 monoclonal antibodies and alkylating agents, in combination or separately. Overall response rate (ORR) and complete response (CR) were analyzed using inverse-variance weighting with Freeman-Tukey double-arcsine transformations. Kaplan-Meier (KM) analysis for progression-free survival (PFS) and overall survival (OS) were conducted using data from digitized curves and prepared using the Guyot algorithm. Survival analyses were stratified by ≥2 prior LOT and ≥3 prior LOT groups and were restricted to the observational cohorts as a sensitivity analysis.
Results: The meta-analysis included 12 studies published from 2014-2020, including three studies that were cohorts using mixed treatments representing currently available treatments. Sample size for response outcomes was 340, for survival outcomes with ≥2 prior LOT was 1024 and for ≥3 prior LOT was 502. The estimated ORR in the ≥2 prior LOT group was 56.0% (95% confidence interval [CI]: 47.2 – 64.5) and proportion of patients with CR was 12.2% (95% CI: 8.0 – 17.3). The median OS was 54.4 months (95% CI: 45.8 – 76.0) and median PFS was 10.3 months (95% CI: 9.3 – 11.1). The 24-month OS decreased from 66% in the ≥2 prior LOT group to 60% in the ≥3 prior LOT group (Table 1), with a similar trend in PFS at 24-month (28% vs 24%).

Table 1: Key outcomes

Population	Median OS months (95% CI)	Median PFS months (95% CI)	OS at 18m (95% CI)	PFS at 18m (95% CI)	OS at 24m (95% CI)	PFS at 24m (95% CI)
Full Analysis* ≥2 prior LOT	54.4 (45.8 – 76.0)	10.3 (9.3 – 11.1)	71% (68 – 74)	35% (33 – 38)	66% (63 – 69)	28% (26 – 30)
Full Analysis* ≥3 prior LOT	40.6 (32.6 – 52.1)	8.4 (7.5 – 9.5)	65% (61 – 70)	31% (28 – 35)	60% (55 – 64)	24% (21 – 27)
Cohorts ≥2 prior LOT	57.9 (46.6 – 78.4)	10.0 (8.6 – 11.1)	71% (68 – 74)	35% (33 – 38)	66% (63 – 70)	29% (26 – 31)
Cohorts ≥3 prior LOT	42.0 (34.8 – 55.3)	8.3 (7.1 – 9.6)	66% (61 – 70)	32% (28 – 35)	60% (56 – 65)	25% (22 – 28)

*Full analysis includes drug trials and cohorts; CI: confidence interval.

Summary/Conclusion: This study found that few r/r FL patients with ≥2 prior LOT achieve CR, and despite some benefit, approximately 1/3 of patients die within 24 months. The shorter median PFS with increasing prior LOT suggest treatment durability is suboptimal in later LOT. These findings indicate that patients are underserved by current treatments, demonstrating a need for new treatments that can achieve high rates of response that are durable in this disease.

PB1572 PHASE 3 STUDY OF TAFASITAMAB + LENALIDOMIDE AND RITUXIMAB VS PLACEBO + LENALIDOMIDE AND RITUXIMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL) OR MARGINAL ZONE LYMPHOMA (MZL): INMIND

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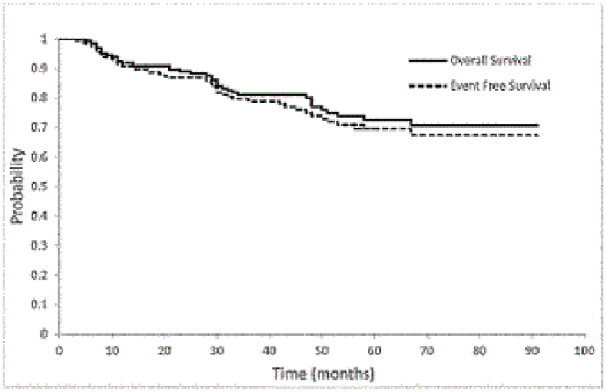
Background: Most patients (pts) with the indolent non-Hodgkin lymphoma (NHL) subtypes FL or MZL respond to first-line treatment but relapse is common, and there is no single standard treatment for pts with relapsed/refractory (R/R) FL or MZL. Tafasitamab is an Fc-engineered humanized monoclonal antibody (mAb) against CD19 which is broadly expressed in FL and MZL, and regulates B-cell proliferation via B-cell receptor signaling. In preclinical studies, tafasitamab has shown activity against NHL cell lines in combination with rituximab (anti-CD20 mAb) and lenalidomide (LEN). Tafasitamab monotherapy has shown promising clinical activity in a phase 2a study in pts with R/R NHL (NCT01685008), with an ORR of 29% (n/N=10/34) in pts with FL and 33% (n/N=3/9) in pts with MZL. In an ongoing phase 2, single-arm study (L-MIND, NCT02399085), tafasitamab plus LEN followed by tafasitamab alone demonstrated an ORR of 57.5% (n/N=46/80) with CR of 40% (n/N=32/80) and median DOR of 34.6 months (95% CI: 26.1–NR), in pts with R/R diffuse large B-cell lymphoma (FDA approved indication). These preclinical and clinical observations from phase 2 trials suggest a potential clinical benefit of tafasitamab plus LEN and rituximab for pts with R/R FL or MZL.
Aims: This phase 3 double-blind, placebo-controlled, randomized study is designed to investigate whether tafasitamab plus LEN and rituximab provides improved clinical benefit compared with LEN and rituximab in pts with R/R FL or R/R MZL.
Methods: Pts will be randomized 1:1 to receive tafasitamab (12 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle [cycles 1–3], then days 1 and 15 [cycles 4–12]) plus LEN (20 mg PO QD [or starting dose 10 mg PO QD if creatinine clearance ≥30 to <60 mL/minute], days 1–21/ cycle for 12 cycles) and rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then day 1 of cycles 2–5), or placebo (0.9% saline solution IV) plus LEN and rituximab. At randomization, stratification factors will include: progression of disease within 24 months (FL; yes vs no), refractoriness to prior anti-CD20 mAb therapy (FL; yes vs no), and number of prior lines of therapy (FL or MZL; <2 vs ≥2). Radiological (PET) assessment will be performed at baseline, every 12 (± 2) weeks in year 1, 16 (± 2) weeks in years 2–3, and 24 (± 3) weeks in years 4–6; additional assessment performed within 4 (± 2) weeks if progressive disease confirmed before end-of-treatment visit. The primary study endpoint is PFS (investigator assessed [INV] by Lugano 2014 criteria) for pts with FL. Key secondary endpoints are PFS (INV) in overall population (FL and MZL), PET-CR rate (INV) at end of treatment (4–8 weeks after last treatment) and OS in pts with FL. Inclusion criteria include age ≥18 y, histologically confirmed FL (grade 1, 2, or 3a) or MZL (nodal, splenic, or extranodal), documented R/R disease, ≥1 prior systemic anti-CD20 therapy (including anti-CD20 refractory disease), ECOG PS ≤2, adequate systemic organ function, and high tumor burden (per GELF criteria). Exclusion criteria include prior rituximab plus LEN treatment, history of radiotherapy for other diseases (≥25% of bone marrow), nonhematologic malignancy, congestive heart failure (LVEF <50%), active systemic infection, known CNS lymphoma, or severe immunocompromised state. inMIND (NCT04680052, EudraCT2020-004407-13) is currently enrolling pts; planned enrollment is 528 pts with R/R FL and 60–90 pts with R/R MZL. Centers across Europe, Asia Pacific and North America are expected to participate in this study.
Results: Not applicable
Summary/Conclusion: Not applicable

PB1573 OUTCOMES OF BENDAMUSTINE + RITUXIMAB FIRST-LINE THERAPY IN PATIENTS WITH INDOLENT NON-HODGKIN'S LYMPHOMA OR MANTLE CELL LYMPHOMA: REAL WORLD EXPERIENCE

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Background: Bendamustine plus rituximab (B+R) was established as a preferred first line therapy for patients with previously untreated indolent non-Hodgkin's lymphoma based on the BRIGHT and STIL trials. However, only few reports on efficacy and safety data of this combination in the real-world setting are available to-date.
Aims: To assess pattern of bendamustine + rituximab administration, efficacy and safety in non-clinical trial setting.
Methods: We conducted a retrospective review of patients who received therapy with B+R in our cancer center from June 2013 to dECEMBER 31, 2020. Patients with indolent non-Hodgkin's lymphoma (iNHL) and mantle cell lymphoma (MCL) who received at least one cycle of B+R were evaluated.
Results: Amongst a total of 201 patients 56% were males and 44% females. Median age at B+R initiation was 72 years (range 34-94). Follicular lymphoma (FL) (50.3%), marginal zone lymphoma (MZL) (19.4%), and lymphoplasmacytic lymphoma (LPL) (14.5%) were the most common iNHL. Stage 3 and 4 diseases represented 19.9% and 68.6% of patients. Extranodal disease was found in 35.8%. The proportion of patients with high-risk disease was 48.5% for FL (FLIPI score ≥3), 86.6% for LPL (WMISS score ≥2), and 80.5% for MCL (MIPI score ≥6.2). History of secondary malignancy was presented in 23.4% of patients; 88.6% had ECOG 1-2, and 11.4% ECOG 3. Most common indications for B+R initiation were bulky symptomatic lymphadenopathy (69.1%), cytopenia (36.8%) and constitutional symptoms (36.8%). Fifty-eight percent of patients had more than one indication for therapy. Median number of B+R cycles delivered was 6 (range: 1-6), median dose of bendamustine was 90 mg/m^2 (range: 45-90). Full doses of bendamustine were given in 66.7% of patients. In patients (33.3%) with dose reduction, the mean dose was 78.3 mg/m^2. A total of 50.8% completed 6 cycles with no delays; and 49.2% of treatment was delayed (mean delay time:1.8 weeks). Overall response was 94.5%, with 77.1% complete and 17.4% partial remission. Median follow-up duration was 35 months (range: 4-91). At the end of follow-up, event free survival (EFS) was 77.1% and overall survival (OS) was 79.6%. Six percent of patients relapsed. In total, 14.5% develop secondary malignancies (6.5% non-hematological and 8% hematological) including 14 cases (7%) of aggressive B-cell lymphoma and 2 cases of myelodysplastic syndroms. A total of 16.9% of patients required support with G-CSF. The total number of adverse events was the highest in cycle one and decreased consistently with each cycle. Grade 3-4 neutropenia was recorded in 17.4%, febrile neutropenia in 8.0%, grade 3-4 anemia in 8.0%, and grade 3-4 thrombocytopenia in 3.9% of patients. Rituximab-associated infusion reactions were the most common in cycle 1 (46%) and 2 (16%). The rate of skin rash, fatigue, nausea/vomiting and infections were similar in each cycle. A total of 84.6% of patients proceeded to rituximab maintenance.



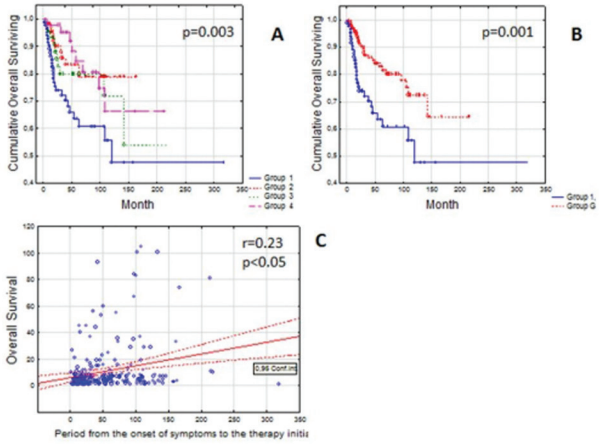
Summary/Conclusion: B+R chemoimmunotherapy was feasible to administer and retained its efficacy in non-clinical trial (real world) setting. HIgehr than previously reported rate of aggressive B-cell lymphoma was noted. No new adverse events of secondary non-hematological malignancies were found.

PB1574 ASSOCIATION OF DISEASE HISTORY DURATION AND SURVIVAL RATES IN FOLLICULAR LYMPHOMA PATIENTS AS A NEW FACTOR OF UNFAVORABLE PROGNOSIS.

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Background: Indolent and aggressive lymphomas differ in clinical course with a short anamnesis and a rapid increase in tumor mass characterized for the latter. However, the factor oh the disease history duration (DHD) is not sufficiently studied within nosological forms. At present DHD as a factor of patient risk stratification is not included in any prognostic scale.
FL grade 3 is a very heterogeneous group of patients with different outcomes of the disease. So new stratification factors research is encouraged for FL grade 3 patients.
As genetic analysis is not readily available in general practice and, moreover, no key unfavorable genetic abnormalities have been identified for FL with an unfavorable prognosis, such a clinical parameter as DHD could be a feature reflecting the biological rate of tumor development.
Aims: To determine the prognostic value of DHD in patients with FL grade 3 and transformation of FL into large-cell lymphoma.
Methods: The medical histories of 257 patients with FL high-grade from 1998 to 2020 were analyzed. Based on DHD values the following groups of patients were formed: group 1, DHD less than 3 months (#85); group 2, DHD from 3 to 6 months (#72); group 3, DHD from 6 to 12 months (#49); group 4, DHD more than 12 months (#51). Statistical analysis was carried out in STATISTICA 12 software (StatSoft, USA). Pearson correlation, $\chi 2$ test, Kaplan-Meyer survival analysis, Log-Rank test were used. Overall (OS) and event-free (EFS) survival were studied as control points.
Results: When comparing four patients groups the lower OS and EFS in group 1 (Figure 1A) were noted. Survival rates in groups 2, 3, and 4 were almost identical, which allowed us to merge into them into general group G. The following statistically significant differences ($p<0.05$) were found between group 1 and group G: 3 year OS was 71% and 87%, and 10-year OS – 47% and 72%, respectively (Figure 1B). 3-year EFS in groups 1 and G were 38% and 61% and 10-year EFS –20% and 41%, respectively (are not illustrated).
The association of DHD and OS was also confirmed by the correlation analysis ($r=0.23$, $p<0.05$) (Figure 1C).
In the $\chi 2$ test, there were no differences between the groups in the following terms: FL grade, complete and partial remission or disease progression frequency, Ann-Arbor stage, bulky lymph nodes presence, bone marrow involvement, as well as immune chemotherapy regimen (high-dose therapy, CHOP, EPOCH and others). In group 1, the frequency of high risk FLIPI-1 values was slightly higher, but not statistically significant.
Thus, clinical features of patients groups with different DHD were comparable, which suggests a reliable association OS, EFS and DHD.



Summary/Conclusion: We suggest that the association of DHD and survival rates in FL patients is not only a clinical observation. Currently, the hematopoiesis chronology phenomenon is not sufficiently studied. This interesting area of hematology implies the existence of regular rhythms of cell differentiation. The tumor stem cell resting period and its proliferation activation time, in contrast to the normal precursor, are apparently individual and predetermined by the tumor genome. So DHD considered in the study may reflect this tumor chronological nature. In this regard, the relationship with patient survival rates becomes clear.
The practical result of this work is the identification of a new factor of unfavorable prognosis, which can potentially be used in FL prognostic scales design.

PB1575 TOWARDS PERSONALIZED MEDICINE FOR RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS: THE CANTERA LUPIAE REGISTRY

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Background: Follicular lymphoma (FL) is a highly heterogeneous entity with variable clinical outcomes. In some patients, the disease follows an indolent course with durable remissions after treatment, while in others transformation or aggressive and chemotherapy-resistant disease develops (Tan et al., Blood 2013). Especially early relapse within 2 years (POD24) identifies a poor-prognosis group of patients with an unmet medical need (Casulo et al., J Clin Oncol 2015). Current knowledge is insufficient to identify patients with high-risk disease, nor to guide treatment decisions.
Aims: In this study we aim to define the prognosis of refractory/relapsed FL after second line therapy, to report current treatment strategies, and to provide rationale for the design of novel treatments strategies. In addition, the project provides ground for an international network of young lymphoma researchers and promotes multicentric collaborations. We here present preliminary data on patient and disease characteristics at diagnosis and at relapse.
Methods: We initiated an international, prospective, observational registry to study the clinical course of relapsed/ refractory (R/R) FL (NCT04587388). Patients with histologically confirmed FL are registered in the study at the time of the first event after first-line treatment, documented by biopsy, imaging, or clinical evaluation. Primary and secondary outcome measures are: (1) rate of progression of disease within 24 months from start of second line treatment (second POD24),

(2) overall survival (OS), (3) progression-free survival after second line therapy (second PFS), and (4) complete response rate at 30 months (CR30) from start of second line treatment (second CR30). The study was approved by the Ethics Committee of all participating centers.
Results: The project was initiated in the Netherlands in 2019, and as of December 2020 46 consecutive R/R FL patients have been included at 11 sites in 6 countries. On 42 patients with available data, one third experienced relapse and one third progression of previously stable/ responding disease, while 13 events occurred during treatment (either induction or maintenance therapy). The median time between initial diagnosis and relapse/ progression was 34 months (range 1-245; n = 38); relapse/ progression occurred within 24 months (POD24) in 12 patients. Details on patients and disease characteristics are summarized in Table 1. Although the number of patients does not allow correlative analysis, various findings stand out, a.o.: (1) the variable use of the FDG-PET scan, especially at initial diagnosis (60%); (2) the differences in choice of chemo-immunotherapy regimen; and (3) more strikingly the variance in application of maintenance therapy after first-line treatment (yes: 51%).

Table 1. Patient and disease characteristics

Patient characteristics		Number (%) at diagnosis	Number (%) at relapse
Age	>60	17/42 (41)	27/46 (59)
Gender	Female	14/46 (30)	
Relevant Medical history	Yes	28/44 (64)	
B-symptoms	Presence	9/43 (21)	5/42 (12)
ECOG-PS	>1	2/42 (5)	5/38 (13)
Disease characteristics			
FL Grade	1-2	31/43 (72)	27/40 (68)
	3a	8/43 (19)	6/40 (15)
	NA	4/43 (9)	3/40 (7)
	3b		1/40 (3)
	tFL		3/40 (7)
Bcl2 translocation	Positive	18/22 (82)	15/17 (88)
Bulky	Present (>7cm)	15/40 (38)	6/41 (15)
Extranodal involvement	Yes	14/40 (35)	15/41 (37)
Bone marrow biopsy	Positive	16/36 (44)	10/26 (38)
Ann Arbor stage	I-II	5/38 (13)	6/39 (15)
	III-IV	33/38 (87)	33/39 (85)
Laboratory results			
Hemoglobin	<12g/dl	10/35 (29)	8/40 (20)
B2M	>UNL	8/17 (47)	8/18 (44)
LDH	>UNL	14/35 (40)	15/39 (39)
Albumin	<3,5g/dl	0/23 (0)	1/28 (4)
Staging and prognostication			
PET-scan	Performed	24/40 (60)	36/41 (88)
FLIPI	0-1	7/34 (21)	
	2	11/34 (32)	
	3-5	16/34 (47)	
FLIPI2	0-2	11/25 (44)	
	3-5	14/25 (56)	
PRIMA-PI	Low	7/28 (25)	
	Intermediate	8/28 (29)	
	High	13/28 (46)	
Treatment			
Immunochemotherapy	R-CHOP	23/39 (59)	3/25 (12)
	R-CVP	5/39 (13)	1/25 (4)
	R-benda	2/39 (5)	7/25 (28)
	R mono	1/39 (3)	1/25 (4)
	Obinu-benda	0/39 (0)	4/25 (16)
	Other	8/39 (20)	9/25 (36)
	HDT	0/39 (0)	2/27 (7)
Maintenance	Yes	20/39 (51)	6/22 (27)
Radiotherapy	Yes	5/42 (12)	1/27 (4)
Response	CR	23/39 (59)	13/18 (72)
	PR	11/39 (28)	2/18 (11)
	PD	5/39 (13)	3/18 (17)

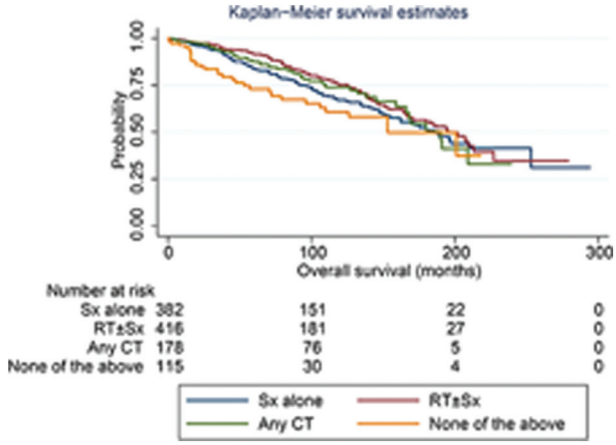
Summary/Conclusion: This is the first report on proceedings of the LUPIAE FL registry. Data on the first set of included patients confirm variability in diagnostic and therapeutic approaches in centers across Europe. We aim to further extend our registry (to 500 patients) to allow characterization of the clinical course of R/R FL. The ultimate goal is to understand the optimal management of patients with POD24 and use these data as a rationale for the design of an interventional trial for this group of patients. Ancillary biological studies will be planned depending on samples availability and enrolment.
Furthermore, this project has already shown the feasibility of a collaboration between junior hematologists across Europe, which will be the base for future initiatives. All hematologists (also from outside of Europe) are invited to join the project.

PB1576 CONVENTIONAL INTERVENTIONS FAILED TO PROVIDE SURVIVAL BENEFIT FOR EARLY-STAGE MAJOR SALIVARY GLAND MARGINAL ZONE LYMPHOMA

H. Liu [1], L. Cao [1], C. Yang [1], Y. Miao [1], X. Du [1], R. Huang [1], H. Zhu [1], X. Shi [1], W. Xu [1], J. Li [1], L. Fan [1,*]

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Background: Major salivary gland marginal zone lymphoma (MSGMZL) is a rare malignant tumor with predominantly early-stage (I/II) lesions.
Aims: This study aims to identify prognostic factors in early-stage MSGMZL and compare long-term outcomes of conventional approaches.
Methods: We conducted a population-based cohort study utilizing the Surveillance Epidemiology and End Results (SEER) database and used log-rank test, Cox regression, and propensity score matching (PSM) analyses to explore the association of characteristics and therapeutic methods with survival.
Results: We identified 1,091 early-stage MSGMZL cases with a median follow-up of 81.0 months. Univariate and multivariate analyses indicated that age over 60 years at diagnosis, diagnosis before 2005, and coexisting malignancy were unfavorable independent predictors for overall survival; the former two also were adverse predictors for disease-specific survival. By PSM, we compared the effects of conventional interventions, including surgery, radiotherapy, and chemotherapy, and found no statistically significant differences between treatments after matching. In the subgroup analysis according to the above prognostic factors, there was inadequate data to identify any one of the conventional therapies as superior to the others. A notable one is patients diagnosed after 2005 had better survival curves than those diagnosed before 2005 with the same strategy, indicating that there might other therapy involved in the treatment of patients with early-stage MSGMZL. According to the literature, the anti-CD20 monoclonal antibody is the most promising drug responsible for improved survival.



Summary/Conclusion: In this retrospective study from a database, conventional interventions failed to provide any survival benefit for early-stage MSGMZL patients. A novel therapy might be a better alternative.

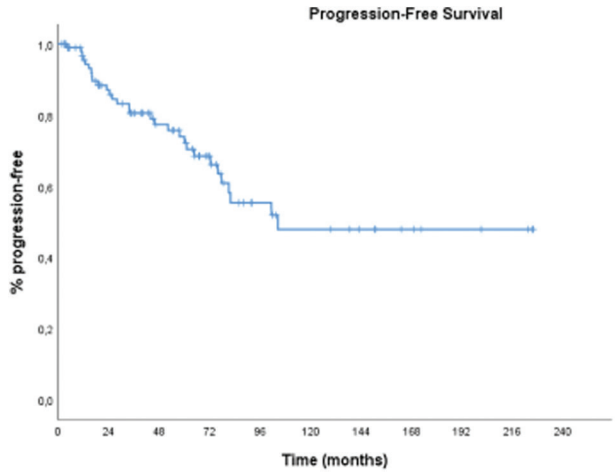
PB1577 EARLY STAGE FOLLICULAR LYMPHOMA: A CURABLE DISEASE? LONG-TERM FOLLOW-UP FROM A SINGLE UNIT.

S. Diavati [1,*], T. Giannikos [1], P. Tsirkinidis [1], M. P. Siakantaris [1], P. Tsaftaridis [1], E. Plata [1], J. V. Asimakopoulos [1], E. Konstantinou [1], D. Galopoulos [1], I. Vassilopoulos [1], E.-F. Triantafyllou [1], M. Belia [1], C. Chatzidimitriou [1], M. Efstathopoulou [1,2], G. Tsourouflis [3], M. Moschogiannis [2], S. Sachanas [2], X. Giakoumi [2], G. A. Pangalis [2], K. Konstantopoulos [1], T. P. Vassilakopoulos [1], M. K. Angelopoulou [1]

[1]Hematology and BMT Department, Laikon General Hospital, [2]Department of Hematology, Psychikon Branch, Iatriko Athinon, [3]2nd Department of Propaedeutic Surgery, Laikon General Hospital, Athens, Greece

Background: Early stage follicular lymphoma (FL) is considered a potentially curable disease. Involved-field radiotherapy (IFRT) ± immunotherapy/immunochemotherapy is the standard treatment approach by most centers, although few data exist from randomized clinical trials. Long-term follow-up is needed to rule out very late relapses.
Aims: The aim of the present study was to assess the long-term outcome and identify prognostic factors and best treatment approaches in a series of patients with localized FL treated in a single unit.
Methods: This is a retrospective analysis on 106 consecutive localized FL patients diagnosed between 2000 and 2020 from a single center. The mean follow-up of the patients is 82.3 months. The following parameters were evaluated as possible prognostic factors: stage, age, gender, histological grade, ki-67, hemoglobin, LDH, monocyte count, lymphocyte count, bulk (>/= 7cm), FLIPI score and type of treatment.
Results: Median patients' age was 56,4 years and 67 (63%) were females. 72 (68%) cases were histological grade 1/2 and the remaining 34 (32%) were grade 3A. 71 patients (67%) were Stage 1 and 35 (33%)

Stage 2; 94 patients (88,7%) had performance status 0. 14 patients (13.3%) has an elevated LDH and 19 (18.1%) had bulky disease. IFRT was delivered in 50 (47.6%) patients and anti CD20+ antibody (Ab) in 74 (70.5%). More specifically 21% received IFRT only, 29% received IFRT+Rituximab, 45% received anti CD20+ Ab+chemotherapy and 5% received chemotherapy only. Complete response was achieved in 92,3 %. 31 patients progressed (among these 35% within 24 months from initiation of treatment; 93% experienced limited stage disease at first relapse). Of note, there was a median progression free survival (PFS) of 104,39 months and a 5-and 10-year PFS of 74% and 48% respectively. Most importantly, a plateau in the PFS curve was observed at 8.7 years. At last follow up, 10 patients (9,4%) had expired but only 5 (4.7%) died due to lymphoma, resulting in a 10-year overall survival (OS) of 88% and a 10-year disease specific survival (DSS) of 95%. There was no significant difference in PFS, OS and DSS according to treatment. Bulky disease was the only poor prognostic factor for PFS, although with marginal significance, whereas stage, bulk and FLIPI score were prognostic for DSS.



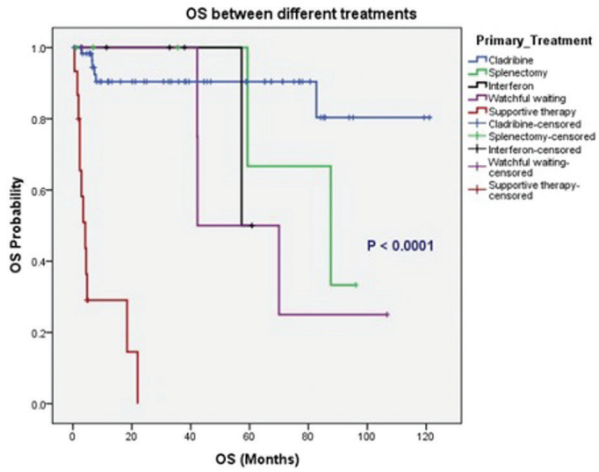
Summary/Conclusion: With long follow-up, early stage FL is a curable disease for the majority of patients with no relapses observed after 8.7 years, irrespectively of treatment. Bulky disease seems to be the most important prognostic parameter.

PB1578 HAIRY CELL LEUKEMIA: SINGLE CENTER EXPERIENCE

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[1]Medical Oncology Unit, Oncology Center, Mansoura University, [2]Medical Oncology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, [3]Adult Bone Marrow Transplantation Unit, [4]Pathology Department, Oncology Center, Mansoura University, [5]Pathology Department, Faculty of Medicine, Mansoura University, [6]Clinical Hematology Unit, Oncology Center, Mansoura University, [7]Clinical Hematology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Background: Hairy cell leukemia (HCL) is an uncommon chronic B cell lymphoproliferative disorder that represents approximately 2% of all leukemias and less than 1% of lymphoid neoplasms. The lack of large national and international registries on HCL has limited the ability to identify clear clinico-epidemiological characteristics in this rare disease.
Aims: To evaluate the hairy cell leukemia patients in Egyptian population as regard epidemiological, pathological, immunophenotypic, clinical data as well as treatment modalities and outcome.
Methods: This is a retrospective observational study in which 92 patients diagnosed with HCL were reviewed through the electronic health records between January 1, 2008 and December 31, 2019.
Results: Median age of patients was 50 years (23-81), patients have < 60 years represented 78.3%. Male to female ratio was 5.5:1. The prevalence of hepatitis c virus (HCV) infection was triple that of the general population and appeared to have no effect on overall survival (OS). Most patients (88%) had no comorbidities. The most common presentations were weakness and fatigue then B symptoms, 80% of patients had splenomegaly with a median of 21 cm (massive) and 19% had splenectomies. Hepatomegaly is reported in 40% of cases and uncommonly less than 2% of the cases had abdominal lymphadenopathy. Most of the patients had varying degree of cytopenia varying from pancytopenia (50%), bicytopenia (43.5%), thrombocytopenia (69.3%), leukopenia (53%) and anemia only (6.5%). Hairy cells in peripheral blood samples were observed in 18.5% of cases, dry bone marrow aspirates were in 40% and lymphoid aggregates in 79% of cases. Diffuse infiltrative pattern in bone marrow biopsies was observed in 75% of the patients and the pattern of infiltration posed no effect on overall survival. Regarding the therapeutic options; 61 patients received cladribine, five patients received interferon (INFa), six patients had palliative splenectomies, five patients were subjected to watchful waiting and 15 patients received supportive therapy. Irrespective of the received treatment; complete remission (CR) was achieved in 43.5% of the patients, 8.7% had partial remission (PR), 26.1% had stationary disease, 3.3% had progressive disease, 5.4% had treatment related mortality and 13% had disease related mortality. The presence of comorbidities, Age >60 years, fever, pancytopenia, hemoglobin level < 8 gm/dl and WBCs < 4 k/ml all inversely affected OS (p-value = 0.028, 0.002, 0.008, 0.03, 0.02, 0.02 respectively). After median follow up of 57 months, 68 cases (73.9%) were alive. The OS% of all the cases regardless of the treatment modality was 78% at 1 year, 65% at 5 years and 53% at 10 years. For the patients who received cladribine; 64% had CR and 11.5% had PR with a relapse rate of 19.5%. The OS with cladribine as first line was 91% at 5 years, 83% at 10 years. Treatment with cladribine improved OS in comparison to other treatment modalities (p < 0.0001).



Summary/Conclusion: HCL in Egypt is a rare NHL that have different clinicopathological features especially in association with hepatitis C infection that necessitate participation in international registries for HCL e.g. Hairy Cell Leukemia Foundation, to investigate the most optimal treatment strategies for these neoplasms in the real world population.

PB1579 MYD88 MUTATION IN WALDENSTROMSÖM MACROGLOBULINEMIA AND TREATMENT OUTCOME. A SINGLE CENTRE EXPERIENCE

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[1]Hematology, [2]Pharmacy, University Hospital Waterford, Waterford, [3]Cancer Molecular Diagnostics, St. James's Hospital, Dublin, Ireland

Background: Waldenstromsöm Macroglobulinemia (WSM) is an indolent mature B-cell neoplasm which accounts for 1 to 2% of all hematological malignancies. WSM is characterized by lymphoplasmacytic cells proliferation associated with a monoclonal immunoglobulin M (IgM). More than 90% of patients with WSM carry point mutation L265P in the MYD88 gene which is shown to be significant for diagnostic and risk stratification purposes.
Aims: This is a retrospective study to evaluate the treatment outcome of WSM patients treated at our institution between 2001 and 2021. Baseline demographic characteristics, clinical features, laboratory findings, including IgM levels and bone marrow findings at diagnosis, International Prognostic Score (IPSS-WM), treatment regimens, response to treatment were analysed. Survival outcomes according to MYD88 mutational status were assessed.
Methods: Patients were identified through our pathology database and data collected using patient's medical records and laboratory results and

patient informed consent obtained. All diagnostic BM aspirates were screened for evidence of MYD88 mutation and results correlated to patient's treatment outcome and survival.

Results: Thirty patients were included in this study, twenty (67%) male and ten (33%) female, with median age of 67years (range 50 – 86). At presentation 80% of patients had anaemia (20% at least grade 3), 60% had lymphadenopathy,30% had splenomegaly, and 30% of patients had IPSS-WM score 3 or greater. Four (13%) cases with bi-clonal B cell disorders (2 Multiple Myeloma, 1 Follicular lymphoma, and 1 Chronic lymphocytic Leukemia) and four patients with immune cytopenia (2 AIHA & 2 ITP). Twenty six patients (87%) received first line treatment (Figure 1). While the remainder four (13%) managed with watch & wait approach due to low disease burden or were not eligible for any treatment due to extreme frailty. Most of treated patients (92%) achieved either a good or very good partial response after first line therapy and only one patient achieved complete response (CR). Six patients (20%) had relapsed and received a second line therapy (1 FCR, 1 Chlorambucil, 1 Ibrutinib, 1 no further therapy due to extreme age, 1 patient with bi-clonal disease with CLL treated with Idelalisib and Rituximab and 1 moved to another institution). One patient underwent autologous stem cell transplant consolidation for relapsed disease after 4 lines of therapy. Twenty (67%) patients' diagnostic samples provide sufficient DNA materials suitable for MYD88 mutation screen. The majority (90%) of analysed samples were positive of MYD88 mutation and only two samples revealed wild-type MYD88 status. The median overall survival (OS) for the entire cohort was ~ 8.5 years (Figure 2). The OS at 36 months was 65%. At the time of the analysis, eighteen patients (60%) are still alive and either on treatment or on active surveillance. Twelve patient (40%) have died, the majority of deaths (67%) were unrelated to WSM but due to comorbidities, 17% related to treatment complications (sepsis) and two (17%) related to disease progression (both MYD88 mutated).

Figure 1 – First line treatment regimens

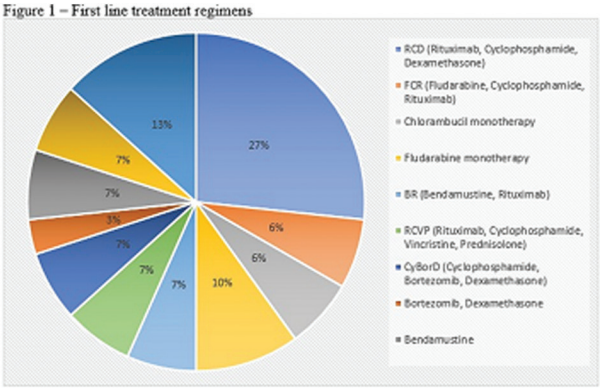
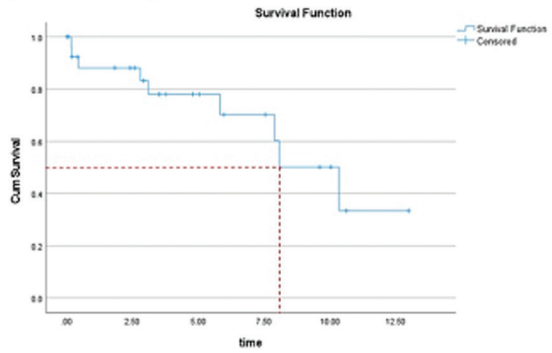


Figure 2 – Survival analysis



Summary/Conclusion: The frequency of MYD88 mutation in our study cohort is comparable with the reported literature. The overall survival in this study was 65% at 36 months and evaluating the MYD88 mutational status impact was limited due the small sample size and retrospective nature of this study. CXCR4 mutation screening for this study cohort is in progress and longer follow up will continue prospectively.

PB1580 RETROSPECTIVE STUDY ON MANTLE CELL LYMPHOMA (MCL) AND TREATMENT OUT-COME-A SINGLE CENTER EXPERIENCE.

E. Elhassadi [1,*], B. Hennessy [2], S. kumar [1], M. Nur [3], C. Shilling [3], L. Sutton [3], M. Catherwood [4]

[1]Haematology Department, [2]University Hospital Waterford, Waterford, Ireland, [3]Pathology Department, University Hospital Waterford, Waterford, Ireland, [4]Molecular Department, Belfast University Hospital, Belfast, United Kingdom

Background: Mantle Cell Lymphoma (MCL) is a rare type of non-Hodgkin lymphoma (NHL), with an aggressive clinical course. MCL is associated with poor prognosis and incurable disease in the majority of the patients. However, a minority of patients will not require any treatment for many years. Although MCL is initially responsive to different conventional chemotherapies, such a response is short-lived. The median overall survival in modern trials incorporating intensive therapy has improved accounting of 8 to 10 years. However *TP53* mutation continue to confers a dismal prognosis in MCL with a median survival of 1.3 years. Targeted therapy and recently more promising CAR-T therapy have revolutionized this disease out-come.

Aims: This is a single-centre, retrospective analysis of MCL patients treated over study period (2006-2020) to evaluate our MCL patients treatment out-come.

Methods: Using our MCL data-base, baseline patient's demographic characteristics, clinical features, laboratory findings, MIPI score, initial/subsequent treatment responses and survival were analysed. Patient's informed consent was obtained. Sub-set of patients have completed p53 disruption screen using both p53 expression on immuno-histochemistry (IHC) and mutational status and this genetic defect impact was evaluated here.

Results: Sixty-one patients were included in this study, with male predominance, median age 67 yrers and the majority with advanced disease. 50% presented with B symptoms and BM involvement in 35 (57%) patients (Table 1). Chemo-immunotherapy (CIT) remains the main treatment modality in our cohort (54/88% patients), resulted in an ORR of 79%, CR 55% and PR 24%, which compares well with the reported literature. 5 (8%) patients were not eligible for any treatment, one patient received IFRT only for early-stage disease and one patient had splenectomy. Rituximab maintenance was used in 29 (48%) and 3 (5%) patient had ASCT. 21 (39%) patients had relapsed disease,11(52%) patients treated with Ibrutinib as a second line, 7 (33%) patients treated with CIT, with one (5%) patient with HL relapse treated with ABVD and 2 (10%) patients were not suitable for further treatment. Eight (38%) experienced further disease relapse, 3 (14%) patients received Ibrutinib and 5 (23%) patient received CIT and 1 (1.6%) patient had Allo-SCT. At time of the study analysis, 40 (67%) patients were still alive and 23 (38%) patients had died. The median survival for all the cohort was 3 years (range 0-14 years). To date, 29 (46%) patient's samples screened for p53 disruptions, only 6 (10%) patient's sample demonstrate a high p53 expression and harboured deleterious *TP53* mutation by NGS sequencing. Most of MCL cases harbouring *TP53* mutations have an aggressive disease course with multiple disease relapses and lymphoma related deaths (80%). In sub-set analyses, the OS was only 4 years in *TP53* mutated disease and was not reached in wild-type *TP53* cohort (P value = 0.007, log rank test) which is comparable to the reported data. The median overall survival (OS) for the entire cohort was 7 years (Fig 1), according to disease sub-type classic vs blastic, the median survival were 8 years vs 2 years respectively.

Patient's Characteristics (61)	Patients No	%
Gender (M *vs* F)	44 *vs* 17	72% *vs* 28%
Median age	67	Range 36-88
Performance status (PS) = or > 2	17	28%
Early *vs* Advance stage	13 *vs* 48	20% *vs* 80%
Nodal *vs* Extra-nodal Disease	39 *vs* 16	64% *vs* 26%
Sub-Type Classical *vs* Blastic *vs* Indolent	54 *vs* 11 *vs* 5	74% *vs* 18% *vs* 8%
MIPI score High *vs* intermediate *vs* low	37 *vs* 12 *vs* 12	60% *vs* 20% *vs* 20%

Table 1 Patient's Characteristics

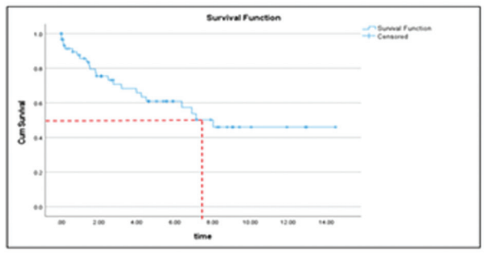


Figure 1 Entire Study Cohort KM OS survival curve

Summary/Conclusion: Mantle cell lymphoma (MCL) continue to be challenging disease to treat with a short lived treatment response and frequent relapses. Genetic risk stratification and clinical trials enrollement are of great importance. Our data showed comparable treatment outcome similar to the reported literatures.

Infections in hematology (incl. supportive care/therapy)

PB1581 PEGFILGRASTIM IN THE SUPPORTIVE CARE OF HEAVILY PRETREATED MULTIPLE MYELOMA IN POMALIDOMIDE-BASED TREATMENT

C. Cerchione [1,*], L. Catalano [2], D. Nappi [3], A. E. Pareto [4], G. Musuraca [1], A. Lucchesi [1], S. Ronconi [1], M. Ceccolini [1], F. Pane [2], G. Martinelli [1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), [2]Hematology, AOU Federico II, Napoli, [3]Hematology, Bolzano Hospital, Bolzano, [4]Hematology, San Giuliano, Giugliano (NA), Italy

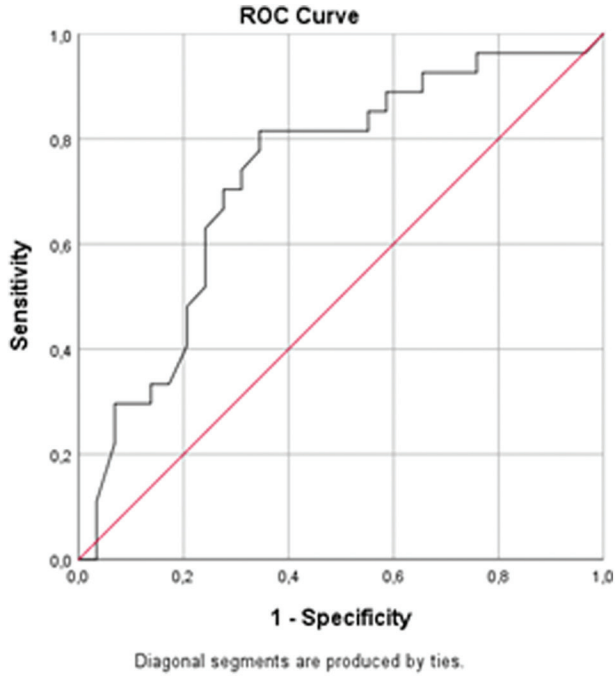
Background: Pegfilgrastim is a pegylated long-acting recombinant form of G-CSF that extends the half-life and allows for once-per-cycle dosing, requiring less frequent dosing than nonpegylated G-CSF.
Aims: The objective of this study was to compare the efficacy and safety of pegfilgrastim in patients affected by heavily pretreated MM, treated with pomalidomide-dexamethasone, in order to determine whether a single subcutaneous injection of pegfilgrastim is as effective as daily injections of standard filgrastim, in terms of haematological toxicity, febrile neutropenic episodes, antibiotic usage and hospedalization duration.
Methods: 57 patients (31 M and 26 F) were enrolled, median age at diagnosis 69 years (r. 52-84), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-12), every refractory to all the drugs previously received, received Pomalidomide-Dexamethasone (P 4 mg for 21 days, D 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. Since first course, received in domestic setting, with a very good compliance, patients performed blood counts once weekly and received, from day +8 to day +19, prophylactic oral chinolonic antibiotics and anti-fungal drugs. During neutropenia after first cycle, Filgrastim (5 µgr/kg/day for 3 days) was given if neutrophils count was <1500 x 10^9 cells/L.
Results: Median number of filgrastim administrations was 4.6 (r. 3-6); nadir neutropenia was registered after a median of 10.4 days (r. 7-14); median of nadir neutrophil count was 1.13 x 10^9 cells/L (r.0.3 – 1.5), with maximum duration of 14 days. From the second course, all patients switched to prophylaxis with pegfilgrastim (6 mg), injected subcutaneously with a single administration on day +3 independently from the neutrophil count at that time. During pegfilgrastim, neutropenia was never longer than 8 days, with a consequent reduction of neutropenia-related infections. Median nadir neutrophil count, evaluated for every patients for at least three courses of therapy (r. 3-6) registered at day +11, was 1.28 (r.0.9-2.2). Only 4 patients needed a supplement of 3 administrations of filgrastim. Pegfilgrastim was well tolerated in all patients: main side effects in our patients were mild fever and bone pain (21.2%).
Summary/Conclusion: In patients affected by heavily pretreated MM treated with pomalidomide-dexamethasone, pegfilgrastim seems to reduce the incidence of severe neutropenia and infections and may increase the possibility to maintain the scheduled time of treatment.

PB1582 PROGNOSTIC SIGNIFICANCE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN THE DETERMINATION OF SEVERE PROGNOSIS OF HEMATOLOGICAL PATIENTS WITH COVID-19 INFECTION. DATA OF MOLDOVAN HEMATOLOGICAL CENTER.

V. Tomacinschii [1,2,*], M. Robu [1], S. Buruiana [1], A. Golub [2], C. Dudnic [1], D. Urescu [1], V. Finciuc [1]

[1]Department of Hematology, Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, [2]Department of Hematology, Institute of Oncology of Republic of Moldova, Chisinau, Moldova, Republic of

Background: COVID-19 infection represents a continuous challenge for the medical society. . Patients with hematologic disease and a COVID-19 infection were found to have a significantly worse prognosis compared to the ones infected with COVID-19 but without hematological cancer.
Aims: Evaluation of neutrophil-to-lymphocyte ratio(NLR) as a potential marker of the severity and morbidity of COVID-19 infection among hematological patients.
Methods: A retrospective study was conducted on 56 COVID positive patients who have been hospitalized between July 2020 and January 2021. Medical records of the cases are analyzed and compared retrospectively for demographic, clinical, laboratory data, and radiological findings. The standard deviation, receiver operating curve (ROC) and area under the curve (AUC) were calculated to compare the diagnostic performance NLR into the determination of the disease severity.
Results: Out of 56 examined patients 29 (51,2%) were females, the median age of infection was 57 years (21–84 years). The most frequent hematological malignancies among the studies group were: Non-Hodgkin lymphomas (46,2%), followed by multiple myeloma(16%), acute leukemias(10,7%), chronic lymphocytic leukemia (7,1%), and others. 35 out of 56 patients developed a severe form of COVID-19 infection(62,5%), out of them, 27(77,1%) necessitating access into an ICU unit. Medium severity was detected in 16 patients(28,6%), mild form being diagnosed in just 5 of them(8,9%). The mortality rate in the study group constitutes 35,7%(20 of 56 patients). NLR had a mean of 8,03±7,41, having a lower index in patients with mild to moderate COVID-19: 6.11±6,09 and higher in the group of patients with severe forms: 9.18±7,96. On receiver operating characteristic curve (ROC) analysis, the predictive ability of NLR to detect critical patients was significant (p= 0.003; AUC:0.729), with an optimal cut-off value of 8.375 having 82% sensitivity and 66.7% specificity to determine the severe COVID-19 cases among hematological patients.



Summary/Conclusion: This study confirmed the high risk of mortality among hematological patients showed previously in the literature. Severe forms of COVID-19 were diagnosed in 62,5% of cases. The mortality rate in the study group constitutes 35,7%. NLR can be a useful tool in the prediction of severe cases of COVID-19 infection with quite high sensitivity (82%) but with a moderate specificity(66,7%).

PB1583 COVID-19 OUTCOMES OF PATIENTS WITH HEMATOLOGIC MALIGNANCIES: A SINGLE CENTER EXPERIENCE

N. Spyridis [1,*], D. Mallouri [1], T. Chatzikonstantinou [1], C. Demosthenous [1], N. Stavroyianni [1], A. Lalayanni [1], I. Batsis [1], I. Sakellari [1], A. Anagnostopoulos [1], D. Sotiropoulos [1]

[1]Hematology Department - HCT Unit, G.Papanikolaou Hospital, Thessaloniki, Greece

Background: SARS-CoV-2 is a novel coronavirus causing an infection, named Coronavirus Disease 2019 (COVID-19). As of February 22, 2021, the virus had affected more than 112 millions individuals and resulted in over 2,4 millions deaths worldwide. Mortality can be as high as 15% in elderly patients, and/or in patients with comorbidities. Data from studies suggest that patients with cancer have a higher incidence of severe events

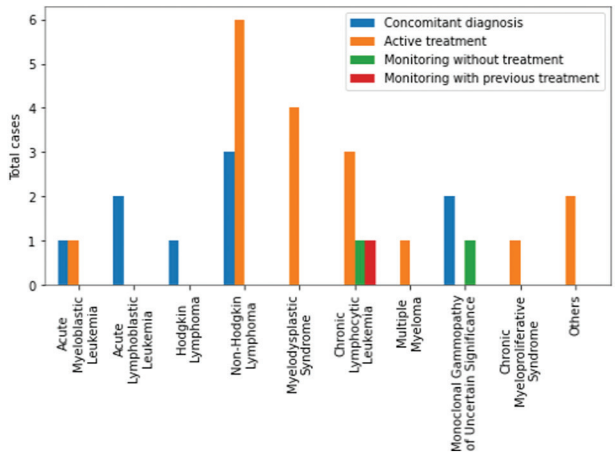
after contacting the virus. Very few data are available on COVID-19 outcomes in patients with hematologic diseases who are highly immunocompromised due to their underlying disease and the treatments they receive, with high risk of morbidity and mortality from COVID-19.
Aims: The purpose of this study was to perform a review to quantify the outcomes (hospitalizations and deaths) of patients with hematologic malignancy and COVID-19.
Methods: Our department consists of Hematology Clinic and BMT Unit. We included patients with a hematologic disease, with laboratory-confirmed COVID-19 infection between October 2020 and February 2021. A confirmed case of COVID-19 was defined by a positive result on RT-PCR assay. We reviewed hematological medical records to collect demographic, clinical, and treatment data and outcomes of COVID-19. We evaluated 73 patients (43 male, 30 female, median age 61). Information extracted included total number of patients, coronavirus symptoms, hospital admission rate, death rate. Hematologic malignancy subtypes were: acquired bone marrow failure syndromes; acute leukemias; lymphomas; chronic lymphocytic leukemia; plasma cell dyscrasias; MPNs; other hematologic conditions; stem cell transplantation.
Results: According to our analysis, regarding COVID-19 symptoms at diagnosis, 47 of 73 pts (64%) presented fever, as single symptom or combined with at least one more symptom, 20 of 73 pts (27%) presented two or more symptoms, including anosmia, cough, shortness of breath, myalgias, fatigue, while 9 of 73 pts (12%) were asymptomatic and diagnosis confirmed only with positive PCR test. Patients presented with moderate or severe COVID-19 were 28 of 73 (38%), while 9 of 28 hospitalized pts (32%) required Intensive Care Unit (ICU) admission.
Data collected regarding hematologic malignancy subtype showed: lymphomas, non including CLL, 24 of 73 pts (33%), CLL, 17 of 73 pts (23%), acute leukemias, 7 of 73 pts (10%), MPNs, 8 of 73 pts (11%), acquired bone marrow failure syndromes, 5 of 73 pts (7%), multiple myeloma, 3 of 73 pts (4%), other hematologic conditions 5 of 73 (7%), while patients who underwent transplantation were 4 of 73 (5%). Regarding treatment, patients divided in two subgroups, 52 of 73 (71%) received anticancer therapy at some time in their lives, while 21 of 73 pts (29%) have never been on treatment.
Total death rate was 23% (17 of 73 pts), while among hospitalized pts was nearly 54% (15 of 28), with all patients requiring ICU not surviving (9 of 9, rate 100%). 2 of 17 pts (11%) died without hospitalization. Death rate in CLL pts was 41% (7 of 17 pts) with 2 of 17 (11%) not on treatment, in lymphomas 16% (4 of 24 pts), while in other hematologic subgroups were reported from 1 to 2 deaths per group.
Summary/Conclusion: Hematological patients appear to be a population very vulnerable to COVID-19 infection, with significant morbidity and mortality. More data are necessary in further surveys from more centers and larger number of patients. Hematology departments should remain COVID-19 free zones dedicated only to hematologic treatment and patients should strictly comply with social distancing.

PB1584 SARS-COV-2 INFECTION IN HAEMATOLOGICAL PATIENTS: DESCRIPTIVE COHORT STUDY OF HOSPITALIZED PATIENTS IN A TERTIARY CARE CENTER

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Background: The novel coronavirus SARS-CoV-2 was officially detected in Spain on January 31, 2020. Since then, the health system has suffered 3 waves of healthcare pressure due to this pandemic infection. There was concern about the impact of Coronavirus 2019 disease (COVID-19) being significant in haematological patients.
Aims: Find out the mortality rate by COVID-19 in a cohort of hematological patients. Identify potential predictive parameters associated with poor outcome in patients with a diagnosis of haematological malignancy and COVID-19.
Methods: Retrospective and descriptive study of hospitalized patients in the Hematology Clinical Management Unit at our center, between February 12, 2020 and February 12, 2021. The patients had a diagnosis of a haematological malignancy and laboratory-confirmed COVID-19. We performed a Pearson correlation test on Phyton between variables of interest.
Results: 356 patients were admitted in the Hematology Unit in the referred period.
Of these, 30 had SARS-CoV-2 infection on arrival or during their hospital stay (10% nosocomial infection rate). We summarize in Table 1 total cases reported by diagnostic and state.
There was a male predominance (69%), with a median age of 67 years old [14-90]. Average days of symptom onset until admission: 7.81 days. Chest X-ray images at the diagnosis: bilateral pneumonia (37.9%), peripheral infiltrates (13.8%), unilateral infiltrates (17.2%).
Patients were treated according to local guidelines with high-dose corticosteroid pulses, remdesivir and interleukin inhibitors. Only 13,3% of them needed additional support in the Intensive Care Unit.
Mortality rate in our cohort was 30%. The mortality rate at our hospital for patients with COVID-19 and no haematological malignancy within the same period of time was 10%. By subgroups, non-Hodgkin's lymphoma (NHL) group was the neoplasm with largest number of deaths. 62.5% of these patients had a 4C Mortality Score between 1 and 8 points, ranking in the intermediate risk group. 55.56% (5/9) of them expired. Myelodysplastic syndrome (MDS) group had the highest 4C Mortality Score, with more than 10 points, placing itself in the high or very high-risk group. 50% (2/4) of them died.
We have found no correlation between the level of ferritin, Interleukin 6 (IL6), neutrophils, monocytes, platelets, D-dimer and successive clinical and radiological evolution in these patients, in contrast with other studies in the general population. We found a weakly positive relationship between the IL6 level at admission and the subsequent need to enter in the Intensive Care Unit ($r = 0.44$, $p<0.05$). We noticed a negative correlation between the IL6 level at admission and clinical improvement after treatment by protocol ($r = -0.21$ $p<0.05$), the day of symptom evolution at admission and age ($r = -0.58$ $p< 0.05$).



Summary/Conclusion:
- SARS-CoV2 infection incidence in our cohort was lower than expected, but the mortality rate was superior compared to hospitalized patients with no haematological malignancy.
- MDS group had the highest risk according to the 4C Mortality Score, with 50% of the patients dying due to the infection in our study. We think it may be related to older patients with more comorbidities. Mortality rate was also high in patients with NHL in spite of lower potential risk. Further prognostic scores should be developed in order to properly predict the risk of poor outcome in hematological patients.
- IL-6 seems to be a key component of the immune response to SARS-CoV-2 as well as clinical evolution, even in immunocompromised patients.

PB1585 CLINICAL CHARCTERISTICS AND RISK FACTORS OF SEVERITY OF COVID19 INFECTION IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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Background: Patients with hematologic malignancies are considered particularly vulnerable to COVID 19 infection due to their underlying malignancy and their anticancer therapy. However, there are still few data on risk factors of mortality in this population.
Aims: This study aimed to determine the clinical and biological characteristics of COVID-19 infection in hematologic patients and the risk factors of COVID-19 severity and mortality
Methods: This prospective study included all consecutives COVID 19 infected patients, treated for hematologic malignancies in the clinical hematology department of Aziza Othmana Hospital, between October 2020 and January 2021. Covid 19 infection was confirmed by PCR or rapid antigenic analysis of a nasopharyngal swab. We collected clinical, biological, radiological and outcomes data
Results: No cases of COVID 19 infection was diagnosed in our departement during the first COVID 19 wave. The first confirmed case was diagnosed on 12th october 2020. A total of 68 patients was included. Median age was 47 years with a sex ratio of 1.5. Twenty-nine (43%) patients were treated for acute leukemia, 24 (37%) for lymphoma, 6 (9%) for chronic lymphocytic leukemia, 6 (9%) for multiple myeloma and 3 (4%) for myelodysplastic syndrome. Forty-three patients (63%) had active disease (AD) while 37% were in remission (RD). Thirty-three patients (46%) had at last 1 comorbidity including diabetes (16%) and obesity (9%). The main symptoms of the infection were fever (63%), cough (49%), dyspnea (40%) and diarrhea (30%). Seventeen patients had a chest scanning, 12 of them (70%) had a damage greater than 25% of the surface area of the lungs (60% and 85% in the AD and RD groups respectively [p=0.15]). During the infection, 44% of patients had lymphopenia and 21% grade 4 neutropenia. Median dosage of C reactive Protein was of 154 mg/l [1.9-658].
Twenty (29%) patients developped severe infection (37% and 16% in the AD and RD groups respectively [p=0.09]). Seven (10%) of them required admission in an intensive care unit (14% and 4% of the AD and RD groups respectively[p=0.14]). Significant risk factors of the severity of the infection were: age >45 years (p= 0.008), the presence of at least 1comorbidity (p=0.009), dyspnea (p< 0.0001) and a dosage of C reactive protein superior to 150 mg/l (p =0.033). Twelve patients (18%) died from COVID19 infection (23% and 8% in the AD and RD groups respectively[p=0.11]). Dyspnea and grade 4 neutropenia were the independent risk factors of death (p=0.011 and p=0.049 respectively).
Summary/Conclusion: In this study of patients with hematological malignancies, high rates of COVID19 infection severity and associated mortality was noted especially in neutropenic patients. Although no difference was observed in the radiological severity between AD and RD groups, there was a trend to a more clinically severe infection in the AD group.

PB1586 BACTEREMIA IN PEDIATRIC PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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Background: Bacteraemia adversely affect the outcome of pediatric patients with hematologic malignancies.
Aims: This study aimed to describe the epidemiology, outcome, and factor influencing mortality of bacteremia in children with hematologic malignancies.
Methods: This is a descriptive retrospective study. Data belonging to bacteraemia in pediatric (<16 years) patients with hematologic malignancies admitted in our department of hematology during the period spanning from January 2010 and November 2019 were analyzed. Risk factors with a P-value less than 0.20 were initially included in the binary logistic regression model to determine the independent risk factors for mortality Bloodstream infection in adult hematologic malignancies. Factors described in previous literature were also included in the model. Then the model was reduced by means of manual backward elimination. P values ≤ 0.05 were considered statistically significant.
Results: One hundred thirty nine bacteremia episodes among 110 patients were identified. Underlying diseases were acute lymphoblastic leukemia (ALL) 106(76.3%) which far exceeds acute myeloid leukemia (AML) 29 (20.9%). The bacteraemia occurred in 68 patients with uncontrolled/relapse or refractory disease. The majority of BSI episodes occurred in the presence of severe neutropenia (62.6%). Ninety-four (67.6%) of the culture isolates were Gram-negative bacteria and 45 (32.4%) were Gram-positive bacteria. Klebsiella species and Escherichia coli were the most common Gram-negative isolates. Staphylococcus aureus and staphylococcus epidermidis were the most common Gram-positive isolates. A multidrug-resistant bacteria was present in 31 (22.3%) cases. In 96 (69.1%) episodes, patients received an appropriate antibiotherapy. Complications occurred in 24 (17.3%) episodes of bacteremia. seven children died during bacteremia, giving a case-fatality rate of 5%. The independent risk Factor influencing mortality were: qSOFA>2 (P: 0.002).
Summary/Conclusion: Bacteremia in these patients was caused mainly by Gram-negative microorganisms and was associated with a low case-fatality rate. Factor influencing mortality was qSOFA>2.

PB1587 INCIDENCE OF CELL-MEDIATED IMMUNODEFICIENCY-RELATED INFECTIOUS DISEASES IN THE HEMATOLOGIC DEPARTMENT OF A COMMUNITY HOSPITAL: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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Background: Cell-mediated immunodeficiency-related infectious diseases occasionally occur in the hematologic department of our hospital, although with much lower incidence than neutropenia-related infections other than stem cell transplantation (SCT).
Aims: In this study, we explored which hematologic diseases (HD) and treatments are most likely to be associated with certain infectious diseases in our hospital.
Methods: We retrospectively extracted data on patients who were infected with specific cell-mediated immunodeficiency-related pathogens prior to December 31 2020 in the hematologic department. Target patients had been diagnosed between January 1 2010 and December 31 2019 with representative HD, which included leukemia, lymphoma, myeloma, myelodysplastic syndrome, myeloproliferative neoplasm, warm autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura, and aplastic anemia. Patients who had more than one HD were categorized according to the predominant disease during infection. The pathogens of focus were Cytomegalovirus (CMV), *Cryptococcus* (Crypto), *Listeria* (Lis), *Nocardia* (Nocar), *Mycobacterium tuberculosis* (TB), *Mycobacterium* other than TB (AM), and *Pneumocystis jirovecii* (PC). These pathogens were selected based on the outbreak situation in our area, diagnostic facilities in the hospital, and pathogens that rarely occur in other immunodeficiency status like neutropenia or humoral immune defect. Infectious pathogens were defined by cell culture, pathology, or PCR and needed treatment. We excluded patients who were: (1) infected and treated before diagnosis of HD; (2) infected after SCT; (3) diagnosed in another hospital and admitted for treatment of the infectious disease; (4) only diagnosed by immunological or serological tests; (5) diagnosed with a rare HD, seen in fewer than one patient per year. Patient characteristics, type of infectious disease, underlying diseases, and treatment outcomes were analyzed.

Results: Of the 1,904 patients who were diagnosed with the HD during the specified period, 22 patients (1.2%) were infected with pathogens CMV (n = 3), Crypto (4), Lis (4), Nocar (1), TB (3), AM (3), and PC (4). Median age of the patients was 71 years (49–94 years). Primary sites of infection were identified as pulmonary for TB, PC, AM, and Nocar (n = 11), meningitis for Crypto and Lys (5), colitis for CMV (3), and sepsis for Lys (3). Types of treatment for HD undertaken at the time of infection were chemotherapy (n = 9) (cyclophosphamide plus steroid [2], R-CHOP [1], daratuzumab [1], anthracycline plus cytarabine [1], dasatinib plus steroid [1], and others [3]), steroid (7), and no treatment or completed (4). Two patients were diagnosed with infections at the time of HD diagnosis. Seventeen patients recovered from the infections, while five patients died during treatment. All deceased patients had poor control of their HD. HD associated with multiple infectious diseases were: AIHA (n = 5/21, 23.8%; Crypto [2], CMV [1], TB [1], AT [1]); angioimmunoblastic T-cell lymphoma (n = 3/29, 10.3%; Crypto [1], CMV [1], PC [1]); multiple myeloma (n = 3/186, 1.6%; PC [2], Lis [1]); acute lymphoblastic leukemia (n = 2/53, 3.8%; PC [1], TB [1]); and diffuse large B cell lymphoma (n = 2/465, 0.4%; TB [1], AM [1]).
Summary/Conclusion: Over 20% of AIHA patients were infected with cell-mediated immunodeficiency-related infectious diseases. Long-term steroid administration may have been the main contributing factor, although underlying diseases that cause immunodeficiency should also be considered.

PB1588 REAL-WORLD GLUCARPIDASE UTILIZATION IN MALIGNANT HEMATOLOGY PATIENTS RECEIVING HIGH-DOSE METHOTREXATE: A SINGLE INSTITUTION EXPERIENCE

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Background: High-dose methotrexate (MTX) is a key agent for several chemotherapy regimens for various disease states. Its main role relates to its ability to penetrate the central nervous system. Toxicity due to inefficient MTX clearance (Cl) can lead to significant morbidity and mortality. Glucarpidase (GP) is a recombinant enzyme that rapidly reduces MTX concentrations and is currently approved by the United States Food and Drug Administration for patients with toxic MTX concentrations associated with delayed Cl due to impaired renal function. Literature regarding its utilization in the off-trial setting is sparse and mainly limited to case reports. Available literature does not frequently address other issues which could concurrently impact MTX Cl and toxicity, such as supportive care measures or alternative causes of delayed drug elimination.
Aims: To assess the real-world utilization, safety, and efficacy of GP in malignant hematology patients receiving high-dose MTX at a single tertiary care cancer institution who developed MTX-related toxicity and delayed Cl.
Methods: A retrospective, single-center chart review of 19 adults with hematological malignancies who received GP after high-dose MTX-based therapy at Moffitt Cancer Center from January 1, 2012 to November 24, 2020 was conducted. Data collected was descriptive in nature and focused on patient demographics, GP utilization, supportive care measures, and outcomes.
Results: Patient demographics, GP utilization, and supportive care measures are featured in Table 1. Subjects received a median 5000 units (range 2000-7000 units) of GP at a median of 54 hours (range 40-86 hours) post-MTX initiation. Fifteen patients had drug levels available ~36-48 hours after MTX initiation (the remaining four's last MTX levels were well before this timeframe and would have skewed the comparison). GP resulted in a median 93% (range 15-97%) decrease in those concentrations at a median of 73 hours (range 61-84 hours) after enzyme administration. No significant adverse events related to GP occurred. The most common MTX-related toxicities included nephrotoxicity (N=19, 100%), neutropenia (N=6, 32%), hepatotoxicity (N=4, 21%), and infection (N=4, 21%). Serum creatinine (SCr) increased a median of 200% (range 38-700%) and renal recovery, defined as SCr return to within 50% above baseline SCr, occurred in fifteen patients (79%) at a median of 14 days (range 4-48 days). Median total duration of hospital stay (from initial admission to discharge) was 15 days (range 9-45 days), while median time to MTX Cl (level ≤ 0.1 µm/L) in the sixteen patients achieving that concentration was 12 days (range 5-19 days). One patient (5%) was rechallenged with MTX in the future and did not require GP. Three (16%) and four patients (21%) experienced 30- and 100-day mortality, respectively. Three subjects (15%) died of toxicity directly attributed to MTX.

Table 1: Patient Demographics, Glucarpidase Utilization, and Supportive Care Measures

Demographics	
Height, cm*	175 (158-199)
Weight, kg*	97 (55-132)
BMI, kg/m²*	30.9 (21-40.4)
BSA, m²*	2.14 (1.56-2.6)
Age, years*	66 (19-74)
Gender	
Male, N (%)	10 (53)
ECOG Performance Status*^	1 (0-3)
KPS Scale*^	70 (40-100)
Disease	
DLBCL, N (%)	6 (32)
PCNSL, N (%)	4 (21)
ALL, N (%)	5 (26)
Other, N (%)	4 (21)
Treatment Setting	
Prophylaxis, N (%)	11 (58)
Suspected/Known CNS Disease, N (%)	8 (42)
Regimen	
HyperCVAD, N (%)	5 (26)
High-Dose MTX +/- Rituximab, N (%)	8 (42)
DeAngelis Regimen, N (%)	2 (11)
Other, N (%)	4 (21)
Prior High-Dose MTX Administration, N (%)	6 (32)
If Received Prior High-Dose MTX, Number of Doses*^	3 (1-5)
MTX Dose, mg/m²*	3500 (1000-8000)
Baseline MTX Dose Adjustment, N (%)	2 (11)
Baseline Serum Creatinine, mg/dL*	0.8 (0.5-1.5)
Drug Interactions in Proximity to MTX Administration, N (%)	1 (5)
Radiographic Contrast 72 Hours Before/After MTX, N (%)	4 (21)
Pleural Effusion or Ascites During Episode, N (%)	7 (37)
GP Utilization	
GP Dose, units*	5000 (2000-7000)
Dosing Weight Used	
Actual Body Weight, N (%)	16 (84)
Other, N (%)	3 (16)
Time to Administration of GP from MTX, hours*	54 (40-86)
Cost of GP, $^&	199446 (79778-279224)
Supportive Care Measures	
Maximum Leucovorin Dose Used, mg/m²*	200 (20-1000)
Leucovorin Duration, days*	15 (8-26)
Urinary pH < 7 During Episode, N (%)	5 (26)
Maximum Maintenance Fluid Rate, mL/hour*	150 (100-250)
Dialysis Utilized, N (%)	1 (5)

*Reported as Median (Range); ^Not All Patients were Assessed – ECOG Performance Status – 13 of 19 assessed, KPS Scale – 15 of 19 assessed, If Received Prior High-Dose MTX, Number of Doses – 6 of 19 assessed, &Cost Estimate Based on Average Wholesale Price as of February 21, 2021
Abbreviations: BMI – Body Mass Index, BSA – Body Surface Area, ECOG – Eastern Cooperative Oncology Group, KPS – Karnofsky Performance Status, DLBCL – Diffuse Large B-Cell Lymphoma, PCNSL – Primary Central Nervous System Lymphoma, ALL – Acute Lymphoblastic Leukemia, CNS – Central Nervous System, MTX – Methotrexate, GP – Glucarpidase

Summary/Conclusion: In this single institution study of malignant hematology patients GP was safe and efficacious in reducing MTX concentrations in patients with delayed Cl, potentially decreasing MTX-related morbidity and mortality. This analysis provides an important insight on the use and activity of GP in the real-world setting for this feared situation. Further studies with larger numbers of patients will be needed in order to analyze factors that can accurately identify patients who will likely need GP.

PB1589 HEPATITIS B AND C IN ACUTE LYMPHOBLASTIC LEUKEMIA: A 2-YEAR STUDY 2015-2016 AT CHILDREN WELFARE TEACHING HOSPITAL

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Background: The risk of acquiring both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in patients with cancer has been documented. Risk of parenteral transmission of viral hepatitis has been well recognized, especially due to blood product transfusions.
Aims: Retrospectively collecting baseline and follow up data to determine the rate of hepatitis B and C infection in children with ALL. To determine the extent of liver toxicity in patients infected with hepatitis B and C compared to those who do not acquire the infections, and to recognize any relation between seroconversion and different variables.
Methods: The duration of the data collection and analysis of the study was from August 2018 till October 2019. A retrospective study included 92 children with Acute Lymphoblastic Leukemia diagnosed consecutively in a 2-year period; 2015-2016 at Oncology Unit in Children Welfare Teaching Hospital. Demographic information, treatment details, vaccination history and baseline hepatitis screen were documented. Follow up data during ALL therapy regarding the mass of blood products received by the patients, regular assessment of liver enzymes and bilirubin as well as hepatitis B and C testing was done every 3 months. Documentation of any interruption or omission of chemotherapy related to liver dysfunction and Neutropenia. Detection of seroconversion for HBV and HCV by serology and viral load if serology was positive, all taken in a chronological manner.
Results: At the time of diagnosis, all patients were serologically negative from HBV and HCV. During the follow up period, there were 19 (20.6%) patients infected with hepatitis by serological method; 18 with hepatitis C and one with hepatitis B. there was no significant correlation between seroconversion with hepatitis and liver dysfunction, blood product transfusions more than 10 times, chemotherapy delay due to liver dysfunction and risk group. The mean duration from date of diagnosis till date of last follow up was 43.7 months (range 28.6-56.2 months), while the duration from date of diagnosis till seroconversion with hepatitis was 44.2 months (range 6.9-56.4 months).
Summary/Conclusion: Low incidence of HBV and high incidence of HCV was noticed in this group of patients, there was no direct significant correlation to blood product transfusions. Primary and secondary prevention from infection as a WHO recommendation and Continuous regular screening for HCV for several years after discontinuation of chemotherapy to detect dormant infection is of paramount role.

PB1590 ETIOLOGICAL CHARACTERISTICS OF BLOODSTREAM INFECTION PATOGENS IN PATIENT WITH ACUTE MYELOID LEUKEMIA

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Background: Bacterial bloodstream infections (BSI) have a significant impact on treatment outcomes in patients with acute myeloid leukemia (AML). According to P. Kalaskar et al. the incidence of BSI during the induction phase is 27.8%, and during consolidation phase is about 25%.
Aims: To explore the epidemiological characteristics and risk factors of BSI in patients with AML, who develop agranulocytosis fever after chemotherapy.
Methods: A retrospective analysis of 221 patients with AML, 26 of which were diagnosed with AML for the first time in 2020, treated in the Department of Hematology of our hospital, was conducted from January 2020 to August 2020 to analyze the incidence of BSI, the distribution and types of pathogenic bacteria. We also determined whether various parameters are risk factors to BSI, including the patient age, gender, agranulocytosis time, the absolute value of neutrophils on the day of agranular fever.
Results: Among the 221 patients, 37 (16.7%) had agranulocytosis fever and were microbiologically confirmed as BSIs, including 17 (65.3%) who were diagnosed for the first time. The patients included 16 (43.3%) males and 21 (56.7%) females, with median age of 44 years (21-71).
Nine pathogens were detected in 37 patients, including 4 G-strains (86.4%) and 5 G+ bacteria (13.6%). Following pathogens were noted: K. pneumoniae - in 18 (48.6%), E. coli - in 12 (32.4%), A. baumannii - in 1 (2.7%), E. cloacae - in 1 (2.7%), S. Haemolyticus - in 1 (2.7%), S. hominis - in 1 (2.7%), S. epidermidis - in 2 (5.4%), S. aureus - in 1 (2.7 %), E. faecalis - in 1 (2.7%).
Also, in several patients, different pathogens of BSI were isolated during one hospitalization. Agranulocytosis was registered in all patients on the day of BSI, of which 34 (91.8%) had absolute value of neutrophils less than 0.2 * 10^9 / L.
As an empiric antibiotic therapy, in 29.7% of cases, a combination of a 4th generation cephalosporin (cefepime) with a 3rd generation aminoglycoside (amikacin) was used, and in 70.3% of cases, a combination of carbapenem (meropenem) with a 3rd generation aminoglycoside (amikacin), while empirical antibiotic therapy was rational in 35.1% of cases, escalation was required in 64.8% of cases.
In 86.4% of cases, the outcome of therapy showed stabilization of the patient's condition and in 13.6% of cases, a lethal outcome was registered.

Table 1 Characteristics of patients diagnosed with acute myeloid leukemia

Markers	AML patients with BSI, n=20	Newly diagnosed AML patients with BSI, n=17
1.Sex, n (%)		
male female	8 (40%) 12 (60%)	8 (47.1%) 9 (52.9%)
2. Age (mean, year)	45.4	42.4
the absolute value of neutrophils at the time of development of febrile neutropenia		
<0.2 >0.2	18 (90%) 2 (10%)	16 (94.2%) 1 (5.8%)
3. CRP at the time of development of febrile neutropenia, mean	105.8	90.4
4. Procalcitonin at the time of development of febrile neutropenia, mean	6.1	2.2
5. Status		
alive dead	17 3	15 2

Summary/Conclusion: 1. In the etiological spectrum of pathogens of bloodstream infections in patients with AML, gram-negative pathogens (86.4%) predominate, mainly of endogenous, most likely intestinal origin.
2. Repetitive cases of bloodstream infections caused by different pathogens during the same hospitalization were noted.
3. In more than 90% of patients with AML and bloodstream infection, this infectious complication was observed with absolute value of neutrophils below 0.2 * 10^9/ L.
95% CI was 91.9% (78.7% -97.2%)
4. All deceased patients had absolute value of neutrophils below 0.2 * 10^9/ L.

PB1591 A SCORING SYSTEM FOR PREDICTING THE PROGNOSIS OF LATE-ONSET SEVERE PNEUMONIA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Late-onset severe pneumonia (LOSP) is defined as severe pneumonia developed during the late phase of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Patients with LOSP have high mortality, so it is important to identify prognostic factors.
Aims: In this study, we aimed to develop a risk score system with broad applicability that could help predict the risk of LOSP-associated mortality.
Methods: We retrospectively analyzed 100 patients with LOSP after allo-HSCT from June 2009 to July 2017. The assessment variables included immune, nutritional and metabolic parameters at the onset of LOSP.
Results: Of all 100 patients who suffered LOSP after allo-HSCT, 45 (45.0%) patients eventually died, and 55 (55.0%) patients were positive for pathogens, with the most common being viruses. In the multivariate analysis, higher monocyte (≥0.20 *vs.* <0.20×10^9/L, *P*=0.001), higher albumin (≥30.5 *vs.* <30.5 g/L, *P*=0.044), lower LDH (<250 *vs.* ≥250 U/L, *P*=0.008) and lower BUN (<7.2 *vs.* ≥7.2 mmol/L, *P*=0.026) levels at the onset of LOSP were significantly associated with better 60-day survival. A risk score system based on the above results showed that the probability of 60-day survival decreased with increasing risk factors and were 96.3% (low-risk group), 49.1% (intermediate-risk group) and 12.5% (high-risk group).
Summary/Conclusion: The results indicated that the scoring system including several variables could stratify patients with different probabilities of survival after LOSP, which is of great clinical significance.

PB1592 GEOTRICHUM CAPITATUM SEPTICEMIA IN NEUTOPENIC PATIENTS WITH ACUTE LEUKEMIA

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Background: Geotrichum Capitatum (G.Capitatum) is uncommon but frequently fatal mycosis in immunocompromised patients.
Aims: We report our experience of systemic Geotrichum Capitatum infection in severe neutropenic patients who were receiving chemotherapy for acute leukemia in the hematology department of sfax in Tunisia.
Methods: It was a retrospective study of cases of G. capitatum septicemia diagnosed in patients followed for acute leukemia in the hematology department of sfax in Tunisia from January 2005 to december2020. G.Capitatum was identified in blood cultures performed in laboratory of Parasitology. For each patient, we collected epidemiological clinical and imaging data, microbiological results, antifungal treatment and evolution disease.
Results: Eleven cases of of G. capitatum septicemia were identified in 4 mens and 7 womens (sex ratio 0,7). The mean age was 35 years (5-55 years).
Nine patients were diagnosed with acute myeloid leukemia and two with acute lymphoblastic leukemia. At the time of infection, all patients had a prolonged profound neutropenia and had received broad-spectrum antibiotics before the onset of the septicemia. Five patient had a central venous catheter.
Disseminated infection were reported in all of patients and pulmonary localization is the most commun. The computed tomography scan showed pulmonary nodules and/or ground glass opacities, in all cases. A concomitant proven invasive pulmonary aspergillosis was noted in one patient and probable pulmonary aspergillosis was suggested in four patients with ground glass opacities in radiographic findings and a positive aspergillus Galactomannan antigenemia.
Involvement of other deep organs (liver, spleen) was reported in 5 patients (45%). Papulo-vesicular or purpuric skin lesions of the trunk and the members were observed in two cases.
In vitro susceptibility findings showed that all fungi were sensitive for amphotericin B and Voriconazol, high Caspofongine and Fluconazole MICs have been found for four and two patients respectively. Resistance has been noted to Caspofongine in 2 patients and to Fluconazol in one patient.
Differents antifungal therapy was proposed to our patients. Monotherapy antifungal for five patients: conventional Amphotericin B in 2 cases, Voriconazol in 2 cases, and Fluconazol in 1 case, the infection was controlled only in one patient receiving Voricnazol.
Five patients were treated by a combination of Amphotericin B and Voriconazole
with favorable outcome in 3 cases. One patient received two combinations of antifungal therapy and a splenectomy because of the extension lesions in the spleen with a fatal outcomes. The mortality rate in our study was 64%.
Summary/Conclusion: G. capitatum is an opportunistic fungus in leukemia patients mostly with acute myeloid leukemia like our patients.
Disseminated infection were reported in 100% of our patients. Pulmonary localizations is the most common reported in G.capitatum septicemia, but lung infiltrates by G.capitatum and Aspergillus may be indistinguishable each other in some cases, like four of our patients.
The optimal therapy for G.capitatum has not been established, the combination of amphotericin B and voriconazole seem to have favorable outcomes in our study.
Despite antifungal therapy, mortality rate exceeding 50%, (64% in our study).

PB1593 A NOVEL PREDICTIVE SCORING MODEL FOR PREDICTING INFECTION

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Background: Infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB) have a negative impact on the outcome of hospitalized patients, especially in regions with a high prevalence of CRGNB. Implementation of infection control measures significantly reduces their spread among critically ill patients in endemic areas. Early identification of rectal carriers of hematologic malignancies CRGNB at risk for clinical infection will facilitate better management and optimal use of healthcare resources.A retrospective study was conducted in a tertiary care hospital in China to identify the main factors associated with clinical infection in rectal carriers of hematological malignancies CRGNB and to develop a model to predict patients with such infection early.
Aims: To investigate the factors contributing to clinical infection in rectal carriers of carbapenem-resistant gram-negative bacteria (CRGNB) in hospitalized patients with hematological malignancies (HM) to develop an effective model for early identification of cases progressing to severe clinical CRGNB infection.
Methods: This retrospective single-center case-control study included CRGNB rectal carriers hospitalized for hematological malignancies from January 2018 to June 2020. The distribution of strains and clinical infection rate were analyzed. Multivariate analysis was performed by logistic regression model to identify risk factors.
Results: In this retrospective case-control study, the top three species detected in the Department of Hematology of our hospital on 2018-2020 (the first two quarters) were: Klebsiella pneumoniae 137 (33.1%), Escherichia coli 72 (17.4%), and Baumannii 69 (16.7%); univariate analysis showed that patients induced remission chemotherapy, transplantation, mucositis, duration of particle deficiency, nutritional status (albumin), infectious drug exposure (such as carbapenems, aminoglycosides, chemotherapy, immunosuppressive agents, glucocorticoids,

antacids (PPIs), etc.); invasive procedures before infection (such as arterial/venous, sputum suction, catheterization, etc.), and the differences were statistically significant ($p < 0.05$). Multivariate logistic regression analysis indicated that remission induction chemotherapy, duration of particle deficiency, mucositis, and nutritional status (hypoalbuminemia) were independent risk factors for clinical infection in CRGNB rectal carriers. Among them, skin mucositis and particle gap time ≥ 15 days were the most important independent risk factors for clinical infection in CRGNB rectal carriers; the model for predicting CRGNB infection was effective, and the predictive efficacy of the risk prediction score table was validated by ROC curve, with an area under the characteristic curve of 0.697 (95% CI 0.647-0.747, $p < 0.05$).

Risk factors	Category	Regression coefficient	βi	Score
Mucocutaneous break		3.248		
	No			0
	Yes			2
Remission induction chemotherapy		1.921		
	No			0
	Yes			1
Particle deficiency state				
	0			0
	1-14	1.959		1
	≥15	2.651		2
Hypoproteinemia		1.837		
	No			0
	Yes			1

Summary/Conclusion: It can help early and accurately predict rectal carriers of hematologic malignancies CRGNB at risk for clinical infection. Patients in the high-risk group (>3.5) should take more effective prophylactic antibiotics and undergo more rigorous monitoring. The model showed excellent predictive performance and showed good discrimination.

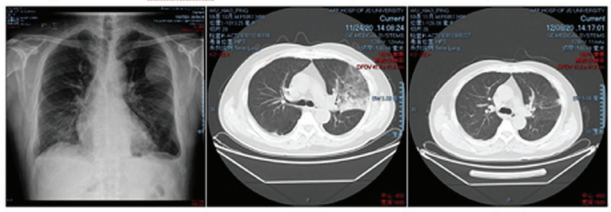
PB1594 NEXT-GENERATION SEQUENCING RAPIDLY IDENTIFY PATHOGENIC MICROBE IN BRONCHOALVEOLAR LAVAGE LIQUID OBTAINED FROM PATIENTS FAILED MULTIPLE LINES OF EMPIRICAL ANTI-MICROBIAL TREATMENT

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Background: Pulmonary infections occur frequently during the management of patients with hematologic malignancies, and usually managed with empirical strategy before the responsible pathogen could be identified. However, conventional techniques such as culture are not sensitive enough and have a long turnaround time. If a patient failed multiple lines of anti-microbial treatment or had an exacerbation of infection, then a rapid and effective way to identify responsible pathogen is critical. Next-generation sequencing (NGS) has the potential to detect pathogenic microbe in a high throughout and rapid way, which is different from the conventional techniques in this respect. However, when and who to integrate NGS into management of pulmonary infection is currently unclear.
Aims: To explore the feasibility and effectiveness of next-generation sequencing (NGS) test to identify responsible microbial pathogens in bronchoscopic bronchoalveolar lavage (BAL) liquid, which was obtained from febrile patients who both failed multiple lines of antimicrobial therapy and had newly emerged pulmonary changes on X-rays or CT scan.
Methods: All the patients had received anti-cancer therapy of underlying hematologic malignancies before infections developed. If a patient developed febrile episodes and still had persistent or recurrent fever even with multiple lines of empirical anti-microbial treatment, once newly emerged pulmonary changes on X-rays or CT scan were documented, bronchoscopic bronchoalveolar lavage (BAL) liquid was then obtained for NGS test. When the definitive microbial pathogen is identified, specific antimicrobial strategy was employed accordingly.
Results: All four cases had been treated for underlying hematologic malignancies in our hospital, two of them for acute lymphoblastic leukemia and the other two cases for multiple myeloma. During the anti-malignancy treatment, all had febrile neutropenia (FN) and received multiple lines of antimicrobial treatment. Even with rigorous combined and multiple lines of antimicrobial agent treatment, three of them had persistent fever and the fourth had recurrent fever. All cases had baseline pulmonary imaging scan and a routine imaging follow-up was employed during anti-microbial treatment. As soon as a newly emerged change was confirmed by either X-rays or CT scan, bronchoscopic BAL liquid was obtained for NGS test in an attempt to identify responsible pathogen. All cases had negative blood and sputum culture, negative galactomannan (GM) and β-D-Glucan assay (G) test before bronchoscope. NGS test had positive findings in all four cases, the pathogens are Lautropia mirabilis, Aspergillus fumigates, Pneumocystis jirovecii and Aspergillus fumigates, respectively. Only one case had subsequent positive serum GM assay and sputum Aspergillus fumigates detection after NGS test. Every case had the antimicrobial agents adjusted according to NGS results, and fever resolved in all cases. Subsequent imaging showed significantly improved or resolved in all four cases.

Representative imagings at baseline, BAL liquid NGS test and post-treatment



Baseline Newly emerged changes post-treatment

Summary/Conclusion: In the management of refractory/recurrent pulmonary infection patients with hematological malignancies, NGS test of bronchoscopic BAL liquid should be considered if previous conventional test cannot identify pathogen, especially when there are newly emerged changes on X-rays or CT scan.

PB1595 REVIEW OF ANTIFUNGAL PROPHYLAXIS PRACTICES AND INCIDENCE OF BREATHROUGH FUNGAL INFECTIONS IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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Background: Antifungal prophylaxis is routinely prescribed in patients with haematological malignancies receiving chemotherapy. Breakthrough fungal infections are still problematic in these patients and can be difficult to treat.
Aims: This review was conducted to determine the incidence of breakthrough fungal infections, and to assess the adequacy of current antifungal prophylactic practices in our Centre.
Methods: All patients admitted in the Haematology Ward at the Sir Anthony Mamo Oncology Centre (Malta) over a total of 19 months were included. Data about the underlying diagnosis and the incidence of fungal infections was obtained from medical notes.
Results: A total of 169 admitted patients with the following malignancies were admitted: 29.6% (n=50) with acute myeloid leukaemia (AML), 45% (n=76) with non-Hodgkin's lymphoma (NHL), 5.9% (n=10) with Hodgkin's lymphoma, 5.9% (n=10) with acute lymphoblastic leukaemia (ALL), 3% (n=5) with Burkitt's lymphoma, and 10.6% (n=18) being a mixture of myeloma, chronic lymphocytic leukaemia (CLL) or post allogeneic transplant patients.
From these 169 patients, 56.8% (n=96) were on fluconazole, with 8.3% (n=8) developing a localized fungal infection and another 8.3% developing a systemic infection. Of the 46 patients on itraconazole, 19.6% (n=9) developed a localized fungal infection and 17.3% (n=8) developed an invasive fungal infection. Three patients were on liposomal amphotericin prophylaxis – one developed a skin infection requiring topical treatment, and two developed an invasive fungal infection requiring escalation to voriconazole. Out of nine patients on Nystatin, there was one systemic fungal infection and no localized infections– only lymphoma patients were on this prophylactic drug.

The antifungal agent with the least incidence of breakthrough infections was posaconazole. 7.1% (n=12) of patients were prescribed this drug. No breakthrough infections were reported.
AML patients predominantly received itraconazole prophylaxis (68%, n=34), as did ALL patients (60%, n=6). Burkitt's lymphoma patients received fluconazole primarily (60%, n=3), with the one case of systemic candidaemia occurring on this drug. Fluconazole was the predominant prophylaxis in patients with NHL (78.9%, n=60), Hodgkin's lymphoma (90%, n=9) and plasma cell disorders (100%, n=11).
Breakthrough fungal infections occurred in 24.3% of admissions (n=41); 53.6% were systemic in nature (n=22). Half of these systemic infections occurred in AML patients (n=11), with five cases of candidaemia and 6 cases of aspergillosis. ALL patients made up 13.6% of these systemic infections (n=3), with one case each of aspergillosis, candidaemia and mucormycosis. The remaining systemic infections were as follows: 31.8% in NHL (n=7) and 5% in Burkitt's (n=1).
Summary/Conclusion: The patients at highest risk of breakthrough fungal infections are the AML group, with a significant incidence in ALL patients, despite itraconazole prophylaxis in these groups. Admitted NHL patients also had a high incidence of systemic fungal infections despite prophylaxis. Those on Nystatin did not seem to be at increased risk however; most likely these are low risk patients which did not receive intensive chemotherapy regimens. Liposomal amphotericin does not seem to provide adequate prophylaxis, as fungal infections still occurred with a 100% rate. Our analysis suggests that posaconazole is the most effective prophylactic antifungal agent prescribed locally.

PB1596 THROMBOELASTOMETRY AND CONVENTIONAL COAGULATION TESTS AS PREDICTORS OF PROGRESSION TO CRITICAL PHASE IN PATIENTS IN THE FEBRILE PHASE OF DENGUE FEVER: A PRELIMINARY PROSPECTIVE CASE CONTROL STUDY

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Background: Dengue fever is a viral infection caused by four distinct serotypes of the dengue virus, transmitted to humans by female mosquitos of Aedes species. It is the most critical mosquito-borne disease globally. Infection leads to clinical manifestations ranging from undifferentiated fever to dengue haemorrhagic fever (DHF) and dengue shock syndrome. DHF has three stages namely febrile phase, critical phase and convalescent phase. Plasma leakage and abnormal haemostasis are the two key characteristic pathophysiological features of DHF. Identifying patients likely to progress to the critical phase, as soon as possible, would be a major advantage in initiating management early.
Aims: Several factors associated with progression to critical phase have been described. The usefulness of ROTEM in predicting which patient will go to critical phase has not been hitherto reported. The main objective of this study was to assess if conventional coagulation tests (CCT) and ROTEM parameters are useful predictors of progression to critical phase in patients in febrile phase of dengue fever.
Methods: A prospective case control study was performed in medical units at National Hospital of Sri Lanka on patients with fever and a positive dengue NS1 antigen test. CCT (PT, APTT & Clauss fibrinogen assay) and ROTEM (EXTEM & INTEM) were performed in patients in febrile phase, on 3rd day of fever, if the platelet count > 100 x 10^9/L and no features of plasma leakage. Patients enrolled were followed up and if they progressed into critical phase were categorized as "cases" and if they did not (recovered from the febrile phase) categorized as "controls".
Results: A prospective case control study was performed in medical units at National Hospital of Sri Lanka on patients with fever and a positive dengue NS1 antigen test. CCT (PT, APTT & Clauss fibrinogen assay) and ROTEM (EXTEM & INTEM) were performed in patients in febrile phase, on 3rd day of fever, if the platelet count > 100 x 10^9/L and no features of plasma leakage. Patients enrolled were followed up and if they progressed into critical phase were categorized as "cases" and if they did not (recovered from the febrile phase) categorized as "controls".
Summary/Conclusion: Conventional coagulation tests were not useful in predicting progression to the critical phase. ROTEM parameters CT & CFT of EXTEM and CFT of INTEM, which can be ascertained at point of care, even in an outpatient setting, in about 10-15 minutes, appeared to be useful in predicting which patient is likely to progress to the critical phase from the febrile phase of dengue fever. When combined, specific cut-off values for each of these 3 parameters gave a NPV of >80% in patients in the febrile phase of dengue fever, on the 3rd day of fever. This preliminary study suggests that a larger study looking at ROTEM parameters, not only on the 3rd day, but also on 4th and 5th days of fever may be useful in predicting which patient with dengue fever is likely to progress to the critical phase.

PB1597 COVID-19 AND MALIGNANT HEMOPATHIES: EXPERIENCE OF THE CLINICAL HEMATOLOGY SERVICE OF THE UNIVERSITY HOSPITAL CENTER IBN SINA IN RABAT

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Background: Since September 2020, Morocco has experienced the 2nd wave of covid-19 infection explaining the high daily rate of new infections and deaths from this infection
Aims: the aims is to describe the state of play of this infection in patients followed for malignant hematologic disease
Methods: This is a retrospective and observational study during the 2nd wave of the COVID-19 pandemic in Morocco (from September 2019 to February 2021) carried out at the clinical hematology service of the Ibn Sina University Hospital center in Rabat concerning patients followed for active malignant hemopathy who presented with COVID-19 infection
Results: we have collected 25 cases. The average age estimated as: 40 years (18-65 years), sex ratio: 1.27 (14 M / 11F). We objectified 40% of patients with large B cell lymphoma, 8% with acute leukemia, 40% with multiple myeloma, 2% with myelodysplasia, and 5% with CLL. At the time of COVID - 19 infection, 80% of patients were on chemotherapy, and another 20%) had not yet started chemotherapy. 9 patients presented with comorbidities: arterial hypertension in 12% of cases, diabetes in 8% of cases, and obesity (BMI> 30) in 16% of cases. The main symptoms of COVID-19 in our patients were: Asthenia (80%) dyspnea (81%), and cough (50%), none of our patients presented neurological, digestive, cutaneous vasculitis, myocarditis,or ORL signs. lymphopenia was noted in 90% of cases, an inflammatory syndrome in 30% of cases. hepatic tests were normal in all patients. 8% of patients had chronic renal failure. D-Dimers were elevated in 40% of patients. thoracic CT revealed pulmonary lesions of the corads 4 and 5 type in 75% of cases, extended between 25-50% of lung surface in 90% of cases, no thrombosis or pulmonary embolism were observed. 18% of patients were paucisymptomatic for COVID-19 infection, 70% of patients had moderate symptoms, and 12% of patients had severe respiratory-type symptoms. 80% of patients had normal initial AAS with 97% O2, 10% had presented respiratory distress with AAS <90% O2. they received oxygen therapy by the high concentration O2 mask, optiflow and CPAP as needed. 16% of patients were hospitalized in intensive care for NIV. All the patients received the anti-covid treatment according to the Moroccan national protocol: azithromycin and vitamin therapy (vit C, D, zinc) in 100% of the patients, and hydroxychloroquine in 70% of the patients. No patient received lopinavir / ritonavir, anakinra or tociluzimab, or remdesivir. because of severe sepsis on bronchopulmonary infection, we used broad-spectrum antibiotics in 8.3% cases. (80%) of patients received corticosteroid therapy (dexamethasone) and 90% had an enoxaparin at a preventive anticoagulant dose. because of the Covid-19 infection, chemotherapy was postponed or not started (2-3 weeks).
ARDS was present in 16%. The average length of stay in hospital was 15 days (10-40 days). All of our patients have recovered from their Covid-19 infection. We deplore 12% of deaths linked to the progression of hemopathy. No patient experienced spontaneous recovery from their hemopathies after infection with Covid-19. 1 patient (4%) followed for CLL under ibrutinib maintained a normal lymphocytosis at 4400/ mm3 persistent after 6 months of evolution. We noted an early relapse of the Covid -19 infection on day 22 of the 1st infection in 4% of patients with hypogammaglobulinemia.

Summary/Conclusion: The COVID-19 pandemic had a significant negative impact on the care of patients with malignant hemopathy, limiting patients' access to chemotherapy.

PB1598 HEMATOLOGIC PARAMETERS IN ASYMPTOMATIC PATIENTS WITH ACTIVE COVID-19 INFECTION.

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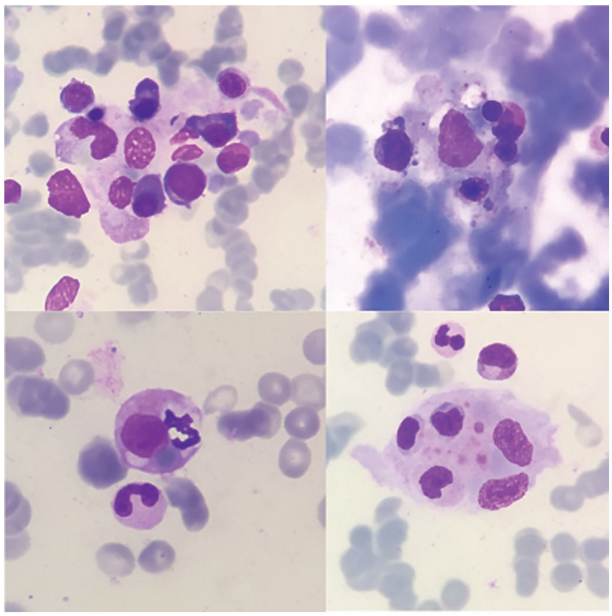
Background: In December 2019, coronavirus disease 2019 (COVID-19) was first found in Wuhan, China caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is currently a pandemic infection reported all around the world. It was previously highlighted that laboratory medicine plays an essential role in the early detection, diagnosis and management of many diseases. Complete blood count is the most available, efficient and economic examination. We compared the data of complete blood count betwen COVID19 pateints and a conrol group.
Aims: This study aims to retrospect and analyze the complete blood count of asymptomatic patients with active COVID-19 infection diagnosed by polymerase chain reaction (PCR) in order to obtain possible indirect key indicators of active disease in asymptomatic patients.
Methods: Sidi Yahya El Gharb Hospital is a field Hospital for asymptomatic patients diagnosed with COVID-19 infection mainly during contact cases screening. Confirmed cases were based on polymerase chain reaction (PCR) nucleic acid testing for SARS-CoV-2 infection. We collected patients from June 20 to July 13, 2020, all of them were isolated and treated according to a national regiment. Patients received hydroxychloroquine 200 mg three times daily for 07 days and azithromycin 500mg once daily for three days. We compared the data of complete blood count, the neutrophil lymphocyte ratio (NLR), the mastocyte lymphocyte ration (MLR) and the platelet lymphocyte ratio (PLR) of our patients with a data of a control group from the Hematologic Laboratory in the Military Hospital Mohammed V of Rabat. The analysis of the data was done using the JAMOVI 1.6.8 statistical programs.
Results: COVID-19 infection was confirmed in 220 patients, no one was febrile. Comparisons made with a control group including 220. The sex ratio was 0,23 vs 0,44. The median values of Leucocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, platelet, the neutrophil lymphocyte ratio (NLR), the mastocyte lymphocyte ration (MLR) and the platelet lymphocyte ratio (PLR) between the COVID-19 group and the control one was as following: 7110[5495-8683] vs 6500[5375-8000], 3200[2165-4400]vs 3700[2775-2500], 2800[2257-3305]vs 2000[1600-2500], 615[460-780] vs500[400-700], 140[70-230]vs 100[100-200], 50[40-72] vs 0[0-100], 13,1[12,2-13,9] vs 13,2[12,3-14,1], 282500[224000-353250]vs234000[196000-297750], 1,12[0,765-1,69] vs 1,42[1,19-2,19], 0,207[0,152-0,277] vs0,212[0,211-0,316] and 103[79-126]vs105[97,9-156].Comparisons made between the two groups revealed a significant difference regarding neutrophils, lymphocyts, basophils, NLR, MLR and PLR ($p < 0.05$).
Summary/Conclusion: Neutrophil, lymphocyts, basophils, NLR, MLR and PLR can be used to predict n COVID-19 infection in asymptomatic patients.

PB1599 BENEFIT OF TREATMENT WITH TOCILIZUMAB IN HEMOPHAGOCYTIC LYMPHYSTIOCYTOSIS SECONDARY TO VISCERAL LEISHMANIASIS INFECTION.

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Background: Visceral Leishmaniasis (VL) is a zoonotic infection produced by the Leishmania spp parasite transmitted through the bite of the Phlebotomus or Lutzomya mosquito. It is more frequent in endemic areas and a common, although underdiagnosed, cause of secondary hemophagocytic lymphohistiocytosis (HHL), consisting of a dysregulation of T lymphocytes and NK cells and uncontrolled macrophage activation. The generated cytokines storm (IFN-gamma, IL-1, 6, 10, 12, and 18) and uncontrolled hemophagocytosis result in a life-threatening hyperinflammatory state. The clinical-analytical manifestations between HLH and VL may overlap, making diagnosis difficult. Amphotericin B is the treatment of choice, together with corticosteroids and immunoglobulins in case of LHHs and no response to initial treatment.
Aims: To express the importance of controlling the cytokine storm in Hemophagocytic Lymphohistiocytosis to avoid the development of the hyperinflammation state.
Methods: Description of clinical case and sample of response to treatment with Tocilizumab. The follow-up was carried out until January 31, 2021.
Results: A 51-year-old man with a personal history of psoriasis arthritis treated with Adalimumab and Methotrexate and cutaneous leishmaniasis on the pinna in February 2019, untreated. Consultation in the Emergency Service for a 2-week fever and general malaise, presenting progressive pancytopenia without remarkable findings in the peripheral blood smear. Viral serologies and PCR for SARS-CoV2 were negative; antigenuria for Leishmania was positive. Abdominal CT showed mild hepatomegaly and splenomegaly of 19 cm. Treatment is started with Liposomal Amphotericin B. The subsequent analytical study showed CRP 77.4 mg/L, IL-6 19.2 pg/mL, Ferritin> 4,500 ng/mL, triglycerides 217 mg/dL, AST/ALT 221/135 U/L and CD25s> 7500 U/mL. A bone marrow aspirate was performed which, together with a positive Leishmania PCR in peripheral blood and bone marrow and HScore with a probability of 94% HLH-2004 score with 6/8 items completed, LHHs to LV were diagnosed, adding Dexamethasone according to the HLH-2004 protocol and Gammaglobulin. Despite the instaured measures, pancytopenia, fever> 38°C, liver involvement and hyperinflammatory status with IL-6 87.5 pg/mL persisted, deciding to administer a single dose of Tocilizumab 8 mg/Kg. The fever disappeared and the laboratory abnormalities were normalized in 1.5 months. Dexamethasone decrease was performed according to protocol. Currently Adalimumab has been restarted and continues with monthly doses of Amphotericin B.



Summary/Conclusion: There is little scientific evidence about the targeted management of the cytokine storm generated in LHHs.
Blocking the action of IL-6 with Tocilizumab at standard doses allowed adequate management of the pro-inflammatory state and the infection, without side effects and with good tolerance.
Experience with Tocilizumab in LV LHHs is extremely limited. Understanding the pathophysiology of this entity and its similarity to other states of hyperactivation and immune dysregulation will allow better therapeutic regimens to be established.
There is little scientific evidence about the targeted management of the cytokine storm generated in LHHs. Blocking the action of IL-6 with Tocilizumab at standard doses allowed adequate management of the pro-inflammatory state and the infection, without side effects. Experience

with Tocilizumab in LV LHHs is extremely limited. Understanding the pathophysiology of this entity and its similarity to other states of hyper-activation and immune dysregulation will allow to establish better therapeutic regimens.

PB1600 INFECTION PROFILE AND OUTCOMES OF ADULT ACUTE LEUKEMIA PATIENTS DEVELOPING CHEMOTHERAPY-ASSOCIATED FEBRILE NEUTROPENIA AT THE PHILIPPINE GENERAL HOSPITAL

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Background: Chemotherapy induced myelosuppression is one of the major dose-limiting toxicities of systemic chemotherapy. It results to dose reductions and treatment delays hence compromising treatment-efficacy and long-term clinical outcomes. Moreover, the burden of these complications to patients as well to their caregivers could be economically troublesome and would require substantial resource allocation.
Aims: This study determined the infection profile and outcomes of adult acute leukemia patients developing chemotherapy-associated febrile neutropenia and identified the antimicrobial sensitivity patterns of the bacterial blood isolates.
Methods: This was a single-center retrospective study which reviewed medical records of 100 adult acute leukemia patients who developed chemotherapy-associated febrile neutropenia. Descriptive statistics was used to summarize demographic and clinical characteristics. Independent Sample T-test, Mann-Whitney U-test and Fisher's Exact/Chi-square test determined difference of mean, rank and frequency between AML and ALL. STATA 13.1 was used for data analysis.
Results: There were 106 microbiological isolates. Most commonly isolated were *Escherichia coli (ESBL-48.39%)*, *Klebsiella pneumoniae (ESBL-61.90%)* and coagulase-negative *Staphylococcus (CoNS)*. Organisms were isolated from blood (57.55%), sputum (15.09%), urine (12.26%), and stool (7.55%). More ALL patients had *Klebsiella pneumoniae* isolates (p-value: <0.001). Presence of Carbapenemase-producing *Klebsiella* was statistically significant in the mortality group (p-value: 0.018). Susceptibility patterns show: (1) *E. coli*susceptible to Carbapenems, Cefepime and Aminoglycosides (2) *K. pneumoniae* to Carbapenems and Aminoglycosides (3) CoNS to Vancomycin.
Summary/Conclusion: This study emphasized the need to identify the most commonly isolated pathogens to aid physicians decide on the appropriate empiric antibiotic/s to use during chemotherapy-associated febrile neutropenia to avoid serious morbidity and mortality. Proper coordination between clinician and microbiological laboratory for prompt pathogen identification and monitoring of microbial susceptibility patterns is vital to provide the best treatment option for this patient population.

Iron metabolism, deficiency and overload

PB1601 SET UP OF A GENE PANEL FOR NEXT GENERATION SEQUENCING IN THE CAUSES OF ERYTHROCYTOSIS

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Background: Persistently raised hemoglobin (Hb) and hematocrit (Ht) levels characterize Erythrocytosis which cause in some cases is not recognized despite a careful study. In these patients a diagnosis of Idiopathic Erythrocytosis (IE) is carried out.
Recent observations suggest that some IE patients carry mutations or polymorphisms of HFE gene. This gene is involved in the Iron Metabolism regulation and these data suggest that some other cases of IE may be due to an alteration of Iron Mechanism involved genes.
Aims: We constructed a genes panel for Next Generation Sequencing (NGS) to search mutations of already known genes involved in Erythrocytosis and in those involved in Iron Metabolism in patients with increased Ht of not defined origin.
Methods: Fifteen genes composed the panel designed for NGS: JAK2, EGLN1 (PHD2), EPOR, FTL, FTH, ASXL1, HFE, HFE2, TFR2, HAMP, SLC40A1, SLC11A2, VHL, BPMG, EPAS1. All the exons part of the 15 genes were analyzed. The approach used for the library preparation was a multiplexing PCR and data were analyzed by bioinformatics tools. In all patients, the mutations found were confirmed with Sanger Sequencing.
Results: We studied 68 patients with erythrocytosis not carrying any JAK2 somatic mutation. We found 44 patients carrying at least one germline mutation in the genes of the panel. The germline mutations found in this study are reported in Table 1: 17 interest oxygen sensing pathway, 4 EPOR, 2 ASXL1 and 5 JAK2 genes. Moreover, we found 25 patients with at least one missense mutation in HFE gene and 7 patients with a mutation in TFR2 gene.

GENE	MUTATION	PATIENTS WITH MUTATION		
		N	alone	multiple
EGLN1	Cys127Ser	6	2	4
	Gln157His	5	2	3
	Ile269Thr	1	1	0
	Cys127Ser + Arg370Gly	1	0	1
EPOR	Ala99Val	1	0	1
	Asp398Glu	1	1	0
	Asn487Ser	1	1	0
	Glu181Asp	1	0	1
VHL	Pro25Leu	3	1	2
HFE	His63Asp	17	10	7
	Cys282Tyr	5	4	1
	Ser65Cys	1	0	1
	His63Asp + Ser65Cys	1	0	1
	His63Asp + Cys282Tyr	1	0	1
TFR2	Arg752His	4	2	2
	Asp602fs	1	1	0
	Ala182Glu	1	0	1
	Asp648Tyr	1	0	1
JAK2	Leu113Val	1	0	1
	Gly571Ser	1	1	0
	Leu393Val	1	0	1
	Gly48Glu	1	0	1
	Asn1108Ser	1	0	1
ASXL1	Pro873Leu	1	0	1
	Gly1102Asp	1	0	1
EPAS1	Phe374Thr	1	0	1

Summary/Conclusion: Our data show the validity of the chosen NGS panel. The use of this panel allowed us to found mutations already known to be related to erythrocytosis, and also to find some cases characterized by mutations of iron metabolism genes, as we previously found with sequencing method. The NGS genes panel evaluated offers the possibility to easily recognize new mutations explaining IE. The researchers have to consider iron metabolism to be possibly involved in the etiology of IE.

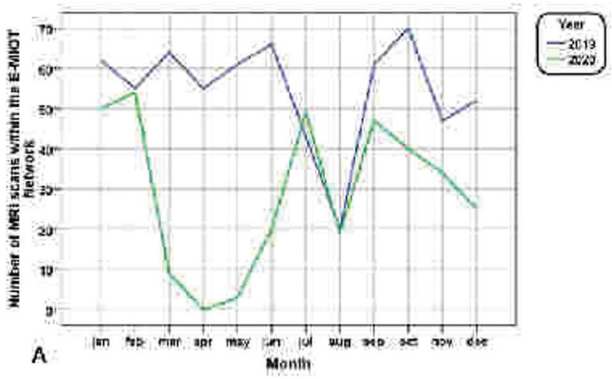
PB1602 IMPACT OF THE COVID-19 PANDEMIC IN THE MR AVAILABILITY FOR IRON OVERLOADED PATIENTS

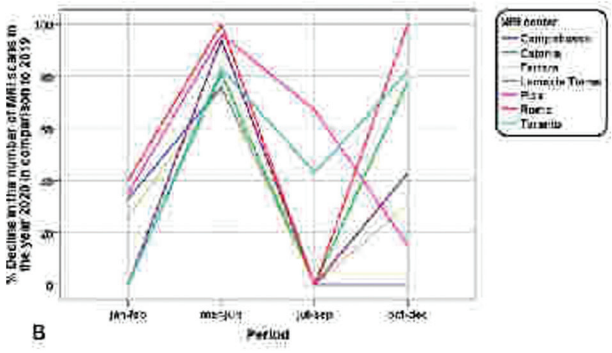
A. Meloni [1,*], L. Pistoia [1], R. Righi [2], M. Missere [3], S. Renne [4], A. Vallone [5], A. Riva [6], P. Fina [7], D. Maddaloni [8], A. Ermini [9], V. Spadola [10], A. Pepe [1]

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Background: The T2* magnetic resonance imaging (MRI) technique for the noninvasive quantification of iron overload has significantly improved the survival of patients with hemoglobinopathies by tailoring the chelation therapy. In Italy, the E-MIOT (Extension-Myocardial Iron Overload in Thalassemia) Network, a collaborative project among MRI and hematological centers, has assured high-quality quantification of iron in vital organs such as heart, liver, and pancreas. The COVID-19 pandemic has disrupted healthcare services around the world, also leading to postpone or delete deferable diagnostic evaluations.
Aims: We evaluated the impact of the COVID-19 pandemic on MRI services for iron overload quantification in Italy.

Methods: The activity of the MRI centers of the E-MIOT Network in the year 2020 was compared to the activity in the same months of 2019. A specific survey was filled out by the MRI operators to evaluate if the availability of MRI slots for patients with hemoglobinothies was reduced and the reasons.
Results: In comparison with the year 2019, in 2020 there was a significant reduction in the number of T2* MRIs performed (350 vs 656; P<0.0001). The comparison month by month between the two years highlighted a marked decline (86.9%) in the four-month period March-June 2020, a reduction in the gap between the two years in the three-month period July-September, and a new decline (41.4%) in the three-month period October-December (Figure 1A). No patient with hemoglobinopathy could undergo an MRI scan during the Italian lockdown (9 March-10 May 2020).
Figure 1B shows the percentage of decline (year 2020 vs 2019) in the number of T2*MRI scans for each MRI center. If no decline or an increase were present, the vertical axis was set at 0. All centers experienced a significant drop in the number of the T2* MRIs in the four-month period March-June (from 75 to 100%). In the three-month period July-September only the centers of Pisa and Taranto dropped the number of T2* MRIs due to the rescheduling of the other MRI appointments deleted during the lockdown. In the three-month period October-December a reduction of the T2* MRI scans was experienced by all centers, except for Campobasso. In the centers of Ferrara and Lamezia Terme the reduction was the consequence of the general reduction in the number of the total MRIs scheduled per day for the sanitation procedures. In the other centers, the availability for T2* MRI scans was unchanged in comparison to 2019, but the patients refused the MRI follow up for fear of getting sick of COVID.





Summary/Conclusion: The COVID-19 pandemic is having a strong negative impact on the quantification of iron overload by MRI, which may seriously worsen the prognosis of patients with hemoglobinopathies. Strategies to ensure proved lifesaving MRI exam and to reassure patients about the health safety of the hospitals are recommended.

PB1603 PROSPECTIVE ANALYSIS OF DIFFERENT ORAL IRON POSOLOGY ON CLINICAL FINDINGS AND SERUM IRON PARAMETERS INCLUDING HEPCIDIN IN PATIENTS WITH IRON DEFICIENCY ANEMIA

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Background: Iron Deficiency Anemia (IDA) is a common health problem in daily clinical practice. A better understanding of iron metabolism in recent years; has created the need for revising treatment regimens in the treatment of IDA.
Aims: Based on these data, we aimed to evaluate the effectiveness of oral ferrous sulfate treatment at different doses, and posologies in premenopausal women diagnosed with IDA, and its relationship with hepcidin, treatment compliance, and gastrointestinal side effects in this study.
Methods: This is a prospective observational study including premenopausal female patients median age 36 (18-50) diagnosed with IDA. This study was approved by local ethic committe and sponsored by Ankara University School of Medicine Scientific Research Projects(BAP proje number 20L0230012) All patients recieved po ferrous sulfate (FS) 80 mg elemental iron) for three months. Patients were classified into three group according to FS dose: Group 1: 2x1/day; Group 2: 1x1/day; Group 3: 1x1every other day. At the time of enrollment, thereafter at the second week of FS and at the third month: Hb level, transferrin saturation(%TS), total iron binding capacity were recorded. Blood was drawn and stored at -20 temperature for hepcidin analysis from patiens who signed informed consent.
Results: We intent to analyse 50 patients for each group, however as a consequence of COVID-19 pandemic, neither patients could come to hospitals nor we could visit them. The patients in each group, ages and results are shown Table At the end of the second week a significant increase in Hb level was observed ($p < 0.01$) and the mean Hb level increased by 1.38 ± 1.04 and 1.03 ± 0.48 in the first and second groups respectively and ≥ 1 g / dl while in the group given every other day it remained <1 g / dl with an increase of 0.69 ± 0.36. ($p = 0.020$, $p = 0.019$, respectively). Comparing the ferritin levels within the three group, it was seen that the ferritin increased significantly in the first group compared to the second and third group ($p < 0.05$). There was no difference between group 2 and group 3 in terms of increase in ferritin level ($p > 0.05$). The increase in TS% and decrease in total iron binding capacity were similar in all three group at the end of the treatment ($p > 0.05$). The change between the second week and the initial hepcidin was mostly observed in the second group ($p = 0.024$) and the change between the three group were similar ($p = 0.708$). Gastrointestinal side effects were observed more in the first group who received 2*1 daily than in the second and third group ($p < 0.05$). While a similar increase in appetite and weight was observed in the patients in group 1 and 2 at the end of the treatment ($p > 0.05$) and there was no increase in appetite and weight in group 3.

	Median Age	Basal Hb g/dl	Sekond Week Hb g/dl	Third Month Hb g/dl	Basal Hepcidin pg/ml	Sekond Week Hepcidin pg/ml	Basal %TS	Third Month % TS	Basal Ferritin ng/ml	Third Month Ferritin ng/ml
Group 1 n=28	35.6 (19-50)	9.42	10.81	13.34	125.53	147.68	5.92	26.54	4.64	25.78
Group 2 n=30	36.8 (22-48)	9.96	10.99	13.75	130.51	192.88	4.70	26.13	2.85	13.74
Group 3 n=32	36.7 (22-50)	10.16	10.79	13.74	117.03	158.46	6.23	23.62	3.84	14.02

Summary/Conclusion: Hb level increase at the end of second week was ≥1 g / dl in the first and second group and <1 g / dl in the third treatment group. However, at the end of the treatment third month anemia was significantly improved in all three group and the increase in Hb level was similar. We consider, 1*1 daily or 1*1 every other day posology

would be more appropriate instead of 2*1 daily due to the significant gastrointestinal side effects in the first group. In addition, we believe in that, the evaluation of Hb response in the second week is too early to decide treatment outcome due to the slower Hb increase in the other day group and serial Hepcidin measurements will give a better idea to better understand the kinetics.

PB1604 THROMBOCYTOPENIA AS AN INITIAL FINDING IN IRON DEFICIENCY ANEMIA

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Background: Iron deficiency anemia (IDA) is typically associated with either normal or elevated platelet counts, likely due to a low iron content in the bone marrow that induces a bias toward megakaryocyte commitment in the megakaryocyte-erythroid progenitors. A much less frequent presentation is iron deficiency-associated thrombocytopenia (IDAT), be it at the time of diagnosis or secondary to iron replacement therapy.
Aims: Given the rarity of these findings, as well as the limited literature available, these cases can lead to diagnostic confusion and unnecessary invasive procedures. Here we present the case of a severe IDA and thrombocytopenia with subsequent progression of the thrombocytopenia after initiation of iron replacement therapy.
Methods: A qualitative case study from the authors' institution diagnosed with the help of standard hematological parameters.
Results: A 45 year old woman was referred to the Emergency Department because of severe anemia (Hemoglobin 4.3 g/dL) and thrombocytopenia (PLT 85 x10^3/µL) in a routine analysis. Her medical history showed an earlier untreated episode of IDA due to menorrhagia, but at the moment the patient reported normal menstruations. The complete blood count showed a microcytic, hypochromic pattern (MCV 62.5 fL, MCHC 28.4 g/dL, RDW 22.1%, WBC 4.14 x10^3/µL), without alterations in the rest of the work-up (no fever, LDH 142 UI/L, total bilirubin 0.56 mg/dL, DAT negative, reticulocytes 20.40 x10^3/µL, creatinine 0.69 mg/dL, no schistocytes in peripheral blood smear). The patient was hospitalized in the department of Internal Medicine for further study and treatment, initiating blood transfusion and intravenous iron replacement therapy the same day. The iron studies showed a ferritin level of <1 ng/mL, total serum iron 8 µg/dL, transferrin 406 mg/dL, and transferrin saturation index 1%. Further diagnostic procedures included abdominal ecography, gastroscopy, colonoscopy, thoracoabdominal CT, bone marrow aspirate, and gynecological work-up, all without alterations. The patient was discharged after 13 days of hospitalization, continuing with oral iron supplementation. The blood parameters during the hospitalization and at 45 days can be seen in the figure.

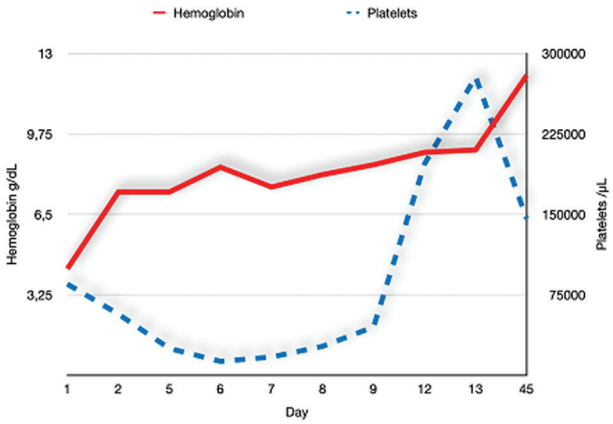


Figure 1. Hemoglobin and platelet-levels from day 1 to 45. Intravenous iron supplementation was initiated at day 1, together with transfusion of red blood cells. Oral iron supplementation was initiated at hospital discharge at day 13.

Summary/Conclusion: This case illustrates how easily the differential diagnosis of an IDA can be complicated by the association of a thrombocytopenia. Discarding hemolysis, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome can usually be done within the Emergency Deparment, but other pathologies like malignancy or IDA secondary to bleeding caused by immune thrombocytopenia (ITP) can be more challenging without being well aware of this uncommon presentation. Studies comparing IDAT and ITP have found that the former usually present with more profound anemia and less severe thrombocytopenia, as well as significantly shorter platelet recovery time. Excluding malignancy, on the other hand, requires invasive procedures that might well be avoided if an early suspicion of IDAT is being addressed. Women of childbearing age with a history of menorrhagia fits the bill in this regard, as they also comprise the majority of the previously reported cases. As demonstrated, the rapid response to intravenous iron replacement therapy, even with an initial worsening of the platelet-count, obviates other invasive diagnostic procedures.

PB1605 THE ANALYSIS OF THE FIRST HEMATOLOGICAL CONSULTATIONS IN CROATIAN HEMATOLOGY OUTPATIENT CLINICS - A KROHEM STUDY

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Background: Patients with anemia are often referred to hematologists and anemia is one of the most common diagnosis in hematological clinics.
Aims: The aim of of this cross-sectional study is to determine the prevalence of anemia among all first examinations in hematological clinics, prevalence of individual types of anemia and specializations of referring physicians who request anemia testing with hematology consultation.
Methods: A multi-center cross-sectional study was performed at five Croatian outpatient hematology clinics which included all patients reffered to hematologists for the first consultation and anemia testing from different specialists from 1st Mar 2019 to 30th Jun 2019. Study was approved by Ethical Committee of each Hospital. Patients completed an appropriate questionnaire and signed informed consent. Descriptive statistics were performed and results are reported as frequencies (percentage) for categorical and as means (±standard deviation) or medians (minimum-maximum), as appropriate, for continuous values.
Results: Data includes 965 patients referred to the hematologist for the first consultation, and total of 280 patients (29 %) were with a referral diagnosis of anemia, 72 men (25.7%) and 208 women (74.3%) median age at diagnosis 51.5 (18 – 94) years. There were 46.8% of patients younger than 50 years and 53.2% older than 50 years. The male to female anemia ratio is 12: 1 within the younger group. The most common referral diagnosis was iron deficiency anemia in 76 % of patients. After hematological consultation and anemia testing, the actual diagnosis of anemia was consistent with referral diagnosis in 63.4% of patients. Anemia of other causes was most common in younger male group (80%), and iron deficiency was the cause of anemia in 90% of women in younger group due to reproductive age. Among women iron deficiency anemia is the most common (72.5%), while in men all other causes of anemia (megaloblastic are more common (61%). In older group other causes of anemia (megaloblastic anemia, MDS, malignancies, hemolytic anemias etc.) are more common among the causes of anemia (53%). Physicians of fifteen different specializations referred patients to hematologists for the anemia testing, most often general practicioners (82 %).
Summary/Conclusion: Iron deficiency anemia is the most prevalent anemia (90 %) among younger women, whereas iron deficiency is the cause of anemia in 63 % of all patients. Among older population other causes of anemias are more frequent than iron deficiency. General practicioners referred most common patients to hematologists for the first examination and anemia testing.

PB1606 AGE AND IRON STATUS IN PATIENTS WITH HFE MUTATIONS AT FIRST TIME REFERRAL TO PHLEBOTOMY

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Background: *HFE* hemochromatosis is characterized by iron overload due to increased iron absorption. Serum ferritin (SF) reflects total body storage iron, and the combination of elevated SF levels and an elevated transferrin saturation (Tsat) offers an easy and inexpensive screening method to detect candidates for *HFE* genetic testing. Overt disease is mainly associated with the C282Y homozygote genotype, and recommendations regarding phlebotomy to achieve iron depletion in these patients are well established. Fewer studies have focused on SF levels and its association with iron overload in other *HFE* genotypes, and accordingly to the controversy regarding risk of a significant iron overload developing in non-C282Y homozygotes, recommendations regarding management of these patients differ.
Aims: Based on these considerations, we wanted to investigate distribution and phenotypic expression of C282Y and H63D *HFE* mutations in patients referred to first time therapeutic phlebotomy, based on clinical suspicion of hemochromatosis or biochemical findings indicating iron overload.
Methods: We conducted a monocenter, cross-sectional study and retrospectively reviewed hospital records of patients who had positive genetic testing for C282Y and/or H63D *HFE* mutations over a 7-year period, and who were referred by their general practitioner to a tertiary referral center upon suspected hereditary hemochromatosis. 431 men and 97 women referred to first time therapeutic phlebotomy by the treating physician were included in the final analysis. Age at referral and last set of laboratory parameters prior to initiation of phlebotomy were obtained, including the following: SF, Tsat, hemoglobin (Hb), leukocyte particle concentration (LPK), thrombocyte particle concentration (TPK) and C-reactive protein (CRP).
Results: Median age at referral was 47.8 years in men and 57.1 years in women ($p < .001$). C282Y homozygosity was the most prevalent while H63D homozygosity was the least prevalent genotype in both genders (fig. 1). C282Y homozygotes represented the youngest group in both men (median 40.1 years, range 18.9 to 76.8) and women (median 53.8 years, range 25.1 to 79.5) ($p < .001$) (fig. 2). In men, H63D heterozygotes had the highest age at referral (median 50.7 years), while H63D homozygotes showed the highest age at referral among women (median 65.7 years). Finally, SF levels were lower in women (median 625 µg/L) than men (median 706 µg/L) ($p < .001$).
Only 10.8% of men and 3.8% of women exhibited SF levels ≥ 1000 µg/L in combination with Tsat level ≥ 50%. C282Y homozygosity was the most prevalent genotype of this group, although other genotypes were also represented. Additionally, 37% of men and 16% of women exhibiting Tsat levels ≥ 50% were non-C282Y homozygotes.

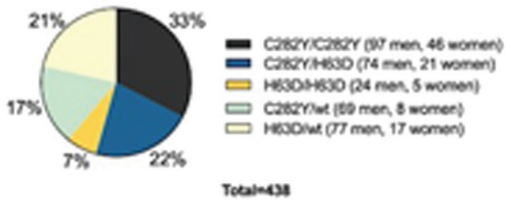


Figure 1. Distribution of *HFE* genotypes in the study population.

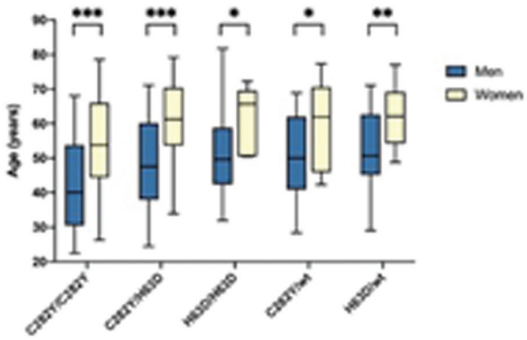


Figure 2. Age at referral for first time phlebotomy. Whiskers represent the 5th and 95th percentile. Men and women of each genotype were compared using Mann-Whitney U test, *p < .05, **p < .01, ***p < .001.

Summary/Conclusion: Our results are in line with previous observations regarding elevated iron indices compatible with iron overload not only in the C282Y homozygous state, but also in other *HFE* genotypes. Clinical practice regarding therapeutic phlebotomy in non-C282Y homozygotes is often restrictive, as risk of complications due to iron overload in these individuals is generally considered as low. Nevertheless, iron overload is not independently dependent on *HFE* mutations status, as environmental and host risk factors may modulate expression and contribute to a variable clinical presentation. Hence, phlebotomy ought to be considered in non-C282Y homozygote patients with persistent hyperferritinemia and suspected iron overload, particularly when other risk factors are present and further assessment is unwarranted.

PB1607 HYPERFERRITINEMIA IN HETEROZYGOUS H63D AND HYPERTRIGLYCERIDEMIA

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Background: Hereditary hemochromatosis (HH) is the most prevalent form of iron overload in Caucasians and comprises a group of disorders that lead to abnormalities in iron homeostasis, increasing intestinal absorption of iron and tissue deposition. If not treated, the accumulated iron can result in tissue damage such as liver cirrhosis, diabetes mellitus, arthropathy, myocardiopathy, endocrine disorders and hepatocarcinoma. Variants C282Y and H63D of the HFE gene (chromosome 6p21.3) are the two polymorphisms most frequently associated with HH. Studies of allele frequencies in northern European populations have reported 10–15% C282Y heterozygotes, 0.25–1.0% C282Y homozygotes, 20–30% H63D heterozygotes and 2% C282Y/H63D compound heterozygotes. The iron-loading risk profile for the possible genotypes is described: C282Y/C282Y >>> C282Y/H63D > C282Y/-, H63D/H63D, H63D/-. Non-C282Y homozygotes with significant iron loading should be investigated for rare iron-loading genotypes. Hypertriglyceridemia (HTG) is a common and important lipid abnormality in Western societies. Approximately 18% of adults have triglycerides over 200mg/dl, defining HTG. The HFE locus is associated with primary HTG, and in approximately 5% of cases, the HFE genotype could play a role in their pathogenesis. It is supposed thatincreased iron deposits associated with certain HFE genotypes induce an overproduction of liver triglycerides in predisposed individuals. In one study, this synergic effect seems to be especially relevant in C282Y/H63D compound heterozygotes; subjects with this genotype are at low risk of iron overload in the general population but, in the presence of HTG, iron overload penetrance seems to be much higher. On the other hand, phlebotomies significantly decreased triglycerides, especially in subjects with basal HTG.
Aims: To describe the characteristics of a patient with hyperferritinemia, H63D heterozygous and hypertriglyceridemia and the evolution after a phlebotomy regimen.
Methods: Case description.
Results: A 44-year-old male was referred to us because of hyperferritinemia. Body mass index 22.86, No toxic habits, including alcohol consumption. High blood pressure diagnosed at 35. Familiar hypertriglyceridemia. Nephritic colic, renal lithiasis and chronic uric acid nephropathy. He was taking carvedilol, manidipine, doxazosin, ezetimibe+atorvastatin, levetiracetam and omega 3. Abdominal ultrasound showed moderate hepatomegaly of left predominance, with no other abnormalities. Abdominal Angio-TC showed bilateral double renal artery.
Since H63D heterozygous is not supposed to justify the intense hyperferritinemia, rare iron loading genotypes were investigated, showing negative results for SLC40A1, TFR2, HFE2 or HAMP mutations.
The outstanding values of the analysis, and the comparison after the 3 phlebotomies are shown in the table.



Summary/Conclusion: H63D heterozygous patients, considered at low risk of iron overload in the general population, can express much higher iron overload penetrance in the presence of hypertriglyceridemia (HTG). Phlebotomies, even in a low number, led to normalization of the ferritin level, improved hypertriglyceridemia and the hepatic impact of the iron overload (leukopenia, macrocytosis, high liver enzymes) was normalized. Along with the specific treatment, this case suggests that therapeutic phlebotomy could be a useful therapeutic approach in patients with HTG and iron overload.

PB1608 EXTRAVASATION OF INTRAVENOUS IRON INFUSION: A CASE REPORT

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Background: Iron deficiency anaemia is the most common anaemia worldwide. Parenteral iron administration (Intramuscular or intravascular) is used when per os administration is contraindicated or is insufficient. Intramuscular (IM) iron administration is rarely used because it is painful and can stain the skin. Intravenous (IV) iron administration is time-consuming and anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. A new iron formulation such as sodium ferric gluconate complex and iron sucrose has led intravenous administration to gain ground over iron deficiency anaemia treatment during the last years. It can be administered in a short time with rare adverse events. Despite that, extravasation of iron solution although rare, may happen, leading to permanent skin hyperpigmentation.
Aims: Herein, a case report of iron extravasation among 200 infusions in 15 years, is reported.
Methods: A 51year-old woman with 3 children, Christian in religion with limited meat consumption throughout the year and regular menstruation, presented complaining of tiredness and headache. The laboratory exams revealed iron deficiency anaemia (Hb8gr/dl, MCV70fl, serum ferritin level 4ng/ml). Initially, she was prescribed sulphate iron per os, but she complained of epigastric pain and nausea a few days later. Thus, it was decided to be administered iron IV (Ferric Carboxymaltose). A few minutes after the initiation of the infusion, the woman complained of left arm oedema. The infusion was immediately stopped, and prevention measures were taken.
Results: Six months later, the skin hyperpigmentation in her left arm persists (photo 1).



Summary/Conclusion: Conclusion: Patients who are candidates to receive IV iron administration should be informed about this rare complication. Furthermore, nurses and physicians should be aware of possible iron extravasation and monitor the patient carefully throughout the infusion process; that way, it can be interrupted early if required. As spontaneous regressions of iron skin hyperpigmentation are rarely reported, there is no sufficient data regarding treatment options. Laser therapy could be beneficial in such cases.

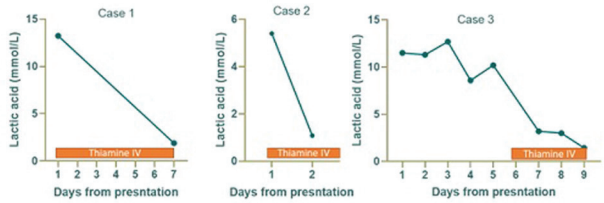
Lymphoma Biology & Translational Research

PB1609 THIAMINE REVERSAL OF LACTIC ACIDOSIS IN HIGH BURDEN HEMATOLOGICAL MALIGNANCY: CASE SERIES

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Background: A malignancy-induced lactic acidosis is a rare event that is largely associated with hematologic malignancies (leukemias and lymphomas). It is a subset of type B lactic acidosis that is mediated without evidence of tissue hypoperfusion, pathophysiology that is centered around the Warburg effect and is associated with poor outcomes. Thiamine pyrophosphate is a vital cofactor for pyruvate dehydrogenase, which irreversibly converts pyruvate to acetyl-CoA, committing the pathway in a way that it cannot be reversed back to anaerobic respiration. We hypothesize in the presence of a high level of cofactors responsible for this step, the glycolysis pathway might be skewed to an otherwise anaerobic preference.
Aims: To evaluate if high dose thiamine can reverse malignancy-induced lactic acidosis in patients with hematological malignancies.
Methods: Retrospective-single center review of malignancy-induced lactic acidosis that has been treated empirically with high dose thiamine between 2015 and 2020. Patients with not enough data on the lactic acid level, or an alternative explanation for the lactic acidosis is present, were excluded.
Results: *Case 1:* 19-year-old male with a history of Classical Hodgkin's Lymphoma 3 years before his presentation with symptoms of fatigue and shortness of breath. His CBC revealed pancytopenia with ANC 0.3 x109/L and platelets of 9 x 109/L. Metabolic acidosis was noted on presentation with bicarbonate 9.5 mmol/L and lactic acid of 13.23 mmol/L. PET scan showed above and below diagram lymphadenopathy with cutaneous and subcutaneous and bone marrow activity. He was given thiamine 100 mg IV TID for 7 days pending the establishment of diagnosis by biopsy. Lactate normalized during this time, with only cofounding agent been steroids. The final diagnosis was T-cell lymphoma with Ki67 of more than 90% with bone marrow showing evidence of hemophagocytic lymphohistiocytosis [Figure].
Case 2: 15-year-old female with no past medical history who presented with gum bleeding and abdominal pain for 7 days. CBC revealed WBC of 10 x109/L and platelets of 12 x109/L. Biochemistry showed metabolic acidosis with bicarbonate of 11 mmol/L and lactic acid of 5.4 mmol/L. LDH was more than the upper limit of detection (>2000). The patient was started on thiamine 100 mg TID for 2 days with normalization of lactate in 36 hours. Bone marrow biopsy was difficult to aspirate and biopsy showed 100% cellularity with 70% blast. Diagnosis of Philadelphia negative B-ALL was made, and the patient was treated on pediatric ALL protocol [Figure].
Case 3: 22-year-old male with no past medical history presented with epistaxis, shortness of breath, scrotal and generalized edema. He had hepatosplenomegaly on the exam with a tender spleen. Imagining revealed renal hypodensities with ascites and bilateral pleural effusion. CBC showed WBC of 16 x109/L and platelets of 8 x109/L. Biochemistry showed LDH of 1123 U/L with a picture of metabolic acidosis. Bicarbonate was 16 mmol/L and lactic acid was 8.6-12.8 mmol/L for four days before starting on thiamine 100 mg IV TID with normalization of lactate in 3 days. The patient's bone marrow showed 100% cellularity with 75% blast. The diagnosis of Philadelphia negative B-ALL was made, and the patient was started on pediatric-inspired protocol [Figure].



Summary/Conclusion: Malignancy-induced lactic acidosis related to the Warburg effect or thiamine pyrophosphate deficiency at a cellular level, high dose thiamine, and/or other cofactors like riboflavin, might be useful in treating this disorder, meriting further investigation.

PB1610 CLONALITY ANALYSIS IN FOLLOW-UP OF PATIENTS WITH NON-HODGKIN LYMPHOMA

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Background: Clonal immunoglobulin and T cell receptor gene rearrangements can be used as tumor-specific markers in patients with non-Hodgkin lymphoma.
Aims: The aim of our study was to evaluate the applicative value of standardized BIOMED-2 gene clonality assay protocols for monitoring of lymphoma recurrence.
Methods: With this purpose, 448 specimens from 93 patients with non-Hodgkin lymphoma submitted for initial diagnosis, post-treatment monitoring and evaluation of lymphoma progression or recurrence from 2011-2020 were retrospectively analyzed. According to the initial diagnosis, our series comprised 65 samples from 23 patients with B-cell lymphomas and 383 samples from 70 patients with non-Hodgkin T-cell lymphomas. Clonality testing and determination of amplicon sizes was performed using the BIOMED-2 clonality assays.
Results: We detected clonal immunoglobulin heavy chain gene (IGH) rearrangements with amplicons of same sizes as at initial diagnosis in all follow-up samples from patients with B cell non-Hodgkin lymphoma (100%). In a group of T cell lymphomas we detected clonal T cell receptor beta (TCRB) or gamma (TCRG) gene rearrangements with amplicons of same sizes as at initial diagnosis in 376 follow-up samples from 62 patients (95.6%).
Summary/Conclusion: In the present study, we confirmed the utility of standardized BIOMED-2 clonality assays not only for initial diagnosis of wide range of lymphoid proliferations but also for post-treatment monitoring and evaluation of lymphoma progression or recurrence.

PB1611 TUMOR-NONSPECIFIC METHYLATION OF THE MIR-145 GENE IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The p53 protein (a product of the TP53 gene) is known to regulate a whole class of micro-RNAs. The direct target of p53, through which it implements its oncosuppressive effects, is miR-145. This microRNA interacts with the 3/ - untranslated mRNA sequence of oncogenes c-MYC and individual cyclinkinases.
Several mechanisms of impaired expression of oncosuppressive microRNAs have been described, among which the methylation of promoters and enhancers encoding their genes is important. It is known that the frequency of methylation of the MIR-145 gene differs in various oncological processes. Thus, in patients with prostate cancer and non-small cell lung cancer, the frequency of methylation of this gene is about 50.0 % (Zaman M. S., 2011; Zhiqiang Y., 2015), and in colon cancer – more than 80.0 % (Pekow J., 2015).
It has been shown that a decrease in miR-145 expression is not only associated with the occurrence of lymphomas, but also a predictor of their more aggressive clinical course (Poli V., 2020). However, studies of the methylation status of MIR-145 in diffuse B-large cell lymphoma (DLBCL) have not been previously conducted.
Aims: To evaluate the frequency of methylation of the MIR-145 gene in the tumor tissue of Diffuse Large B-cell Lymphoma.
Methods: Genomic DNA was isolated by phenol-chloroform extraction using guanidine from paraffinized blocks of biopsy samples of tumor lymph nodes and extranodal lesions of patients with DLBCL. The DNA of a healthy donor was used to assess the specificity of methylation. The Human Methylated and Unmethylated DNA Control Kit (Zymo Research, USA) was used as a controls. Bisulfite DNA conversion was performed using the EZ DNA Methylation-Gold Kit (Zymo Research, USA). The methylation status of the gene was determined by the method of methyl-specific PCR using pairs of primers to the methylated and unmethylated sequences.
Results: Currently, 25 DNA samples have been analyzed. It was shown that the frequency of methylation of the MIR-145 gene was 23\25 (92%). In the healthy tissue MIR-145 was also in the methylated state.
Summary/Conclusion: The results obtained indicate that the methylation of the MIR-145 gene in the lymphoid tissue of patients with DLBCL is not tumor-nonspecific.

Myelodysplastic syndromes - Biology & Translational Research

PB1612 COMBINING FLOW CYTOMETRY AND MOLECULAR GENETICS FOR PROGNOSIS IN MYELODYSPLASTIC SYNDROME

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Background: Refinement of prognosis is crucial for improvement of outcome in patients with myelodyslastic syndrome (MDS). Flow cytometry and molecular genetics can be used for this purpose.
Aims: In our study we tried to combine these two approaches to define subgroups of MDS patients with different clinical course.
Methods: We performed flow cytometry to quantitatively assess T- and NK-cells, myeloid progenitors, T-regulators, myeloid-derived suppressor cells in bone marrow of 38 adult MDS patients after signing informed consent for participation in research. In each cell population we measured expression of PD-1, PD-L1, PD-L2, CD80, CTLA-4, LAG3, TIM3, ICOS-L. In 23 patients we carried out Sanger sequencing of SF3B1, DNMT3A, RUNX1, ASXL1, TP53 genes. We tracked the 2-year outcome of the included patients regarding the defined flow and molecular parameters. This work was supported by Russian Science Foundation, grant No 17-75-20145-П.
Results: We observed significant role of PD-L1 expressing regulatory T-cells (PDL1-Tregs) subpopulation level. Patients with PDL1-Tregs higher than 0.003% of all nucleated cells showed lower 2-year overall (OS2) and relapse-free (RFS2) survival (41.3% and 35.8% vs. 85.7% and 85.7% in those with PDL1-Tregs lower than 0.003%, respectively, $p<0.05$). The number of mutations significantly influenced OS2 (80%, 60%, and 0% for 0, 1, and 2 mutations, respectively, $p<0.05$) and RFS2 (72.2%, 60%, and 0% for 0, 1, and 2 mutations, respectively, $p<0.05$). When combining these results we managed to derive the compound index consisting of two binary variables: PDL1-Tregs higher or lower than 0.003% of all nucleated cells and presence or absence of at least one molecular mutation obtaining 4 subgroups of MDS patients with significantly different OS2 and RFS2. Thus, in lower PDL1-Tregs without mutations, lower PDL1-Tregs with mutations, higher PDL1-Tregs without mutations, and higher PDL1-Tregs with mutations OS2 was 100%, 50%, 72%, and 0% ($p<0.05$), respectively, and RFS2 was 100%, 50%, 80%, and 0% ($p<0.05$), respectively.
Summary/Conclusion: Our preliminary results underline the importance of using parallel approaches and new methods for prognosis in MDS patients. Further studies are warranted.

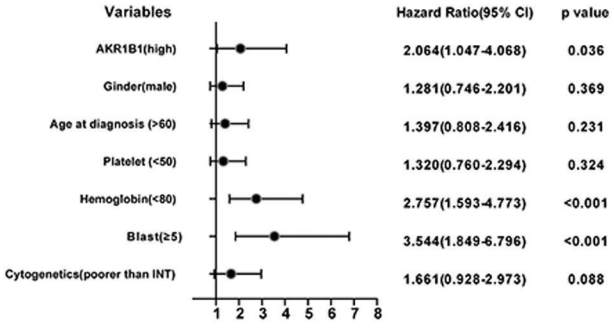
PB1613 SUPPRESSION OF AKR1B1 REDUCES CELL PROLIFERATION AND ENHANCES SENSITIVITY TO HYPOMETHYLATING AGENTS BY INHIBITING MTORC1 SIGNALING PATHWAY IN HIGH-RISK MYELODYSPLASTIC SYNDROME

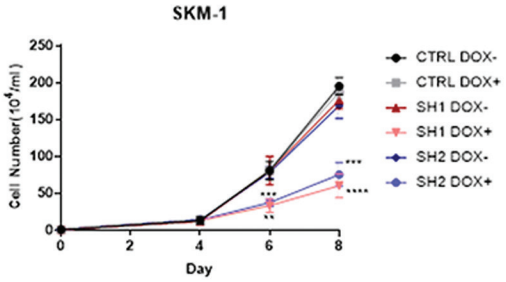
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Background: High-risk myelodysplastic syndrome (HR-MDS) patients have a short survival time and a poor prognosis. Moreover, there is dearth of therapeutic targets for treatment of this malignancy. Aldo-keto reductase AKR1B1 was reported to be highly expressed in a variety of tumors and promote the tumor cell proliferation.
Aims: The main objective was the identification of the role of the AKR1B1 axis in the progression of HR-MDS and its druggable potential
Methods: Kaplan Meier curve was used to evaluate the relationship of AKR1B1 expression level and overall survival in HR-MDS. The effect of AKR1B1 knockdown and overexpression and the effect of AKR1B1 inhibitor epalrestat was studied in cell viability. To evaluate the combined effect of epalrestat and hypomethylating agents (HMAs), data were analyzed by the CalcuSyn software. The related signaling pathways

of AKR1B1 in MDS were investigated by gene set enrichment analysis (GSEA) and verified by Western blot. Co-immunoprecipitation (Co-IP) was performed to detect proteins that interact with AKR1B1.
Results: AKR1B1 was upregulated in high-risk MDS, not low-risk MDS. AKR1B1 expression was increased in EZH2 mutant MDS patients. In the hematopoietic stem and progenitor cells (HSPCs), AKR1B1 was barely expressed. High expression of AKR1B1 was associated with shorter OS and EFS in HR-MDS. Multivariate analysis revealed that higher AKR1B1 expression was an independent, unfavourable prognostic factor for OS in HR-MDS, not in the total MDS.
Genetic or pharmacological inhibition of AKR1B1 markedly decreased cell viability of MDS cell lines. Similar results were obtained in primary MDS cells. SKM-1 cells overexpressing AKR1B1 had a higher proliferation rate under serum starvation. Epalrestat enhances the toxicity of HMA in MDS cell line and primary MDS cells.
GSEA results suggested that AKR1B1 might participate in the mTORC1 signaling pathway, which was confirmed by Westernblot. Mechanistically, AKR1B1 interacted with RHEB to regulate the phosphorylation of mTOR.





Summary/Conclusion: AKR1B1 is negatively correlated with overall survival in HR-MDS. Inhibition of AKR1B1 not only suppressed the proliferation of MDS cells but also increase the drug susceptibility to HMAs. AKR1B1 interacts with RHEB to modulate mTORC1 activity. In conclusion, suppression of AKR1B1 reduces cell proliferation and enhances sensitivity to HMAs by inhibiting mTORC1 signaling pathway in HR-MDS.

PB1614 U2AF1 MUTATION PROMOTES TUMORIGENICITY THROUGH FACILITATING AUTOPHAGY FLUX MEDIATED BY FOXO3A ACTIVATION IN MYELODYSPLASTIC SYNDROMES

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Background: Mutations in the U2 small nuclear RNA auxiliary factor 1 (U2AF1) gene are the common feature of a major subset in myelodysplastic syndromes (MDS). However, the genetic landscape and molecular pathogenesis of oncogenic U2AF1S34F mutation in MDS are not totally understood.
Aims: To explore the molecular pathogenesis of oncogenic U2AF1S34F mutation in MDS, we carried out the current study.
Methods: We performed comprehensive analysis for prognostic significance of U2AF1 mutations in acute myeloid leukemia (AML) cohort based on The Cancer Genome Atlas (TCGA) database. Functional analysis of U2AF1S34F mutation was performed in vitro. Differentially expressed genes (DEGs) and significantly enriched pathways were identified by RNA-sequencing. The forkhead box protein O3a (FOXO3a) was investigated to mediate the function of U2AF1S34F mutation in cell models using lentivirus. Chromatin immunoprecipitation, immunoblotting analyses and immunofluorescence assays were also conducted.
Results: U2AF1 mutations were associated with poor prognosis in MDS and AML samples, which significantly inhibited cell proliferation and induced cellular apoptosis in cell models. Our data identified that U2AF1-mutant cell lines undergo FOXO3a-dependent apoptosis and NLRP3 inflammasome activation, which induces pyroptotic cell death. Particularly, an increase in the level of FOXO3a promoted the progression of MDS in association with restored autophagy program leading to NLRP3 inflammasome activation in response to U2AF1S34F mutation. Based on the result that U2AF1S34F mutation promoted the transcriptional activity of Bim through up-regulating FOXO3a with transactivation of cell cycle regulators p21Cip1 and p27Kip1, FoxO3a, a potentially cancer-associated transcription factor, was identified as the key molecule on which these pathways converge. death. Particularly, an increase in the level of FOXO3a promoted the progression of MDS in association with restored autophagy program leading to NLRP3 inflammasome activation in response to U2AF1S34F mutation. Based on the result that U2AF1S34F mutation promoted the transcriptional activity of Bim through up-regulating FOXO3a with transactivation of cell cycle regulators p21Cip1 and p27Kip1, FoxO3a, a potentially cancer-associated transcription factor, was identified as the key molecule on which these pathways converge.
Summary/Conclusion: Overall, our studies provide new insights that U2AF1S34F mutation functions the crucial roles in mediating MDS disease progression via FOXO3a activation, and demonstrate novel targets of U2AF1 mutations to the pathogenesis of MDS.

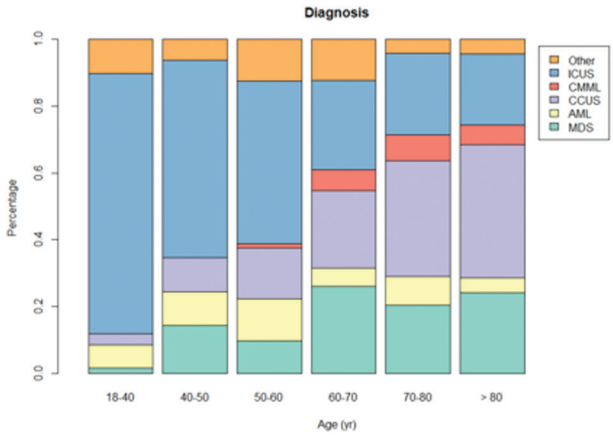
PB1615 THE UTILITY AND OUTCOME OF NEXT GENERATION SEQUENCING IN THE DIAGNOSTIC WORK UP OF PATIENTS WITH UNEXPLAINED CYTOPENIA AT A PRIMARY REFERRAL CENTER

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Background: With increasing availability, next generation sequencing (NGS) is becoming a useful supplement in the diagnostic work up of patients with cytopenia.
Aims: This study aimed to improve the rational use of NGS by analyzing the occurrence of mutations in 593 patients with cytopenias from 2015-2020, referred for primary work up for a suspected hematological malignancy.
Methods: NGS of 20 genes associated with myeloid malignancies was performed in all patients, and 97% and 88% had a bone marrow biopsy and cytogenetics performed, respectively.
Results: Mutations were found in 311 (52.4%) patients and the most commonly mutated genes were *TET2*, *DNMT3A*, *ASXL1*, *SRSF2* and *SF3B1*. Among patients with mutations, the most prominent diagnosis was CCUS (45%) followed by MDS (30%), AML (11%) and CMML (9%). The presence of one or more mutations increased the risk of having a malignant disorder diagnosed on the bone marrow (OR: 4.48, $p < 0.0001$). The median number of mutations per patient was one (range 0-12). High variant allele frequency was associated with abnormal bone marrow ($p < 0.0001$) with median VAF for MDS patients being 37% (IQR: 23%>44%), whereas patients with CCUS had a median VAF of 22% (9%>40%). Most patients presented with isolated cytopenia (42.7%), while 37.6% and 20.7% had bicytopenia and pancytopenia, respectively. The highest risk of mutations was in patients with bicytopenia, where 58.5% had at least one mutation. ICUS patients were the youngest, with a median age of 58 years (IQR: 43-70 yr) compared to 66 (51-73), 70 (64-77), 73 (67-78) and 71 (68-76) for AML, MDS, CCUS and CMML, respectively. We found a positive correlation between age and the risk of having a mutation, as the amount of patients with 1 or more mutations increased from 22% to 66%, regardless of final diagnosis, in age groups < 60 years and ≥ 60, respectively (OR: 7.0, $p < 0.0001$). In the age group above 60 years, CCUS was the most prominent

diagnosis (32%), and 37% received a malignant hematological diagnosis (MDS, AML or CMML).



Summary/Conclusion: In conclusion, NGS can be a valuable tool in the diagnostic work up of patients with cytopenia, and CCUS is the most common disease in patients above 60 years referred due to unexplained cytopenia.

PB1616 MUTATIONAL PROFILE AND IMMUNOPHENOTYPIC CHANGES IN BONE MARROW COMPARTMENTS OF CHRONIC MYELOMONOCYTIC LEUKEMIA PATIENTS

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Background: Chronic Myelomonocytic Leukemia (CMML) is a heterogeneous disease, with overlapping features of myelodysplastic and myeloproliferative syndromes. Both immunophenotypic alterations and recurrent somatic mutations are found in CMML patients and can provide useful information on diagnosis and prognosis.
Aims: Immunophenotypic characterization of bone marrow compartments and its correlation with genetic alterations in a group of CMML patients (WHO2016).
Methods: Retrospective immunophenotypic analysis was performed according to EuroFlow panels and the Mean Fluorescence Intensity (MFI) from bone marrow (BM) granulocyte, monocyte and erythroid compartments of CMML patients (n=47) and from a normal BM (healthy group HG, n=16) was recorded. In 33 patients, targeted gene sequencing of 45 genes recurrently mutated in myeloid malignancies was performed on an Ion S5 (Thermo Fisher). Statistical analysis was done using SPSSv26.
Results: CMML patients were 70% male, median age 72y. WHO Classification: 42% CMML-0; 42% CMML-1; 16% CMML-2. FAB-Classification: 40% proliferative, 60% dysplastic. AML progression occurred in 13%, with a median time of 15 months. Mutations were identified in 97% of patients, with a median of 3 (0-7). *ASXL1* (55%), *TET2* (52%) and *RAS* pathway (22%) were the most frequently mutated genes. CPSS-Mol risk score was: 14% low; 20% int-1; 33% int-2; 33% high. Mutations in epigenetic modifiers genes alone (group A) were found in 21% and simultaneously with signal transduction genes (group B) in 36% of patients. Patients with mutated epigenetic modifiers had lower hemoglobin levels ($p<0.05$). We found an association between *ASXL1* mutations and increased leukocyte count and between *ASXL1* and *RAS* mutations with proliferative-CMML ($p<0.05$).
Flow cytometry analysis of CMML BM revealed statistically significant differences in MFI in granulocyte (CD10, CD13, CD45), monocyte (CD11b, CD36, CD45, HLA-DR) and erythroid (CD45, CD105, CD117) maturation, compared with HG. Both genetic groups A and B showed an increased MFI in CD45 in granulocyte and CD36, CD45, HLA-DR in monocyte maturation when compared to HG and increased CD11b MFI in monocyte maturation on group B. Decreased MFI in CD10, CD13 in granulocyte and CD45, CD105, CD117 in erythroid maturation also occurred in both groups. The more pronounced changes found in erythroid maturation in group A patients could be related to their lower hemoglobin levels, but further studies are required.
We observed no differences in MFI in the analysed markers among WHO classification or CPSS-Mol Score groups, but progression to AML was associated with increased MFI in CD45, CD11b, CD13 in granulocyte and CD45, HLA-DR in monocyte maturation ($p<0.05$).
Summary/Conclusion: In CMML, there seems to be a specific immunophenotypic expression pattern in granulocyte, monocyte and erythroid maturation. Contrary to the remaining CMML BM, patients with mutations in epigenetic modifiers genes alone did not show a significant increase in CD11b expression in monocyte maturation.
In our cohort, progression to AML was associated with specific immunophenotypic changes.
Detailed immunophenotyping of different BM maturation compartments can further improve our understanding of CMML and help to better refine risk and prognosis classification of such heterogeneous disease.

PB1617 AKT KINASE REGULATES TIM-3 EXPRESSION IN MYELOID NEOPLASMS

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Background: Myelodysplastic syndrome (MDS) is a heterogeneous clonal disease characterized by the presence of cytopenia in the peripheral blood and dysplasia in the bone marrow. The rate of progression to acute myeloid leukemia (AML) is significant and median time to progression varies from months to years according to biological and clinical feature. Recent preclinical and clinical research indicated the significance of TIM3 signaling checkpoint pathways in progression of MDS and AML and showed the utility of TIM3 inhibition by monoclonal antidotes in inducing clinical remission.
Aims: To investigate the potential targets for therapy of myeloid neoplasms.
Methods: The ability of signaling pathway inhibitors to decrease the expression level of TIM-3 on the membrane surface was tested using the THP-1 cell line of the M2 variant of AML. We tested the panAKT inhibitor MK-2206, mTOR (Rapamycin), PKC (Enzastaurin), RAF (Sorafenib) and ERK (PD98,059). Also the patient's bone marrow with transformation into AML was plated with a 1:20 dilution in RPMI-1640 medium with/without the inhibitor. The surface expression of TIM-3 was assessed by flow cytometry after incubation for 24 and 48h. Additionally, fresh cells from the bone marrow was cultivated only with MK-2206 for 24h.
Results: We found that after the addition of panAKT inhibitor MK-2206 to THP-1 cells and its cultivation for 24 hours, the percentage of TIM-3+ cells decreased from 96.4% to 27.5% at 5 µm and to 16.5% at 10 µm. After 48 hours of cultivation, the sustained decrease persisted up to 40% and 43.2%, respectively. No difference in TIM3 expression after THP-1 cultivation with other inhibitors was observed ($p> 0.05$). The same pattern was observed in native MDS bone marrow: after its cultivation with 10 µm MK-2206, the percentage of TIM-3+ cells decreased from an average of 10.7% to 5.9%.
Summary/Conclusion: A promising direction for further research in AML and MDS is not only blockage of TIM3 signaling by monoclonal antibodies, but also elucidation of pathways leading to TIM3 expression on malignant cells. Further research is required to identify the mechanisms of Akt-mediated TIM3 downregulation.

PB1618 POLYMORPHISM OF GSTM1, GSTT1 AND CYTOKINE GENES IN PATIENTS WITH MYELODYSPLASTIC SYNDROME

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Background: Cytokine and cytokine receptors are important regulators of hematopoiesis. Overexpression of cytokine are observed in multiple myeloid diseases such as myelodysplastic syndrome (MDS). Glutathione S-transferases (GST) modulate the effects of exposure to various cytotoxic and genotoxic agents, including those associated with increased risks of the myelodysplastic syndrome. Polymorphisms in carcinogen-metabolizing genes may affect enzyme activity and subsequently influence carcinogen activation.
Aims: The aim of this study was to assess the features of alleles and genotypes distributions of GSTM1, GSTT1 and cytokine genes in MDS patients.
Methods: Thirty-nine patients with MDS (17 men and 22 women, mean age 62.4 yrs) and 150 healthy controls (HC) (cancer-free 102 men and 48 women, mean age 52.1 yrs) from North-Western Russia were genotyped for the GSTM1, GSTT1, IL-6 G174C, TNF-α G308A, IL-1β T31C polymorphisms by PCR and PCR-RFLP technique. The differences in allele and genotype frequencies between patient and HC groups were assessed by Fisher's exact test with computation of odds ratios (OR), their 95% confidence intervals (CI) and p-values.
Results: The frequencies of the *null* alleles GSTM1 and GSTT1 differed slightly in both patients with MDS and in the control group. At the same time, the simultaneous presence of the IL-6 174C allele and GSTM1 *null* allele was more often detected in male MDS group compared to male HC group (58.8% vs. 26.4%, OR=3.9, 95%CI: 1.4-11.5, p=0.011), in female MDS patients was not different to female HC group (36.3%, vs. 33.3%, respectively). The frequency of the IL-1β 31C allele in patients MDS with GSTM1 *null* allele was nearly 2-fold higher, than in those HC group (41% vs 23,3 % respectively, OR=2.3, 95% CI: 1.1-4.8, p=0.04), In contrast, IL-1β 31C allele was observed 5.5 -fold higher in men HC group compared in men MDS group with undeleted GSTM1 allele (33.3% vs 5,9 %, OR=8.0, 95% CI: 1.0-63.0, p=0.022). At availability genotype IL-6 174CC with GSTT1 *null* allele in the male patients MDS were found more often than the same male group HC (11,8% vs 1%, OR=13.5, 95% CI: 1.1-157, p=0.053, respectively). Genotype IL-1β T31C in the presence undeleted GSTT1 allele was more often in female MDS group compared to female HC group (50% vs. 22,9%, OR=3.4, 95%CI: 1.1-9.8, p=0.03). TNF-α G308A polymorphism in patients were not statistically different from those in HC group.
Summary/Conclusion: We believe that the distribution of alleles and genotypes of the GSTM1, GSTT1 and cytokine genes in patients with MDS is multifactorial and requires further study to identify risk factors for the development of the disease and explain the causes of their occurrence.

Myelodysplastic syndromes - Clinical

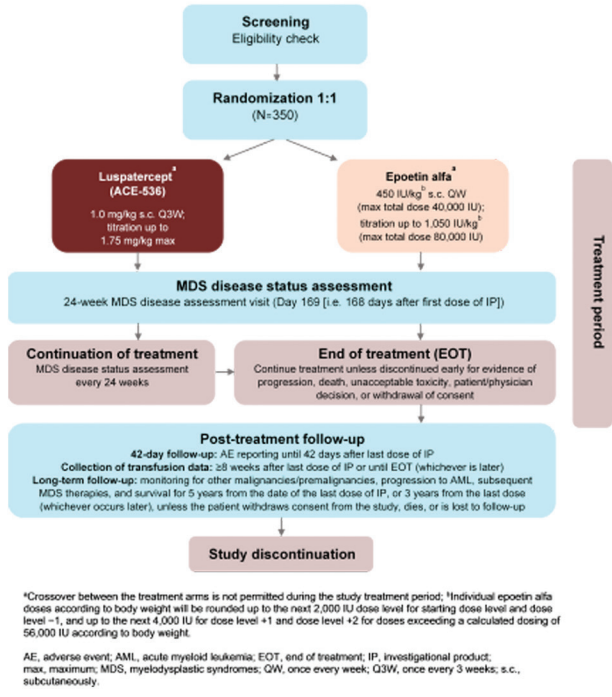
PB1619 A PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF LUSPATERCEPT VERSUS EPOETIN ALFA FOR THE TREATMENT OF ANEMIA DUE TO LOWER-RISK MDS IN ESA-NAIVE PATIENTS REQUIRING RBC TRANSFUSIONS (THE COMMANDS TRIAL)

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Background: Patients (pts) with myelodysplastic syndromes (MDS) often suffer from anemia and other consequences of regular red blood cell (RBC) transfusions. Erythropoiesis-stimulating agents (ESAs) are a standard of care for pts with lower-risk MDS (LR-MDS). Epoetin alfa and darbepoetin alfa have shown efficacy among pts with LR-MDS, but the pt population in whom a clinically significant effect is seen may be limited. An important clinical benefit in this LR-MDS pt population would be to increase the frequency of response and the duration of RBC transfusion independence (TI). Luspatercept, a first-in-class erythroid maturation agent with a mechanism of action distinct from ESAs, is now approved in both the EU and the USA for pts with LR-MDS with ring sideroblasts (RS) who require RBC transfusions and are refractory, intolerant, or ineligible to receive ESAs. Luspatercept may also be beneficial in treating anemia in pts with ESA-naive, LR-MDS who require RBC transfusions. In a phase 2 study in anemic pts with LR-MDS, 63% of pts receiving luspatercept (0.75–1.75 mg/kg) achieved a modified hematologic improvement–erythroid (mHI-E) response; when analyzed by RS status, 69% of pts with ≥15% RS and 43% of pts with <15% RS achieved mHI-E response (Platzbecker U, et al. *Lancet Oncol* 2017;18:1338–1347).
Aims: The COMMANDS is a phase 3, open-label, randomized trial comparing the efficacy and safety of luspatercept vs epoetin alfa in anemic pts with IPSS-R-defined LR-MDS, with or without ≥15% RS, who are ESA naive, and who require regular RBC transfusions.
Methods: To be eligible, pts must be ≥18 years old, have a diagnosis of IPSS-R-defined LR-MDS with <5% blasts in the bone marrow, serum erythropoietin (sEPO) levels <500 U/L, and require RBC transfusions (defined as transfusion requirement of 2–6 RBC units/8 weeks for ≥8 weeks immediately prior to randomization). Exclusion criteria include prior use of ESAs (≤2 doses of prior epoetin alfa permitted if ≥8 weeks from randomization date and sEPO confirmed as ≤ 500 U/L), granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor, unless administered for treatment of febrile neutropenia; disease-modifying agents (e.g. lenalidomide), or hypomethylating agents; and presence of del(5q) cytogenetic abnormality. Eligible pts (N≈350) will be stratified and randomized 1:1 to either luspatercept (starting dose 1.0 mg/kg with titration up to 1.75 mg/kg) subcutaneously (s.c.) once every 3 weeks or epoetin alfa (starting dose 450 IU/kg with titration up to 1,050 IU/kg) s.c. once every week, for a minimum of 24 weeks (Figure). Best supportive care, including RBC transfusions, is permitted in combination with study treatment in both arms. Stratification factors include: baseline RBC transfusion burden (<4 vs ≥4 RBC units/8 weeks), baseline sEPO level (≤200 U/L vs >200 U/L), and RS status (with RS+ defined as RS ≥15%, or ≥5% [but <15%] if *SF3B1* mutation is present). Additionally, ≥40% and ≤60% of randomized pts will be RS+, and ≥25% will have sEPO >200 U/L.
Results: The primary endpoint is defined as achievement of RBC-TI for 12 weeks during Weeks 1–24 of study, with a concurrent mean hemoglobin (Hb) increase of ≥1.5 g/dL compared to baseline. Key secondary endpoints include duration of RBC-TI, change in Hb levels, achievement of HI-E (per International Working Group [IWG] 2006), and safety.

Figure. Design of the COMMANDS trial



[a]Crossover between the treatment arms is not permitted during the study treatment period; [b]Individual epoetin alfa doses according to body weight will be rounded up to the next 2,000 IU dose level for starting dose level and dose level −1, and up to the next 4,000 IU for dose level +1 and dose level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight.

AE, adverse event; AML, acute myeloid leukemia; EOT, end of treatment; IP, investigational product; max, maximum; MDS, myelodysplastic syndromes; QW, once every week; Q3W, once every 3 weeks; s.c., subcutaneously.

Summary/Conclusion: The COMMANDS trial is registered at EudraCT (number 2017-003190-34) and ClinicalTrials.gov (NCT03682536). This abstract was presented previously (Della Porta et al. *Blood* 2020;136(suppl 1):1–2).

PB1621 MUTATIONAL ANALYSIS IN LOW RISK MYELODYSPLASTIC SYNDROMES: A SINGLE CENTER REPORT

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Background: Myelodysplastic syndromes (LR-MDS) are a very heterogeneous group of diseases ranging from mild forms to life-treathening cytopenias. Recently, a deeper knowledge of LR MDS molecular landscape paved the way to novel treatments, such as luspatercept for SF3B1 mutated patients with ring sideroblasts. Less is known about the prevalence and type of other mutations in LR-MDS and their clinical significance.

Aims: To evaluate the prevalence of somatic mutations of myeloid genes in LR-MDS patients and their relationship with clinical/laboratory features and outcome.

Methods: Fifty out of 160 LR-MDS patients regularly followed at a tertiary hematologic center have been evaluated by next generation sequence (NGS) technology (Ion Torrents5) Ion Reporters software 5.2 which evaluates mutational status of 69 potentially oncogenic genes present in the Oncomine Myeloid Research Assay diagnostic panel, including hotspot genes, full genes, and fusion transcripts. Only variants with an allelic frequency (VAF) > 5% were reported. NGS results were matched with clinical and hematologic variables that have been retrospectively collected

Results: Table 1 shows the clinical features in mutated and unmutated patients. Seventy-two % of cases showed at least one mutation involving SF3B1 (N=16), TET2 (N=10), DNMT3A (N=4), SRSF2 (N=6), ASXL1 (N=5), ZRSR2 (N=3), IDH2 (N=3), IDH1 (N=2), SH2B3 (N=2), U2AF1 (N=4), P53 (N=1), ETV6 (N=1), PHF6 (N=2), STAG2 (N=1), RUNX1 (N=2), JAK2 V617F (N=2), FLT3 (N=1). The median VAF was 30%, and 15 patients showed 1 mutation, 10 patients 2 mutations, and 11 patients 3 or more. Subjects harbouring at least one mutation were older as compared to NGS negative cases (p<0.01), and more frequently displayed a normo/hypercellular bone marrow (p=0.01). Interestingly, mutated cases showed a higher response rate to recombinant erythropoietin (70.3% versus 50%), although not significantly. Subsequent analyses were made according to the number and type of genetic defects: harbouring 2 or more mutations was associated with older age [76 (41-86) versus 71 (48-85) years, p< 0.05], lower neutrophil counts at diagnosis [1.47 (0.4-4.2) versus 2.71 (0.4-5.8) x10^9/L, p<0.01], and to shorter time to response to recombinant EPO [2.2 (1.5-8.8) months versus 6.3 (1.5-16) months, p=0.06]. Neutropenia was even more marked in patients with 3 or more mutations [1.1 (0.2-2) versus 2.6 (1.9-5.2) x10^9/L, p<0.01]. Mutations involving the splicing pathway (i.e. SF3B1, U2AF1, and ZRSR2) were the most common, and correlated with older age (76 versus 71, p=0.01), increased bone marrow cellularity [50 (25-90) versus 40 (20-50)%, p<0.01], higher platelet [209 (41-564) versus 105 (20-332) x10^9/L, p=0.02] and neutrophil counts [2.8 (0.37-5.8 versus 1.8 (0.4-3.5) x10^9/L, p=0.03].

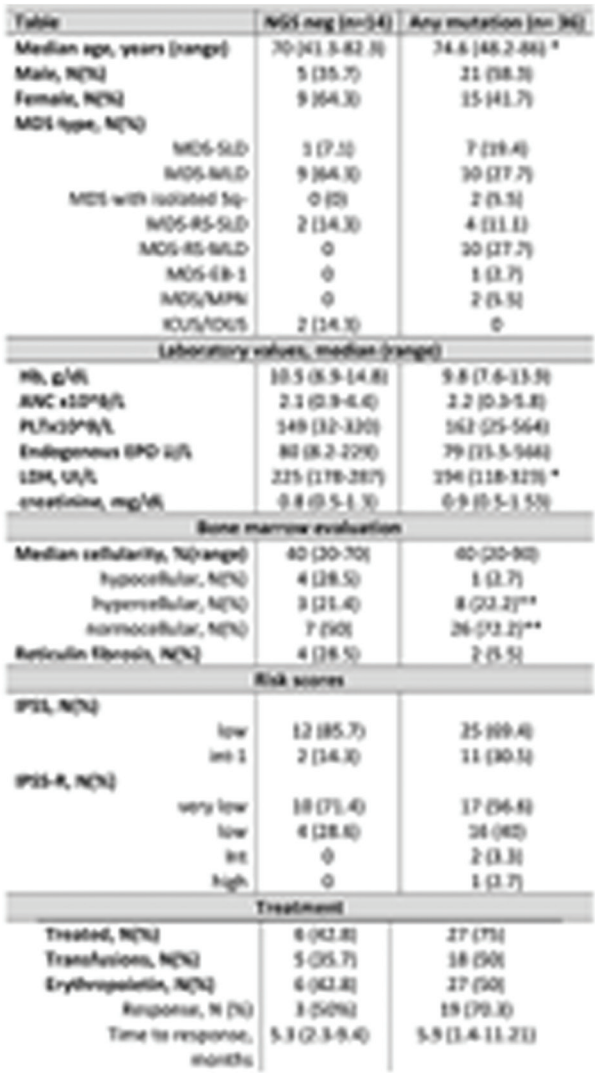


Table	NGS neg (n=54)	Any mutation (n=36)
Median age, years (range)	70 (41.3-82.3)	74.6 (48.2-86) *
Male, N(%)	5 (35.7)	21 (58.3)
Female, N(%)	9 (64.3)	15 (41.7)
MDS type, N(%)		
MDS-SLD	1 (7.1)	7 (19.4)
MDS-MLD	9 (64.3)	10 (27.7)
MDS with isolated 5q-	0 (0)	2 (5.5)
MDS-RS-SLD	2 (14.3)	4 (11.1)
MDS-RS-MLD	0	10 (27.7)
MDS-EB-1	0	1 (2.7)
MDS/MPN	0	2 (5.5)
IDUS/IDUS	2 (14.3)	0
Laboratory values, median (range)		
Hb, g/dl	10.5 (8.9-14.8)	9.8 (7.6-13.5)
ANC x10^9/l	2.1 (0.3-6.4)	2.2 (0.3-5.8)
PLTx10^9/l	149 (32-320)	162 (25-564)
Endogenous EPO u/l	80 (8.2-229)	79 (15.5-566)
LDH, UI/l	225 (178-287)	294 (118-323) *
creatinine, mg/dl	0.8 (0.5-1.3)	0.9 (0.5-1.55)
Bone marrow evaluation		
Median cellularity, %(range)	40 (20-70)	40 (20-90)
hypocellular, N(%)	4 (28.5)	1 (2.7)
hypercellular, N(%)	3 (21.4)	8 (22.2)**
normocellular, N(%)	7 (50)	26 (72.2)**
Reticulin fibrosis, N(%)	4 (28.5)	2 (5.5)
Risk scores		
IPSS, N(%)		
low	12 (85.7)	25 (69.4)
int-1	2 (14.3)	11 (30.5)
IPSS-R, N(%)		
very low	10 (71.4)	17 (56.6)
low	4 (28.6)	16 (40)
int	0	2 (3.3)
high	0	1 (2.7)
Treatment		
Treated, N(%)	6 (42.8)	27 (75)
Transfusions, N(%)	5 (35.7)	18 (50)
Erythropoietin, N(%)	6 (42.8)	27 (50)
Response, N (%)	3 (50%)	19 (70.3)
Time to response, months	5.3 (2.3-9.4)	5.9 (1.4-11.21)

*p=0.03, **p=0.01

Summary/Conclusion: Somatic mutations involving myeloid genes were frequent in patients with LR-MDS and mainly correlated with older age and deeper cytopenias. The latter worsened along with the increase of mutations number. Considering mutation types, expectedly, those involving splicing pathway correlated with a more proliferative phenotype. Interestingly, somatic mutations did not negatively impact on response to recombinant erythropoietin

PB1624 MAGROLIMAB + AZACITIDINE VERSUS AZACITIDINE + PLACEBO IN UNTREATED, HIGHER-RISK (HR) MYELODYSPLASTIC SYNDROME: THE PHASE 3, RANDOMIZED, ENHANCE STUDY

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Background: Myelodysplastic syndrome (MDS) is a clonal myeloid disorder characterized by cytopenia and ineffective hematopoiesis. The median age of diagnosis is approximately 70 years of age, and prognosis and treatment are guided by the Revised International Prognostic Scoring System (IPSS-R) criteria. Patients with intermediate, high, and very high risk MDS have a median overall survival (OS) of 0.8 to 3.7 years. Despite the high unmet need in this patient population, azacitidine (AZA) is the only approved therapy for HR-MDS that has improved OS in clinical trials to date. However, these agents lead to low complete response (CR) rates (10-17%) with limited OS (<2 years), indicating a need for alternative therapy. Magrolimab (Magro) is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint CD47, a "do not eat me" signal overexpressed on tumor cells. Binding of Magro to CD47 leads to phagocytosis of tumor cells. AZA increases expression of prophagocytic "eat me" signals, facilitating synergy with Magro. In an ongoing phase 1b study, the combination of Magro+AZA led to high response rates (objective response rate 91%, with a CR of 42%) and an acceptable safety profile without significant immune-related adverse events.
Aims: ENHANCE (NCT04313881) is a phase 3 trial to compare the efficacy and safety of Magro+AZA with that of AZA+placebo (PBO) in previously untreated patients with HR-MDS.
Methods: Patients ≥18 years old with previously untreated intermediate to very high risk-MDS by IPSS-R are eligible for ENHANCE. Randomization is 1:1 to Magro+AZA or AZA+PBO with no crossover allowed. Magro or PBO is administered intravenously (IV) with an initial 1 mg/kg priming dose to mitigate on-target anemia. An intrapatient dose-escalation regimen up to 30 mg/kg is then administered through Cycle 1, 30 mg/kg weekly dosing in Cycle 2, with 30 mg/kg dosing every 2 weeks in Cycle 3 and beyond. AZA is administered per regional prescribing information. Patients may remain on treatment until disease progression, relapse, loss of clinical benefit, or until unacceptable toxicities occur. Two primary efficacy endpoints are CR rate and OS. For patients undergoing allogeneic stem cell transplantation (ASCT), data for the CR rate will be censored at the time of ASCT and OS will be censored at the last known alive date. Secondary efficacy endpoints include red blood cell transfusion independence rate, event-free survival, minimal residual disease-negative rate, time to acute myeloid leukemia transformation, and patient-reported Functional Assessment of Cancer Therapy (FACT)–Anemia response rate. Biomarkers of immune cell recruitment, immune cell signaling, and bone marrow penetration of Magro will also be explored. Planned enrollment is approximately 520 patients globally, which began in September 2020.
Results: Trial in progress.
Summary/Conclusion: Accrual is ongoing.

PB1625 TREATMENTS AND OUTCOMES FOR PATIENTS WITH MYELODYSPLASTIC SYNDROME (MDS) BY REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) SCORES AT THE HUNTSMAN CANCER INSTITUTE

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Background: IPSS-R is used to classify risk of disease progression & guide treatment decisions for patients with MDS. Recent data shows mutational profiling may improve the prognostic stratification of MDS. Minimal real-world evidence exists for this population.
Aims: Primary objectives were to assess treatment patterns & clinical outcomes in patients with MDS by IPSS-R risk scores.
Methods: A retrospective cohort study assessed real-world, patient-level data from adults diagnosed with MDS between 2010-2019 at the Huntsman Cancer Institute (HCI), a NCCN, NCI-designated Comprehensive Cancer Center. All data were obtained via chart review from electronic medical records. IPSS-R scores were manually calculated from lab & cytogenetic data derived within 30 days of diagnosis. Patients with an intermediate to very-high IPSS-R score comprised the higher risk (HR) cohort; those with low or very low-risk IPSS-R comprised the lower risk (LR) cohort.
Results: Of the 259 MDS patients at HCI, 90 had an available IPSS-R score at diagnosis (ANC results were missing for 64% of cohort). After excluding clinical trial participants, 65 patients were included. Distribution of IPSS-R scores was: 15% (n=10) very low, 28% (n=18) low, 22% (n=14) intermediate, 23% (n=15) high, & 12% (n=8) very high. The average age of subjects was 68 years. 52% (n=34) of patients were female, 91% (n=59) were white, 8% (n=5) had autoimmune disorders, & 5% (n=3) had cerebrovascular disease. Twelve percent of NGS-tested patients had *TP53* alterations (n=7), while the most frequently altered gene for both cohorts was *DNMT3A* (19%, n=11). In the HR cohort, HMAs were used to treat 62% (n=23) of patients (median 2 cycles), while 27% (n=10) received no MDS-directed therapy, & 11% (n=4) received other MDS-related medications. In the LR cohort HMAs were used to treat 54% (n=15) (median 5.5 cycles), 39% (n=11) received no MDS-related medications, & 7% (n=2) received lenalidomide. Second-line treatment was received by 8% (n=5) of patients across both cohorts. Stem-cell transplant (SCT) was received more frequently (n=13, 35%) & sooner (median 4.8 months from diagnosis) by HR patients compared to LR patients (18%, n=5; median 15.0 months from diagnosis). Complete or partial response was achieved by 17% (n=4) of HR patients treated with a HMA versus 7% (n=1) of LR patients treated with a HMA. Transfusion independence was achieved by 60% (n=3) & 100% (n=4) of HR & LR HMA-treated patients that received PLT or pRBC prior to treatment initiation, respectively. Disease progression or death occurred in 82% (n=53) of patients during the study period with a median progression free survival (PFS) of 8.3 months & 25.3 months for HR & LR patients, respectively. PFS was significantly shorter for patients with *TP53* alterations compared to wild-type (HR: 3.07, 95% CI: 1.13-8.28), while controlling for IPSS-R using multivariable cox regression. Median overall survival was 18.8 & 31.0 months for HR & LR patients, respectively.
Summary/Conclusion: These results show that patients with MDS have a low likelihood of achieving & maintaining complete remission. In addition, few patients receive second-line therapy, revealing a large unmet need. Real world data are further limited by the reduction of patients with calculable IPSS-R scores at diagnosis. Specific genetic profiles may indicate the need for more aggressive treatments & management of relevant comorbidities. Updated results will be presented, including economic outcomes.

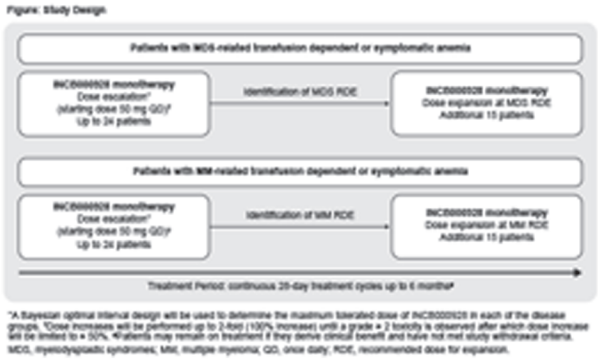
PB1626 A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY OF INCB000928 MONOTHERAPY IN PATIENTS WITH ANEMIA DUE TO MYELODYSPLASTIC SYNDROMES OR MULTIPLE MYELOMA

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Background: Disease-related anemia presents a therapeutic challenge in patients (pts) with myelodysplastic syndromes (MDS) or multiple myeloma (MM). Regular red blood cell (RBC) transfusions in pts with MDS can lead to iron overload with potential clinical consequences, and one-third of pts with MM do not respond to erythropoietin-stimulating agents (ESAs). Activin receptor-like kinase-2 (ALK2) is an upstream regulator of hepcidin, the key regulatory hormone in iron homeostasis. Disrupted hepcidin homeostasis or elevated serum hepcidin levels can contribute to anemia in pts with MDS or MM. INCB000928, a selective ALK2 inhibitor, reduced hepcidin-induced anemia in preclinical models.
Aims: INCB 00928-105 (NCT04582539) is a phase 1/2, open-label, multicenter dose-escalation and dose-expansion study evaluating INCB000928 as monotherapy for pts with MDS- or MM-related anemia. The primary objective is to evaluate the safety and tolerability of INCB000928 monotherapy in pts with MDS or MM who present with

transfusion-dependent or symptomatic anemia. Secondary objectives are to determine efficacy and pharmacokinetics of INCB000928, and effects of INCB000928 treatment on iron homeostasis and erythropoiesis parameters in pts with MDS or MM.
Methods: Pts aged ≥18 years with histologically confirmed MDS (or chronic myelomonocytic leukemia or unclassifiable MDS/myeloproliferative neoplasm [MPN] overlap syndrome) or MM who present with transfusion-dependent (RBC transfusion ≥4 units during 28 days pretreatment, or ≥4 units during 8 weeks pretreatment with hemoglobin [Hgb] <8.5 g/dL) or symptomatic anemia (baseline Hgb <10 g/dL on 3 separate occasions ≥7 days apart) are eligible to enroll. Other key inclusion criteria are: ineligibility for or lack of response to standard anemia treatments including ESAs; failure of standard MM treatments including alkylating agents, glucocorticoids, immunomodulators, proteasome inhibitors, daratumumab; ECOG PS ≤1 (dose-escalation) or ≤2 (dose-expansion); and life expectancy >6 months. Key exclusion criteria are: presence of MDS with ring sideroblasts or with atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, or MDS/MPN overlap syndromes with ring sideroblasts and thrombocytosis; MDS requiring cytoreductive treatment other than hydroxyurea; MDS with bone marrow and peripheral blood myeloblast count ≥10%; platelet count <50 × 10^9/L; or prior allogeneic stem cell transplantation. Treatment with oral INCB000928 monotherapy will start at 50 mg once daily in 28-day cycles (Figure). Dose escalation will follow a Bayesian optimal-interval design, independently and in parallel in each group, to determine the maximum tolerated doses; recommended doses for expansion (RDE) for each group will be based on safety and PK/PD data. Dose increases will be performed up to 2-fold until a dose-limiting toxicity is observed; subsequent increases will be limited to ≤50% of the prior dose. It is expected that up to 24 pts will be treated in each dose-escalation, and an additional 15 pts at the RDE in each dose-expansion. Pts will receive treatment for up to 6 months and may continue if deriving clinical benefit and no progression occurs. Sites are opening in the United States, France, and Italy.
Results: Not applicable



Summary/Conclusion: Not applicable

PB1627 SWITCHING TO AN ALTERNATIVE RECOMBINANT ERYTHROPOIETIN AGENT MAY BE EFFECTIVE IN PATIENTS WITH MYELODYSPLASTIC SYNDROME

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Background: Low risk myelodysplastic syndromes (MDS) are a heterogeneous group of diseases that mainly present with anemia. The latter ranges from mild/asymptomatic to transfusion dependent and benefits from recombinant erythropoietin (rEPO) treatment in about 70% of cases. Several types of rEPO are available, and it is a matter of debate which one is the most effective and at what dose. Moreover, median duration of response is limited, and subsequent therapeutic options are scanty, so that most subjects would finally become transfusion dependent.
Aims: To evaluate the efficacy of an alternative rEPO product in patients with MDS refractory or relapsed after the first rEPO course.
Methods: MDS patients followed at two tertiary hematologic centers in Milan, Italy, subsequently treated with two different rEPO products have been included. Hematologic parameters, including endogenous EPO (eEPO) and transfusion dependence have been analysed before each rEPO course and response rates have been evaluated according to the International Working Group 2006 criteria.
Results: A total of 25 patients (14 males/15 females), with a median age of 74 years (59-85), followed for a median of 51 months (12-225) have been included. The majority suffered from MDS with ring sideroblasts (N=13) followed by MDS with multi-lineage dysplasia (N=7), single lineage dysplasia (N=2), 5q deletion (N=2), and excess of blasts type 1 (N=1); 15 cases had a low and 11 an intermediate-1 IPSS score. Bone marrow was hyper/normocellular in all cases but one, 10 patients showed reticulin fibrosis (MF-0), and 4 subjects harboured a cytogenetic aberration (including 5q and 11q23 deletions, and trisomy 8). Table 1 shows rEPO agents used and the relative doses/responses. Considering the first course, median eEPO pre-dose was 59 U/L (3-257) and 12 patients were transfusion dependent with a median need of 4 units/8 weeks (2-7). The first product utilized was mainly epoetin alpha (N=16, biosimilar in 9), followed by epoetin zeta (N=4), beta (N=3), and darbepoietin (N=2), with a median initial dose of 40,000 U/week, resulting in an overall response rate of 60% after 2.4 months (0.8-18). Median treatment duration was 20 months (2.4-81) with the first product, and patients were switched to an alternative compound due to loss of response (N=15), inefficacy (N=8), and toxicity (N=2). All had been increased to the maximal dose before switching. At the beginning of the second rEPO course 14 patients were transfusion dependant, and pre-dose eEPO was 142 U/L (43-390). Most patients started the alternative rEPO at high dose (80,000 U/w) and mainly shifted from alpha biosimilar to epoetin alpha (N=9) or vice versa (N=2), from alpha to zeta (N=4) or vice versa (N=4), from beta to alpha (N=3) or vice vera (N=1), and from darbepoietin to alpha (N=2). 44% of patients responded after a median of 1.9 months (0.7-5.2) from the switch, including 3 cases refractory to the first rEPO. Interestingly, 10/11 responders had been switched to epoetin alpha (p=0.03), 1 to the biosimilar, and only 27% were transfusion dependent before the switch (versus 78% in non-responders p=0.01). At the last follow up, 3 patients were still on rEPO, whilst 8 stopped it due to loss of response (N=6) or intolerance (N=2) after a median of 15.8 months (11.6-17.5).

Patient	First EPO type	Dose/week	Response	Second EPO type	Dose/week	Response
1	Darbepoietin alpha	40,000	0	Epoetin alpha	40,000	1
2	Darbepoietin alpha	500	1	Epoetin alpha	40,000	1
3	Epoetin alpha	80,000	0	Epoetin zeta	80,000	0
4	Epoetin alpha	40,000	1	Epoetin zeta	40,000	0
5	Epoetin alpha	40,000	0	Epoetin zeta	40,000	0
6	Epoetin alpha	40,000	0	Epoetin zeta	40,000	
7	Epoetin alpha	40,000	0	Epoetin alpha biosimilar	80,000	0
8	Epoetin alpha	3,000	0	Epoetin beta	80,000	0
9	Epoetin alpha	80,000	0	Epoetin alpha biosimilar	80,000	0
10	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	0
11	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	1
12	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	1
13	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	1
14	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	0
15	Epoetin alpha biosimilar	40,000	0	Epoetin alpha	80,000	0
16	Epoetin alpha biosimilar	40,000	1	Epoetin alpha	80,000	0
17	Epoetin alpha biosimilar	80,000	0	Epoetin alpha	80,000	0
18	Epoteina alpha biosimilar	40,000	1	Epoetin alpha	80,000	0
19	Epoetin beta	30,000	1	Epoetin alpha biosimilar	80,000	1
20	Epoetin beta	30,000	1	Epoetin alpha	80,000	0
21	Epoetin beta	30,000	1	Epoetin alpha	80,000	1
22	Epoetin zeta	40,000	1	Epoetin alpha	80,000	1
23	Epoetin zeta	40,000	0	Epoetin alpha	80,000	1
24	Epoetin zeta	40,000	1	Epoetin alpha	80,000	1
25	Epoetin zeta	40,000	1	Epoetin alpha	40,000	1

Summary/Conclusion: Switching to an alternative rEPO was effective in 44% of cases, particularly in transfusion independent patients shifted to epoetin alpha. These results may suggest a try of an alternative rEPO product in both primary refractory MDS patients and in those relapsing after a first agent.

PB1628 A CLINICAL STUDY ON MYELODYSPLASTIC SYNDROMES

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Background: Myelodysplastic Syndromes (MDS) compound a heterogeneous group of malignant hematological diseases presenting an

ineffective hematopoiesis and a tendency of evolution to acute myeloblastic leukemia. The natural course of MDS is very different among the subgroups emphasizing the importance of the correct stratification / subclassification of those patients to better diagnose and treat them.
Aims: To study the incidence of Myelodysplastic Syndromes (MDS), risk factors, concomitant diseases, genetic abnormalities at the moment of the diagnosis.Our study aims to evaluate the median survival and the overall survival of MDS patients, the evolution in the acute myeloblastic leukemia of MDS patients and to evaluate the effect of different etiological factors on it.
Methods: Our study is a case-control study of 294 patients diagnosed with MDS from January 1999 to 2013 and followed up until 5 years after the moment of the diagnosis. Data were analyzed with IBM SPSS Statistics version 24, MedCal Software BVBA and Wizard Pro statistical software. In all the tests $p < 0,05$ was considered statistically important.
Results: Median incidence of MDS during the interval of time from 1999 to 2013 in the Albanian population resulted in 0,65 /100,000 inhabitants, 19-20 new cases/year. The median age at the moment of the diagnosis resulted in 61.5 ±15.08years (17 to 88-years). 65% of the patients diagnosed with MDS were at the moment of the diagnosis ≧ 60 years, with a ratio F: M ~1:1.39. 92,5% of the patients were diagnosed with primary MDS and only 7,5% were secondary MDS. According to the FAB classification, 173 patients studied retrospectively during the interval of time from 1999 to 2008 resulted: 91(53%) AREB, 28(16,2%) RA, 24(about 14%) AREB-T, 10 (5,8%) RARS, and the same result for CMML, and 9(5,2%) t- MDS. Only one patient was diagnosed with MDS-U. During the prospective phase were diagnosed 121 pacients with MDS classified according to WHO 2008: 31(25,4%) RCMD, 29(23.8%) AREB-1, 20(16.4%)AREB-2, and 12(9,8%) t- MDS. Only two patients were diagnosed with isolated del 5q-, one patient was diagnosed with RARS and 3 (2,5%) RCMD-RS. RA were 13,9% of all the patients with MDS. OS resulted 4,6 years (95%CI 3.837 to5.441). The role of karyotype in OS (years) resulted in highly significative $P < 0.001$. All the MDS patients classified as higher risk (N=56/64) evolved in Acute Leukemia within 2,8 years, meanwhile, in the lower risk, MDS group resulted in 7,29 years. The presence of concomitant diseases at the moment of the diagnosis is an independent prognostic factor P =0,016 for the median survival (years) of MDS patients, but data shown no evidence of prediction in the evolution on acute myeloblastic leukemia of those patients(P=0.3346).
Summary/Conclusion: Myelodysplastic syndromes represent a heterogeneous group of malignant diseases characterized of an ineffective hematopoiesis and a tendency of evolution to acute myeloblastic leukemia. The incidence of MDS increases significantly with the age and is more frequent in males than females over 60 years old. The natural course of MDS is very different among the subgroups emphasizing the importance of the stratification and of the subclassification of those patients according to IPSS to better diagnose and treat the MDS patients.

PB1629 ALLOGENEIC STEM CELL TRANSPLANTATION IN 34 PATIENTS WITH MYELODYSPLASTIC SYNDROME

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Background: Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders of pluripotent stem cells, characterized by ineffective hematopoiesis, richmarrow dysplasia resulting in cytopenias. In addition, MDS frequently progresses to acute myeloid leukemia and is the most common preleukemic state in adults. Allogeneic hematopoietic stem cell transplantation (HSCT) currently is the only potentially curative therapy for MDS. It can be performed in patients (pts) aged less than 60 years from an HLA compatible or haplo-identical donor.
Aims: Long term series study
Methods: Between May 2001 to March 2019 (18 years period), thirty four pts with MDS underwent allogeneic HSCT (geno-identical: 31 pts, haplo-identical: 3 pts). The median age of the pts is 36 years (4 - 58), the Sex ratio is 1,42 (20M/14F). Median time from diagnosis to allogeneic HSCT was 11 months (2-81). The pre-transplant status of pts according to the WHO 2016 classification is (MDS with unilineage dysplasia: 4 including 2 with ring sideroblasts and 1 with isolated del 5q, MDS with multilineage dysplasia: 30 including 07 with excess blasts-1 and 09 with excess blasts -2). The treatments received before the transplant are: Ciclosporin: 07 pts, EPO: 07 pts, Danazol: 03 pts, Revlimid: 02 pts, Azacytidine: 01 pt, Aracytine: 01 pt, Rituximab: 01 pt and 33 pts were transfusion-dependent before the graft with an average of 32 RBC unit/pt (3 - 135). All the patients received myeloablative conditioning [classic MAC: 13 pts (Santos, TUTSHKA, Haplo); Flu-Bu4: 21 pts]. GVHD prophylaxis consisted on association of Cyclosporin and Methotrexate according to the Seattle protocol in 31 pts of which 10 pts received anti thymocyte globulin; Post-transplant Endoxan and Mycophenolate mofetil without Methotrexate for 3 pts. All pts received G-CSF alone mobilised peripheral blood stem cells, with a median CD34+ cell count: $7,62.10^6$ / kg (3.18-19.9). In addition to the CSP graft, one patient received a bone marrow graft.
Results: Neutropenia occured in all pts and the median duration of aplasia was14 (7-31) days. Median time to achieve neutrophils count > $0,5.10^9$/l: 14 days (11-25) and platelets > 20.10^9/l: 13 days (9-35). Thirty pts (88%) required red blood cells transfusion (8.7 unit/pt) and 31 pts (91%) needed platelet transfusions (6.6 units/pt). Three pts (8.8%) presented VOD, one of which was severe. Grade II-IV acute GVHD was observed in 08/26 pts (30.7%) and chronic GVHD in 11/20 pts (55%) of whom 5 with an extensive form. Relapse was observed in 2/26 pts (7.6%) within 4 and 20 months post transplant. At July 31, 2020, the median follow-up is 94.5 months (16-202), 16 pts (47%) are still alive (15 pts in complete remission and 1 pts in relapse on Azacytidine), 18 pts (53%) are died including 17 pts (50%) of TRM (early infection: 06, VOD: 01, thrombotic microangiopathy: 1, acute GVHD: 04, pneumopathy: 02, fulminant hepatitis: 01, metabolic disorders: 02) and 1 pt of relapse. The overall survival (OS) is 47%, relapse-free survival (EFS) 44%, and GVHD-free and relapse-free survival (GRFS) 32%.
Summary/Conclusion: Allogeneic HSCT, in our study, was a curative option in 44% of patients with MDS with 16 years of follow-up. Thirty-two% are alive with a good quality of life.

Myeloma and other monoclonal gammopathies - Biology & Translational Research

PB1630 UNRAVELLING RESISTANCE MECHANISMS TO PROTEASOME INHIBITORS IN MULTIPLE MYELOMA

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Background: The development of proteasome inhibitors (PI) – Bortezomib (BTZ), Carfilzomib (CFZ), Ixazomib (IXA) - for the treatment of multiple myeloma (MM) has dramatically increased treatment responses and improved patient outcomes. However, the acquisition of resistance is a major limitation in PI therapy. Many mechanisms have been proposed for PI resistance, including genetic mutations in proteasome subunits, alterations in drug efflux transporters and antioxidant response pathways, among others.
Aims: In this study, we investigate the molecular mechanisms of PI resistance and the existence of cross-resistance between the three PI. Additionally, we explore potential strategies to overcome PI resistance.
Methods: Three PI-resistant MM cell lines were established by chronic exposure of PI-sensitive cells (NCI-H929) to non-lethal doses of BTZ (H929-BTZ cells), CFZ (H929-CFZ cells) and IXA (H929-IXA cells). The validation of the PI resistant models, the evaluation of the potential cross-resistance between PIs and the efficacy of the immunomodulatory drugs (IMiDs), lenalidomide (LEN) and pomalidomide (POM), were assessed using the fluorometric microculture cytotoxicity assay (FMCA). Expression and activity of ATP Binding Cassette (ABC) family efflux transporters (P-glycoprotein; multidrug resistance protein 1 (MRP1) and MRP2; breast cancer resistance protein (BCRP)) were analysed by flow cytometry. Gene expression analysis (Nuclear Factor, Erythroid 2 Like 2 (NFE2L2; Kelch Like ECH Associated Protein 1 (KEAP1), Nuclear Factor Kappa B Subunit 1 (NFKB1); ABC Subfamily B Member 1 (ABCB1); ABC Subfamily G Member 2 (ABCG2); ABC Subfamily

C Member 1 (ABCC1) and ABCC2) was performed by qPCR assay. A p-value of 0,05 was used as cut-off for significance.
Results: The confirmation of the resistance of the three PI-resistant MM cell lines was shown by the increase of the half maximal inhibitory concentration (IC50) by 4.7 folds (H929-BTZ IC50 2.8nM), 6.7 folds (H929-CFZ IC50 2.0nM) and 10.5 folds (H929-IXA IC50 20nM) compared to the IC50 value of sensitive cells (IC50 BTZ 0.6nM, IC50 CFZ 0.3nM and IC50 IXA 1.9Nm, respectively). BTZ-resistant cells displayed cross-resistance to CFZ; however, cells resistant to these two PI did not display cross-resistance to IXA (H929-BTZ IC50 IXA 0.5nM; H929-CFZ IC50 IXA 1.9nM). H929-CFZ showed an increased expression of *ABCB1* and *ABCG2* genes. There were not statistically significant differences in the expression levels of the other evaluated genes (*NFE2L2, KEAP1, NFKB1, ABCC1, ABCC2*) in PI-resistant cell lines compared to PI-sensitive cell lines. Expression levels of protein efflux transporters were also similar between all cell lines; however, the activity of MRP1/2 in all PI-resistant cell lines was significantly higher than in sensitive cells. The association of IMiDs with PI was effective to overcome PI resistance.
Summary/Conclusion: Our results suggest that PI resistance may be mediated by an increased activity of MRP1/2. The absence of cross-resistance between IXA and the other two PI suggest that IXA can be effective even in the presence of resistance to BTZ and/or to CFZ. The association of IMiDs with PI appears effective in overcoming PI resistance. Additional studies are required for a better understanding of the mechanisms of PI-resistance in MM, in order to improve novel therapeutic strategies for refractory and relapsed patients.

PB1631 EFFECTS OF DARATUMUMAB(DARA), CYCLOPHOSPHAMIDE (C), THALIDOMIDE (T) AND DEXAMETHASONE (D) COMBINATION ON LYMPHOCYTE POPULATIONS OF TRANSPLANT ELIGIBLE NEWLY DIAGNOSE MULTIPLE MYELOMA PATIENTS

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Background: The CTD combination have both an immunomodulatory and immunosuppressive activity on multiple myeloma (MM) patients (pts) treatment. The advance of immunotherapy has been demonstrated by the development of new agents like anti CD38-antibody Dara, that are increasing the overall and progression-free survival of MM pts. Dara effect on the immune system was already described, but few studies analyzed specifically lymphocytes population. We hypothesized that Dara-CTD combination could impact on lymphocytes subsets during treatment.
Aims: The primary endpoint was to quantify subpopulations of lymphocytes in pts with newly diagnosed multiple myeloma (NDMM) transplant eligible (TE) pts, during Dara-CTD treatment phases (induction, consolidation and maintenance). Secondary endpoint was to describe B cells subsets during the same phases
Methods: Peripheral blood of 14 pts at four different time points was collected: at diagnose, after four cycles of Dara-CTD, after two consolidation cycles post-autologous stem cell transplantation (ASCT) and before maintenance therapy. Flow cytometry was used to detect lymphocyte surface molecules including CD3, CD4, CD5, CD8, CD16, CD19, CD20, CD38, CD45 and CD56 in the scatter plot. B cells were isolated and subpopulations (naïve B cells, non-class switched memory B cells, class switched memory B cells, IgD-CD27- memory B cells and plasmablasts) were detected by CD20, CD24, CD27, CD38, CD45 and IgD. Statistics was performed using the SPSS® v25.0
Results: The pts median age was 55 range (41-65) years old, and 57% were female. The median of T, B and NK lymphocytes subsets at diagnosis were 1153 x 10^3/µL, 205x 10^3/µL and 284 x 10^3/µL cells, respectively. After four cycles of Dara-CTD the median of T, B and NK cells dropped significantly to 889 x 10^3/µL, 12 x 10^3/µL and 11 x 10^3/µL, respectively ($p \leq 0.05$). The number of the cells after two consolidation cycles post-ASCT, showed T cells full recovery (1087 x 10^3/µL) while B and NK cells had weakly reconstitution (15 x 10^3/µL and 34 x 10^3/µL, respectively). Before maintenance therapy, the median of T, B and NK cells were 1456 x 10^3/µL, 24 x 10^3/µL and 33 x 10^3/µL, respectively. Regarding B cell population, the median of naïve B cell decreased after 4 induction cycles from 32 x 10^3/µL to 1 x 10^3/µL. Then, after two consolidation cycles post-ASCT the number of B cell increased to 14 x 10^3/µL and to 18 x 10^3/µL before maintenance
Summary/Conclusion: Lymphopenia have been shown with different protocols using Dara as single agent or in combination. The present study confirmed that there is a decrease in the number of different lymphocytes populations (T, B and NK) after induction therapy with Dara-CTD. The T cells number recovery after two consolidation cycles post-ASCT, but B and NK cells remain low after the same period. There was a slowly but continuously recovering of B and NK cells, suggesting that Dara-CTD combination allows lymphocytes reconstitution. Analyzing the B cells subpopulations, the naive B cell was the first to show a more significant recovery, although it was below the reference range (33 – 259). In conclusion, this is the first study that report the lymphocyte profile during Dara-CTD treatment. This preliminary data suggest that Dara-CTD induces general lymphopenia on (T, B and NK) populations after induction phase. It was identified that T cells recovery was complete after two consolidations cycles while the recovery of B and NK cells was slowly but continuously.

PB1633 ROLE OF PROTEIN KINASE CK1 ALPHA AND LENALIDOMIDE IN THE INTERACTIONS BETWEEN MULTIPLE MYELOMA PLASMA CELLS AND BONE MARROW STROMAL CELLS: THERAPEUTIC IMPLICATIONS

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Background: Multiple myeloma (MM) plasma cells (PC) growth and the associated bone disease is tightly dependent on bone marrow (BM) microenvironment. Survival pathways, such as NF-κB, Hedgehog and Wnt/β-catenin, support the MM clone and bone homeostasis imbalance. The Wnt/β-catenin pathway is pivotal for bone formation since it stimulates *RUNX2* expression, the master gene regulator of osteoblastogenesis. It has been shown that MM PC cells inhibit RUNX2 activity in mesenchymal stromal cells (MSC). Moreover, RUNX2 overexpression in MM cells is also associated to osteoblastogenesis inhibition. Protein kinase CK1α supports MM PC growth and it is a known target of Lenalidomide (Lena). Our preliminary data show that CK1α gene silencing in MSC sustains *RUNX2* gene expression, favoring the osteogenic program.
It is known that Lena works through a novel drug mechanism, modulating Cereblon E3 ubiquitin ligase. It induces the ubiquitination and the subsequent proteasomal degradation of Ikaros, Aiolos and CK1α leading to MM cells death. The effects of the Lena-CK1a axis on the MSC osteogenic potential and the MM BM-dependent growth are unknown.
Aims: To investigate the effects of Lena-induced CK1α degradation in MSC on: 1) cell survival. 2) the MSC osteoblastic phenotype, including *RUNX2* and *ALP* expression.
To study the impact of Lena in a MSC-MM PC crosstalk BM microenvironment culture model on: 1) MM PC growth/survival 2) the MM PC-induced anti-osteogenic phenotype.
Methods: Cell lines and cultures: the IL-6 dependent INA-6 MM cell line and the MSC-hTERT stromal cell line have been used. A BM microenvironment model was obtained by plating INA-6 on a layer of MSC-hTERT cells. MM cells and MSC pure populations were obtained by cell sorting since MSC express GFP. Primary BM stromal cells were isolated from MM and MGUS sample patients. All the experiments were performed adding Lena to the culture medium. The rate of apoptosis was detected through Annexin V and Propidium Iodide staining. qRT-PCR and WB analysis were used to analyze mRNA and protein level expression of CK1α, RUNX2 and other osteogenic markers.
Results: Lena treatment did not change MSC viability, while it induced MM cells apoptosis. CK1α protein level was reduced after Lena treatment, not only in MM cells, but also in MSC cultured alone or with PC. Surprisingly, despite CK1α degradation, both *RUNX2* and *ALP* mRNA expression was reduced in MSC-hTERT and preliminarly in primary MSC, suggesting a negative effect of Lena on osteogenic differentiation. In the MM-BM stromal cells co-culture model, we found reduced RUNX2 expression levels both in MM cells and in MSC

Summary/Conclusion: Lena induced CK1α reduction does not seem to be sufficient to recover the MSC osteogenic program, while it is sufficient to reduce RUNX2 expression in MM cells, inducing cell death. Further studies will be necessary to investigate if combining CK1α silencing/chemical inhibition to Lena, in the co-culture model system, could be promising not only to cause PC death, but also to rescue the MSC osteoblastic phenotype.

PB1634 THE FIRST MYELOMA PATIENT DERIVED XENOGRAFT FROM TREATMENT REFRACTORY HUMAN MYELOMA CELLS IN SWEDEN AND THE EFFECT OF BROMODOMAIN-INHIBITORS ON MYELOMA CELLS IN VIVO

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Background: Multiple myeloma is a plasma cell malignancy and the second most common haematological cancer in Sweden. *In vivo* studies of myeloma in mice are usually done by injecting commercial cell lines intravenously. If we could successfully transplant treatment refractory human myeloma cells intratibially it would be a substantial benefit to test novel treatments and predict clinical outcome in patients. The bromodomain inhibitors (BETi), which inhibit reading of epigenetic modifications and block transcriptional activity, have sparked a lot of interest and showed promising results in animal studies of myeloma. An in-house compound under development called BETi-1 has shown promising results *in vitro* on commercial cell lines exhibiting at minimum equal potency as the widely-used compound JQ1 (data not yet published).
Aims: The primary objective of this project was to investigate whether it is possible to develop a patient derived xenograft (PDX) from human bone marrow aspirates of treatment refractory multiple myeloma. Secondary objectives were to examine if BETi affect the viability of myeloma cells *in vivo*.
Methods: In this translational study, biobank material consisting of cryopreserved bone marrow samples acquired from patients receiving treatments at Sahlgrenska University Hospital between 2017 and 2020 with relapsed/refractory multiple myeloma (RRMM), were thawed and transplanted intratibially on immunodeficient mice (NOD-SCID-IL2 receptor gamma knockout, NOG/NSG) to develop a patient-derived xenograft (PDX). Tumour progression was monitored with lambda- and kappa ELISA every other week. When progression was confirmed, the mice received either vehicle or treatment with BETi-1. At sacrifice, long bones and sternum were analysed with immunohistochemistry and FACS to verify presence of clonal plasma cells. All experiments were approved by the regional Ethical Committees in Gothenburg.
Results: We show a successfully established and serially transplanted myeloma PDX from human treatment refractory myeloma cells verified by two independent methods exhibiting clonal plasma cells with the ability to disseminate in NOG/NSG mice. *In vivo* experiment with BETi-1 treatment is still ongoing and will be presented in due time

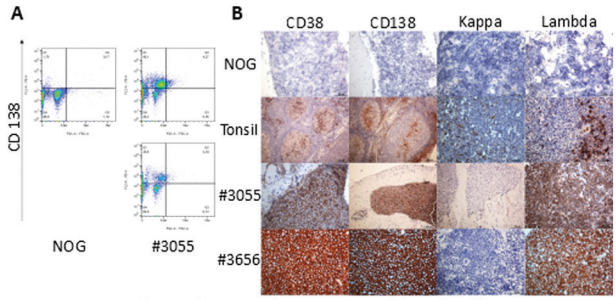


Figure 1. FACS-analysis with CD138 of negative control (NOG) and bone marrow extracted from the injection site of #3055 (lower) and contralateral tibia (upper) upon sacrifice (A). Staining for CD38, CD138, Kappa and Lambda on NOG (negative control), Tonsil (positive control), #3055 (mouse with hindleg paralysis) and #3656 (transplanted with cells from #3055) identifies human tumour cells in #3055 and #3656, thus confirm a successful serially transplanted patient -derived xenograft (B). Cells not stained are blue and cells with positive staining are brown.

Summary/Conclusion: In this translational study we have established a multiple myeloma PDX model from human treatment refractory myeloma cells and thus developed a platform for examining new treatment options in multiple myeloma.

PB1635 CYTOKINE GENE POLYMORPHISMS AND AUTOLOGICAL TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS IN PATIENTS WITH MULTIPLE MYELOMA

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Background: Important role of certain cytokines in the regulation of hematopoiesis and immune response in multiple myeloma (MM) patients has been established. The lack of improvement in the quality of response after autologous hematopoietic stem cell transplantation (auto-HSCT), which is observed in some patients, may lead to decrease in the effectiveness of treatment. There is a little data on the significance of immune genes variations in predicting the effect of auto-HSCT in patients with MM.
Aims: To assess effect of several immune system genes (IL-6, TNF-A, IL-1B, IL-10) polymorphisms in patients with MM during auto-HSCT.
Methods: We included 28 MM patients (15 men and 13 women, mean age 53.7 ± 6.8 years) who underwent auto-HSCT in the study. Improvement in the quality of response after the first auto-HSCT was observed in 16 (57.1%) patients, whereas other 12 (42.9%) patients did not achieve such improvement. Genotyping for the IL-6 -174G/C, TNF-A -308G/A, IL-1B -31T/C, IL-10 -592C/A polymorphisms was performed by PCR-RFLP. Odds ratios (OR) and p-values were determined by Fisher's exact test to characterize intergroup differences in distributions of genotypes and their combinations.
Results: Genotype frequencies for the TNF-A, IL-1B and IL-10 polymorphisms were not significantly different between the groups of patients with or without improvement in the quality of response after the first auto-HSCT. However, the frequency of homozygotes for the rare -592A allele of the IL-10 gene was almost 3 times higher in patients with improved quality of response than in those without improvement (20.0% vs 8.3%, respectively; p=0.12; OR=3.3). The frequency of the IL-1B -31TT genotype was also increased in patients with effective auto-HSCT when compared to "no improvement" group (37.5% vs 16.7%, respectively; p=0.4; OR=3.0). Finally, proportion of the IL-6 -174C allele carriers among patients with improved response was almost 2-fold higher (81.3% vs 41.6% in the group with no improvement in the quality of response; p=0.05; OR=6.1).
Summary/Conclusion: In this study, we observed possible association between the IL-6 -174G/C gene polymorphism and effectiveness of the first auto-HSCT in patients with MM. Further studies are needed to clarify the significance of immune genes variations in predicting the effect of auto-HSCT in patients with MM.

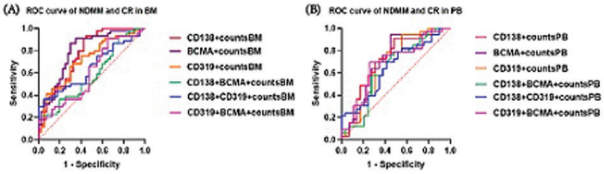
PB1636 THE POTENTIAL DIAGNOSTIC ROLE OF CD138+/BCMA+/CD319+ MICROPARTICLES FROM THE PLASMA CELL IN MULTIPLE MYELOMA CLINICAL MONITORING BY FLOW CYTOMETRY

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Background: Multiple myeloma (MM) is malignant tumor with abnormal proliferation of bone marrow plasma cells. The existing clinical tools used to determine treatment response and minimal residual disease (MRD) are affected by focal distribution of myeloma cell in bone marrow and the quantity of sample. In our previous study, we demonstrated that the counts of $CD138^+$microparticles (MPs) in BM showed to be a potential marker to monitor the load of MM. On this basis, we further investigated the feasibility of $BCMA^+$MPs and $CD319^+$MPs to monitor MM load.
Aims: 1.The number of MPs produced by a single myeloma cell.
2.If $CD138^+$/$BCMA^+$/$CD319^+$MPs can monitor the load of multiple myeloma.

Methods: Peripheral blood and bone marrow of MM patients and healthy donors were collected. Microparticles were isolated by differential centrifugation, and MPs were immunolabeled and detected by flow cytometry (Cyto-FLEX). Mann-Whitney (U) test was conducted for the nonparametric data. New diagnosed MM (NDMM) patients and CR patients were compared, and ROC curves were used to identify cutoff points with optimal sensitivity and specificity concerning the counts of MPs in BM and PB.



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Summary/Conclusion: Our research showed that similar to CD138, the counts of BCMA$^+$MPs and CD319$^+$MPs was also a powerful marker for monitoring MM cell, and the accuracy of monitoring MM using BCMA$^+$MPs was higher than CD138; MM-MPs from the plasma provided support for a potential monitoring biomarker of MM.

PB1637 GLOBAL DNA METHYLATION AND PROMOTER GENE METHYLATION IN MGUS AND DIFFERENT STAGES OF MULTIPLE MYELOMA

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Background: Multiple myeloma is biologically heterogenic disease with wide spectrum of genetic and epigenetic changes. Global hypomethylation and gene-specific promoter hypermethylation are supposed to be included in mechanism in myelomagenesis.
Aims: The study is focused on global DNA methylation assessment and its relationship to methylation level of promoter and 1. exon sequences of *PDLIM4* and *CDKN2B* genes.
Methods: The set of 94 un-sorted samples of bone marrow aspirate from patients with MGUS and multiple myeloma (MM) in different disease stages (smoldering myeloma, MM diagnosis, MM remission, MM relapse), were examined in our study. An informed consent from all patient was obtained. For determination of the global DNA methylation level, the Luminometric Methylation Analysis (LUMA) was newly implemented. Methylation analysis of particular gene sequences was performed by bisulfite pyrosequencing.
Results: While *CDKN2B* gene methylation level was generally low (median between 4 % and 5,5 % in first exon and between 1 % and 4 % in promotor), the increased promoter *PDLIM4* methylation was determined in newly diagnosed patients with multiple myeloma (median 19 %). The highest global DNA methylation level was detected in MGUS samples (76,5 %), and its gradual decreasing during myeloma progression was observed (medians: 73,1 % in smoldering myeloma, 72,5 % in MM diagnosis and 69,4% MM relapse). In the subgroup of myeloma remission patients, the level of global DNA methylation showed an upward trend (median 73,4 %).
Summary/Conclusion: The LUMA method proved to be an effective procedure and ease to perform. Our results of global DNA methylation assessment are in accordance with literature data relating to haemato-oncological malignancies. Further, the use of a bone marrow of the un-sorted cell population could be an advantage of the method procedure. Moreover, our data support an important role of the *PDLIM4* gene in the onset and progression of multiple myeloma disease. In contrast with some other studies, we did not confirm any methylation changes in CDKN2B gene analysed sequences, which indicates its unmethylated state.

PB1638 PROGNOSTIC ROLE OF MONOMERIC C-REACTIVE PROTEIN IN NEWLY DIAGNOSED MULTIPLE MYELOMA AS A MARKER OF THE BONE LOSS DEGREE

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Background: C-reactive protein (CRP) is the most used clinical indicator of inflammation, which under certain circumstances can dissociate into insoluble monomers (mCRP). A recent study identified that mCRP can increase the number of osteoclasts in the culture medium. It is known that osteolytic lesions are a hallmark of MM, causing severe bone pain and pathological fractures. The malignant plasma cells induce bone resorption by activating osteoclasts. On the other hand, a Renal impairment (RI) is others common in MM)], with up to 40% of the patients experiencing this complication. RI increases risk of early death and affects disease management in multiple ways, as it may complicate treatment options and dosing, and render pts more susceptible to infections and prolonged hospitalizations. In addition, in the case of RI, traditional prognostic markers such as albumin and beta2-microglobulin are less accurate in terms of disease prevalence and tumor volume.
Aims: The target was to study the importance of mCRP as a marker of bone resorption for this kind of patients.
Methods: Blood samples were collected from patients before starting chemotherapy. To distinguish between mCRP and pentameric CRP, we combined the FITC-labeled monoclonal antibody to pCRP (mAb to pCRP), clone 372 (ImTek, Moscow, Russia), and PE-labeled mAb to mCRP with cross-reactivity to pCRP (mAb to mCRP), clone 328 (ImTek, Moscow, Russia). We used a non-specific FITC-labeled mouse IgG as a negative control. In each test at least 10,000 events were registered. We prospectively evaluated 15 patients with newly diagnosed MM (median age at diagnosis 67 years, range 55-74 years, female-9/male-6). A feature of our population of patients was a severe renal failure with a median of CKD-EPI 6.3 [Q25 5.2; Q75 12.3] ml/min/1.73 m2.
Results: The degree of bone destruction was assessed using X-ray, based on which, the patients were divided into 2 groups. For patients with limited bone loss (corresponds to stages Durie-Salmon 1-2, Groupe I, n=6), the median of mCRP was 47.6 [35.3; 62.5] versus 112.6 [75.6; 183.2] ng/ml (p = 0.02) for advanced lytic bone lesions (DS stage 3, Groupe B, n=9). This is much more than healthy people who have an mCRP level of 1 ng/ml. Only the concentration of mCRP, but not CRP, Ca2+, albumin, β2-microglobulin or NT-proBNP, correlated with bone destruction (Table 1).

Table 1. Analysis of the predictive value of individual biological markers by matching groups

Parameters	CKD-EPI, ml/min/1.73 m2	NT-proBNP, pg/ml	hs-CRP, mg/l	mCRP, ng/ml	Ca2+, mmol/l	Albumin, g/l	β2-MG, mg/l
Groupe I (n=6)							
Median	7.7	2483	6.50	**47.6**	2.25	36.8	17.8
Range	3.0 – 14.9	1082 - 35000	2.26 – 26.2	**26.4 – 64.9**	2.02 – 2.82	29.5 – 39.7	12.0 – 19.0
Groupe II (n=9)							
Median	6.0	5500	15.9	**112.2**	2.51	36.3	19.0
Range	2.1 – 26.0	560 - 35000	1.95 – 134,0	**42.2 – 260.6**	1.90 – 3.49	27.5 – 45.3	10.6 – 19.7
F (χ2)	0.07	0.48	2.27	**4.48**	1.50	1.03	0.21
P value	0.79	0.83	0.16	**0.05**	0.25	0.33	0.66

Abbreviations: hs-CRP - high-sensitivity C-reactive protein; β2-MG – β2-microglobulin; mCRP – monomeric C-reactive protein; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; NT-proBNP – N-terminal pro-brain natriuretic peptide.

Summary/Conclusion: Thus, we concluded that there is a relationship between the degree of bone destruction and mCRP concentration. Hence mCRP plays an important role in the increase in the number of osteoclasts and increasing their activity, it can serve as a good marker of bone resorption.

PB1639 VALIDATION OF ALGORITHMS TO IDENTIFY FIRST-LINE THERAPY (INDUCTION AND MAINTENANCE) FOR MULTIPLE MYELOMA FOR USE IN ELECTRONIC HEALTHCARE DATABASES

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Background: Treatment for multiple myeloma (MM) is complex, involving several agents that may be used to induce and/or maintain response. While large electronic health databases (claims or electronic medical records [EMR]) represent sources of rich information on real-world use of these therapies and associated outcomes, they lack sufficient clinical detail needed to determine lines of therapy (LOTs) or treatment intent. Clinically robust and validated algorithms are required in order to use these data to identify LOTs—including when maintenance therapy (MT) is used and its constituent medication(s)—in MM.
Aims: To develop and assess performance of algorithms to identify LOTs among MM patients.
Methods: Algorithms for LOT identification were previously developed with hematologists/oncologists and in accordance with guidelines (Table). Validation of the algorithms was conducted using data from the Henry Ford Health System (HFHS). We identified adults with MM enrolled in the HFHS Health Alliance Plan (HAP) between January 1, 2006 and December 31, 2017. Patients whose HAP enrollment coincided with available medical chart data, and who had evidence of ≥1 "CRAB" (i.e., hypercalcemia, renal insufficiency, anemia, bone lesions) symptoms, were included. Starting from the date of the initial MM diagnosis, agents used to treat MM were identified in claims and EMR data. LOTs were then constituted based on the algorithms. First, individual agents were combined into small "mini-LOTs" using a series of defined rules (e.g., concomitant drugs) dependent on medications received. Next, mini-LOTs were combined into final LOTs based on additional rules that included: (1) receipt of ≥1 "new" agents of interest (not received in prior mini-LOT), including switches/augmentation; (2) days between mini-LOTs; (3) duration of prior mini-LOTs; and (4) whether the patient had undergone frontline stem-cell transplant (SCT). Attention was focused on the first LOT following diagnosis (LOT1). Use of MT within LOT1 was determined based on specific criteria, including duration and composition of mini-LOTs and SCT status. LOTs derived by these algorithms were then validated via review of all relevant clinical data in patients' medical records by two independent hematologists/oncologists, with discordant cases adjudicated by a third arbitrator. Sensitivity, specificity, positive predictive value (PPV), and accuracy were estimated.
Results: A total of 133 patients (89 non-SCT [nSCT]; 44 SCT) were identified. Mean (standard deviation) age was 67.5 (11.6) years, 53.4% were male, and 60.9% were African American; 24.8%, 57.1%, 84.2%, and 39.1% had hypercalcemia, renal insufficiency, anemia, and bone lesions, respectively. The 3 most commonly used LOT1 regimens (Table) collectively represented 74.4% of patients. Overall accuracy of algorithms to identify LOT1 was 85.0% (88.8% nSCT; 77.3% SCT). For MT, it was 85.7% (87.6% nSCT; 81.8% SCT). PPVs for the most commonly used regimens ranged between 90.9%>92.9% for nSCT patients and 70.6%>100.0% for SCT patients. See the Table for validation statistics by regimens.

Table. LOT Algorithm Performance, by SCT Status

	Regimen	nSCT Cohort, N=89					SCT Cohort, N=44				
		N Per Patient Chart	N Per Algorithm	Sens. (%)	Spec. (%)	PPV (%)	Acc. (%)	N Per Patient Chart	N Per Algorithm	Sens. (%)	Spec. (%)	PPV (%)	Acc. (%)
Overall LOT, N=133	V + steroids	42	44	95.2	91.5	90.9	93.3	12	8	66.7	100.0	100.0	90.9
	VR + steroids	36	34	83.3	98.9	92.9	95.5	12	17	100.0	64.4	70.6	88.6
	R + steroids	11	12	100.0	98.7	91.7	98.9	6	4	66.7	100.0	100.0	95.5
	V	2	2	0.0	97.7	0.0	95.5	0	0	—	—	—	—
	M* + steroids	4	4	100.0	100.0	100.0	100.0	0	0	—	—	—	—
	T + steroids	3	3	100.0	100.0	100.0	100.0	5	3	60.0	100.0	100.0	95.5
	VT + steroids	3	2	66.7	100.0	100.0	98.9	0	0	—	—	—	—
	Cyclo + steroids	1	1	100.0	100.0	100.0	100.0	3	3	100.0	100.0	100.0	100.0
	Dexamethasone	2	2	100.0	100.0	100.0	100.0	0	0	—	—	—	—
	VM* + steroids	1	2	100.0	98.9	50.0	98.9	0	0	—	—	—	—
	T	1	1	100.0	98.9	50.0	98.9	0	0	—	—	—	—
	M* + T + steroids	1	1	100.0	100.0	100.0	100.0	0	0	—	—	—	—
	KR + steroids	1	0	0.0	100.0	NA	98.9	0	0	—	—	—	—
	Cy + A + Vin + steroids	0	1	NA	98.9	0.0	98.9	0	0	—	—	—	—
	A + Vin + steroids	0	0	—	—	—	—	3	2	66.7	100.0	100.0	97.7
	Cyclo + R + steroids	0	0	—	—	—	—	3	2	66.7	100.0	100.0	97.7
	Cy + Vin + steroids	1	0	0.0	100.0	NA	98.9	0	0	—	—	—	—
	V + A + T + Vin + steroids	0	0	—	—	—	—	0	1	NA	97.7	0.0	97.7
	V + A + R + steroids	0	0	—	—	—	—	0	1	NA	97.7	0.0	97.7
	Int + T + steroids	0	0	—	—	—	—	0	1	NA	97.7	0.0	97.7
	V + E + Cy + A + R + Vin + steroids	0	0	—	—	—	—	0	1	NA	97.7	0.0	97.7
	RT + steroids	0	0	—	—	—	—	0	1	NA	97.7	0.0	97.7
		nSCT Cohort, N=89						SCT Cohort, N=44					
Maintenance, N=33	R	3	3	33.3	97.7	33.3	95.5	12	12	83.3	93.8	83.3	90.9
	Dexamethasone	3	2	66.7	100.0	100.0	98.9	0	3	NA	93.2	0.0	93.2
	V	2	0	0.0	100.0	NA	97.8	0	1	NA	97.7	0.0	97.7
	V + steroids	1	1	0.0	98.9	0.0	97.8	0	0	—	—	—	—
	T	1	1	0.0	98.9	0.0	97.8	0	0	—	—	—	—
	VR	1	0	0.0	100.0	NA	98.9	0	0	—	—	—	—
	R + steroids	0	1	NA	98.9	0.0	98.9	0	2	NA	95.5	0.0	95.5
	None identified	78	81	96.2	45.5	92.6	83.9	32	26	81.3	100.0	100.0	86.4

*Oral preparations only

Abbreviations: LOT = line of therapy; SCT = stem cell transplant; nSCT = non SCT; sens = sensitivity; spec = specificity; PPV = positive predictive value; acc = accuracy; V = bortezomib; R = lenalidomide; M = melphalan; T = thalidomide; Cyclo = cyclophosphamide + bortezomib; A = doxorubicin; Vin = vincristine; K = carfilzomib; Cy = cyclophosphamide; Int = interferon; NA = not applicable

NOTE: Sensitivity was estimated by dividing the number of true positives by the total number of patients who received the regimen (true positives + false negatives); specificity by dividing the number of true negatives by the total number of patients who did not receive the regimen (true negatives + false positives); PPV by dividing the number of true positives by the total number of patients who were allocated to the regimen by the algorithm (true positives + false positives); and accuracy by dividing the number of patients correctly allocated by the algorithm (true positives + true negatives) by the total number of patients to whom the algorithm was applied.

Algorithms for LOT identification were previously developed with hematologists/oncologists and in accordance with published guidelines and literature (References: 1. Rajkumar SV, *et al. Blood. 2015 May 5;125(20):3069-3*; 2.NCCN.org [Internet].2020. Available from: www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf ; 3. Rajkumar SV, *et al. Blood. 2015 Aug 13;126(7):922-2*.

Summary/Conclusion: Algorithms to identify LOT1 and use of MT therein performed well, with an overall accuracy of 85.0% among patients with newly diagnosed MM. The algorithms performed numerically better in nSCT patients than SCT patients, although the latter had relatively smaller sample size. Further study in other large electronic healthcare databases is warranted to determine the consistency with which these algorithms can accurately constitute LOTs for the treatment of MM.

PB1640 COMPARISON OF THE EXPRESSION PROFILE AND PROMOTER GENE METHYLATION OF SELECTED TUMOR-SUPPRESSOR GENES IN MYELOMA CELLS

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Background: Epigenetic regulations play an important role in the etiopathogenesis of multifactorial diseases such as multiple myeloma. DNA methylation is the most studied epigenetic modification and has an impact on gene expression and genome stability.
Aims: The gene expression profile was compared with DNA methylation level in selected promoter regions of two tumor suppressor genes.
Methods: 5 samples of bone marrow aspirates (after sorting of $CD138^+$ cells) were used for quantification of *RBP1* and *GPX3* genes expressions followed by pyrosequencing methylation analysis of the promoter gene sequence. These expression and methylation analysis of studied tumor suppressor genes were also performed in myeloma cell lines KMS12-BM and KMS12-PE after their treatment with demethylation agents, 5-aza-2´-deoxycytidine and 5-azacytidine.
Results: In $CD138^+$ sorted patient samples, strong negative correlation (r = -0,635) between *GPX3* gene expression and its promoter gene sequence methylation was determined, and the low negative correlation was detected in two from three analysed promoter sequences of *RBP1* gene (r = -0,304 for As11; r = -0,154 for As10; r = 0,207 for As12). In comparison to untreated cells, the re-expression and/or increased expression of *RBP1* and *GPX3* genes after their demethylation treatment of both KMS12-BM and KMS12-PE cell lines was found.
Summary/Conclusion: Negative correlation between gene expression and promoter gene methylation of both studied *GPX3* and *RBP1* genes indicates DNA methylation impact on expression of these tumor suppressors, which could play an important role in myelomagenesis.

Myeloma and other monoclonal gammopathies - Clinical

PB1641 EFFICACY AND SAFETY OF VENETOCLAX COMBINATIONS IN T(11;14) MULTIPLE MYELOMA: REAL WORLD DATA OF 50 PATIENTS COLLECTED FROM 7 HUNGARIAN CENTERS

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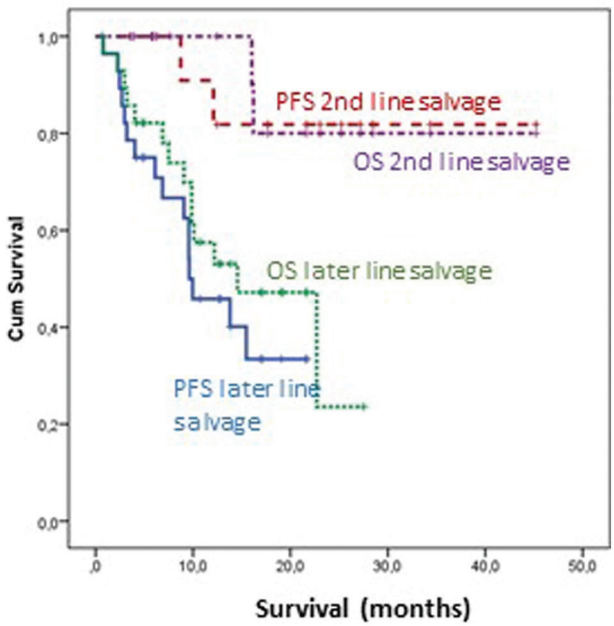
Background: Venetoclax, a selective bcl-2 inhibitor first approved for CLL has been investigated for the treatment of relapsed myeloma patients, and although it failed to show benefit for myeloma patients as a whole, t(11;14) patients demonstrated exceptional responses in the Bellini trial (Lancet Oncol 2020; 21:1630), thus paving the way towards the first genetically targeted treatment in myeloma.
Aims: Off label use of venetoclax is on the rise, even though clinicians have to face unanswered questions regarding the right dosage and length of therapy, as well as the potential for adverse events (AEs), especially infections. Real world data could help to elucidate its optimal use, but is very limited as of yet.
Methods: We addressed all Hungarian centers treating myeloma to evaluate the efficacy and safety of venetoclax in their practice treating t(11;14) myeloma, collecting data about the treatment duration, AEs, dose modifications and treatment discontinuations, and analyzed response rates as well as progression free and overall survivals (PFS, OS).
Results: 50 patients were reported from 7 Hungarian sites. 33 patients were relapsed and heavily pretreated with an average of 4.8 prior lines, whereas 17 patients received venetoclax after a suboptimal initial response to their first line treatment (8 PR, 7 SD, 2 PD) as planned

pre-transplantation salvage. Most patients had venetoclax in combination with a proteasome inhibitor and dexamethasone. The response rate was remarkably high given the refractoriness of this cohort: all but two patients responded, with 28% CRs, 38% VGPRs and 30% PRs. The median PFS and OS calculated from initiation of venetoclax dosing were 15.5 and 24 months, respectively, Figure 1. shows the PFS and OS curves of the 2nd line and late line cohorts. The most common AEs were cytopenias, gastrointestinal toxicities and infections, reported in 8, 9 and 10 patients with 1 fatal infection. Two patients had COVID-19 related hospitalization, both recovered.

An important point to emphasize is the very high risk nature of this cohort. 13 out of the 47 patients had deletion 17p before venetoclax dosing was initiated, explaining their refractoriness to standard treatments. Notably, of these patients 2 reached CR, 9 VGPR, 1 PR, and only one progressed while on venetoclax treatment. The median PFS and OS were 9.6 and 10 months, respectively. Five patients had plasma cell leukaemia and 1 CNS involvement, the PFS and OS of these ultra-high risk patients were 10 and 12 months.

Another important aspect of our analysis was the question of venetoclax dosing, as the appropriate dose in this indication is not yet clear. Reflecting this uncertainty, as well as funding difficulties with this off-label drug, only 2 patients received the 800 mg dose as seen in the Bellini trial; one received 600 mg daily, with all others taking 400 mg or less. To counteract this many centers employed a combination with either clarithromycin or fluconazole, CYP3A inhibitors known to increase venetoclax serum levels two- to threefold. Where available, serum venetoclax levels were monitored to ensure serum levels comparable to regular dosing.

Figure 1. Overall and progression free survival of 11;14 translocated multiple myeloma patients treated with venetoclax based therapy



Summary/Conclusion: Our results highlight the importance of targeted treatments in multiple myeloma. We experienced lasting responses in quadruple-refractory patients, many with other high risk features. In the newly diagnosed group, where the depth of pre-ASCT response has great impact on PFS, venetoclax may have a role converting suboptimal responses into CRs by eliminating residual disease.

PB1642 FIRST CASE OF SYSTEMIC LIGHT CHAIN (AL) AMYLOIDOSIS TREATED WITH ANTI-B CELL MATURATION ANTIGEN -CAR T CELLS

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Background: Chimeric antigen receptor T cell (CART) therapy is a groundbreaking approach in the treatment of relapsed/refractory hematological malignancies. Given that multiple myeloma (MM) remains an incurable disease to current standard of care therapies, several investigational CAR-T constructs are in development in clinical trials. However, some MM patients may evolve to light-chain (AL) amyloidosis which is currently an exclusion criterion for these trials.

Aims: We present the first case reported of a patient with systemic AL amyloidosis, evolved from a MM, and successfully treated with CART therapy.

Methods: Our institution has developed an academic second generation humanized 41BB-based CART targeting B cell maturation antigen (BCMA), called ARI-0002h, which is currently being tested on the CARTBCMA-HCP-01 clinical trial for patients with relapsed/refractory MM. The patient underwent treatment with ARI-0002h as a compassionate use after approval by the local Health Care Ethics Committee and the Spanish Drugs Agency. An informed consent form was obtained. Lymphodepletion was performed with fludarabine (90 mg/m^2) and cyclophosphamide (900 mg/m^2), followed by infusion of 3 x10^6 ARI-0002h cells/kg in a fractionated manner (3 doses). Patient medical records were collected for analysis.

Results: A 61-year-old woman was diagnosed with an IgA-lambda symptomatic MM in 2014. She received several lines of treatment including an autologous stem cell transplantation, proteasome inhibitors, immunomodulatory drugs and the CD38-targeted antibody daratumumab. Despite the previous therapies, the patient relapsed with a serum M-protein of 20.7 g/L, kappa/lambda serum-free light-chain of 2/231 mg/L and bone marrow infiltration by 23% plasma cells (normal FISH), without evidence of extramedullary disease by PET-CT or other CRAB signs. However, she developed edema and significant non-selective albuminuria (24-hour proteinuria of 2626 mg with urinary M-protein of 307 mg). Therefore, subcutaneous fat aspirate and renal biopsy were performed showing amyloid deposits of lambda type. Diagnosis of systemic AL amyloidosis with renal involvement (revised Mayo Stage II) was stablished. Cardiac involvement was ruled out. BCMA expression in bone marrow plasma cells before CART infusion was 23%. The patient received ARI-0002h after lymphodepletion, developing a grade I cytokine release syndrome, treatment-related grade 4 neutropenia and grade 2 thrombocytopenia, with no evidence of neurotoxicity. On day +28 the patient had achieved a hematological complete response (CR) with negative minimal residual disease (MRD) in the bone marrow by next generation flow cytometry. Six months later, the patient remained in MRD negative CR and had achieved a renal response, with a 78% decrease of proteinuria (Figure 1). Renal response at 3 months was not assessable due to a BK virus hemorrhagic cystitis. The highest peak of ARI-0002h expansion was detected at +21 days after infusion and was detectable until day +107 by either flow cytometry and quantitative RT-PCR techniques (Figure 1).

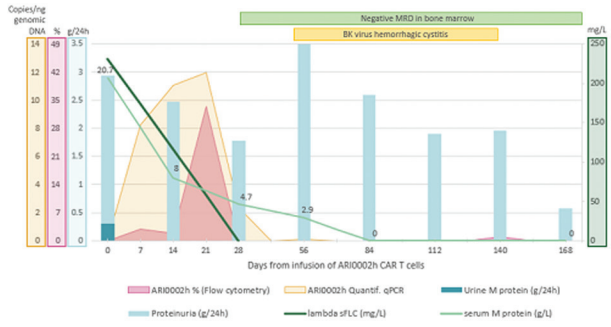


Figure 1. Evolution of clinical and laboratory findings after infusion of ARI-0002h. In the first six months after infusion of ARI-0002h a progressive decline in serum M-protein and lambda serum free light chain (sFLC) was observed. MRD was negative on day +28 and remains negative at 6 months. A renal response with a 78% decrease in proteinuria was observed at six months with an intermediate period in which, due to hemorrhagic cystitis, proteinuria is not assessable. Expansion of CART cells by either flow cytometry and qRT-PCR are also represented, with a peak at day +21.

Summary/Conclusion: We report the first case to our knowledge of a patient diagnosed with light-chain amyloidosis successfully treated with BCMA-CART therapy. Despite the fact that only a low proportion of clonal plasma cells expressed BCMA, the patient achieved a hematologic CR on day 28 and a renal response at 6 months after CART infusion. Considering the importance of obtaining fast and deep hematologic responses in this disease, CART cells could be a promising therapeutic strategy in AL amyloidosis.

PB1643 OUTCOMES OF DARATUMUMAB-CONTAINING REGIMENS IN THE TREATMENT OF RELAPSED MULTIPLE MYELOMA: REAL-WORLD DATA FROM THE CANADIAN MYELOMA RESEARCH GROUP DATABASE

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Background: Multiple myeloma (MM) remains an incurable disease with significant morbidity and mortality. Daratumumab (Dara)-containing regimens, both in monotherapy and in combinations with other agents, have significantly altered the therapeutic landscape of MM especially in the relapsed setting.
Aims: The aim of this study was to evaluate the outcomes of Dara-containing regimens in the Canadian real-world setting among MM patients, many of whom may have been ineligible for the landmark trials.
Methods: We performed a retrospective study using the Canadian Myeloma Research Group Database (CMRG-DB), containing real-world data on myeloma outcomes in Canadian academic centers. We identified 798 patients previously exposed to Dara up to 31/08/2020, of which 710 were treated in the relapsed setting. This includes patients for whom Dara was added within 6 months from initiation of a treatment and considered the same line of therapy. Objectives were to evaluate progression-free survival (PFS) and overall survival (OS) using 6 different Dara-based regimens (in monotherapy, with cyclophosphamide, with bortezomib, with lenalidomide, with pomalidomide ± cyclophosphamide), considering median prior lines of therapy.
Results: Of the 710 MM patients receiving Dara-based therapy in ^{3} 2nd-line treatment, 58.5% were male, 18% had high-risk [del17p, t(4;14) and/or t(14;16)] cytogenetic disease and 34% were ISS 3. Overall, the median number of prior lines of therapy was 3 (range 2-11). After a median follow-up of 13 months, the median PFS and median OS for the entire cohort were 13 months (95% CI 11-15) and 38 months (95% CI 31-72), with 23 months and not reached (NR) in 2nd-line, 14 and 38 months in 3rd-line, and 8 and 20 months in 4th-line treatment, respectively. Additional demographic and outcome data stratified by different Dara-containing regimens are shown in Table 1. Dara in monotherapy ± corticosteroids after a median of 5 prior lines of therapy resulted in a median PFS of 3.7 months and median OS of 20.6 months, similar to the SIRIUS trial (Lonial et al. Lancet 2016). The inclusion of cyclophosphamide with Dara after a median of 3 prior lines of therapy resulted in a median PFS of 15.8 months (median OS NR). DVd, after a median of 3 prior lines of therapy, resulted in a median PFS of 7.8 months and median OS of 27.8 months -- significantly less than the results in the latest CASTOR trial update (Mateos et al. Clin Lymphoma Myeloma Leuk 2020) although their patients were less pre-treated. DRd, after a median of 2 prior lines of therapy, resulted in a median PFS of 26.6 months and median OS of 32.9 months which is significantly inferior to results of the last update of the POLLUX trial (Bahlis et al. Leukemia 2020) although their patients were also less pre-treated. DPd, used after a median of 3 prior lines of therapy, resulted in a median PFS of 9.7 months and median OS of 31.3 months similar to what is expected from the EQUULEUS (Chari et al. Blood 2017) and APOLLO trials (Dimopoulos et al. ASH 2020) after a median of 4 and 2 prior lines of therapy, respectively. The addition of cyclophosphamide to Dara and pomalidomide significantly increased the median PFS (22.7 months) and OS (median NR).

Table 1. Patient information grouped by daratumumab-based regimens

	Dara ± steroids	DCd	DVd	DRd	DPd	DPCd
N	100	49	143	263	77	45
Age in years; median (range)	66 (36-85)	64 (47-87)	69 (43-88)	70 (39-88)	63 (40-85)	65 (44-82)
Male n (%)	57 (57)	23 (47)	89 (62)	150 (57)	48 (62)	26 (58)
ISS Stage n (%)						
I	29 (35.8)	15 (34.88)	33 (29.73)	52 (22.91)	17 (23.61)	8 (18.60)
II	29 (35.8)	14 (32.56)	39 (35.14)	87 (38.33)	30 (41.67)	22 (51.16)
III	23 (28.4)	14 (32.56)	39 (35.14)	88 (38.77)	25 (34.72)	13 (30.23)
missing	19	6	32	36	5	2
HR genetics (%)	28%	33%	35%	26%	33%	34%
DoT in days; median (range)	98 (0-1121)	368 (21-883)	130 (8-670)	192 (11-1911)	254 (7-995)	386 (27-847)
TTNT in days; median (range)	204 (27-802)	336 (22-902)	155 (59-671)	239 (29-930)	319 (56-1028)	462 (62-868)
ORR n (%)	38 (45.24)	33 (71.74)	69 (57.98)	198 (84.98)	47 (66.20)	40 (88.89)
≥VGPR n (%)	18 (21.43)	20 (43.48)	34 (28.57)	137 (58.80)	27 (38.03)	32 (71.11)
Prior PI (%)	100	98	87	97	94	100
Prior IMID (%)	96	73	66	37	71	69
Prior ASCT (%)	71	84	68	56	78	80
Median follow-up (months)	13.7 (0.1-71.5)	20.7 (1.6-44.2)	8.9 (0.5-27.8)	11.8 (0.1-73.5)	19.3 (0.5-47.8)	23.9 (1.4-32.9)
Median PFS months (95% CI)	3.7 (2.9-4.6)	15.8 (9.7-23.4)	7.8 (5.9-9.5)	26.6 (20.7-62.8)	9.7 (7.6-13.8)	22.7 (12.9-NR)
Median OS months (95% CI)	20.6 (15.1-37.9)	NR	27.8 (17.2-27.8)	32.9 (27.1-NR)	31.3 (18.2-NR)	NR

Abbreviation: ASCT: autologous stem cell transplantation; Dara: daratumumab; DCd: daratumumab-cyclophosphamide-dexamethasone; DoT: duration of therapy; DPd: daratumumab-pomalidomide-dexamethasone; DPCd: daratumumab-pomalidomide-cyclophosphamide-dexamethasone; DRd: daratumumab-lenalidomide-dexamethasone; DVd: daratumumab-bortezomib-dexamethasone; HR: high-risk; IMiD: immunomodulator; ISS: international staging system; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PI: proteasome inhibitor; TTNT: time to next treatment; Tx: treatment; VGPR: very good partial response

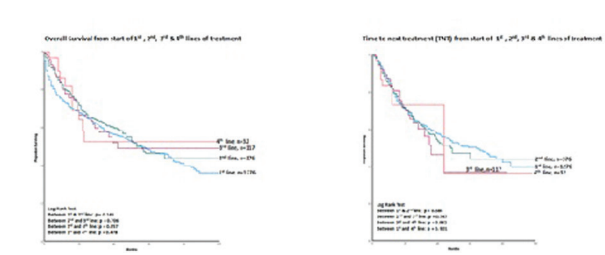
Summary/Conclusion: Our results demonstrate that Dara-based therapy is effective in relapsed MM patients even in real-world practice. Our observations suggest that the addition of oral cyclophosphamide to Dara-based therapy results in more favourable outcomes and deserves further evaluation.

PB1644 THE NATURAL HISTORY OF SYSTEMIC AL AMYLOIDOSIS FOLLOWING UPFRONT TREATMENT WITH BORTEZOMIB: AN ANALYSIS OF REAL-WORLD LONGITUDINAL DATA

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Background: AL amyloidosis is an incurable disorder. The real natural history of this condition is incompletely understood.
Aims: In this study, we describe the natural history of the disease based on analysis of real-world longitudinal data.
Methods: All patients seen at the National amyloidosis Centre, the UK between Feb 2010 and Aug 2019 and treated with upfront Bortezomib are included in this analysis.
Results: 1276 patients received 1st line treatment. 26% of patients had died within 12 months of 1st line treatment. 376 (29.5%), 117 (9.2%), 32 (2.5%), 8 (0.6%) and 2 (0.2%) patients had received 2nd, 3rd, 4th, 5th and six lines of treatment, respectively. 77.2% of patients who required more than one line of treatment received the 2nd line within the first two years of 1st line treatment. There was no significant difference in survival from 1st, 2nd, 3^{rd,} and 4th lines of treatment (p=.478). The OS from 1st, 2nd, 3^{rd,} and 4th lines treatment was 56 month, 53 months, 42 months and not reached, respectively (Figure 1). There was no significant difference in TNT from 1st, 2nd, 3rd, and 4th lines of treatment (p=.901). The TNT from 1st, 2nd, 3^{rd,} and 4th lines of treatment was 64 months, 48 months, 36 months, and 44 months, respectively (Figure 1).



Summary/Conclusion: AL Amyloidosis is an incurable disease, and most patients require further treatment. However, even multiply relapsed AL patients have a good outcome and prolonged remission periods. Prospective trials are needed to refine treatments in the patients with relapsed AL amyloidosis.

PB1645 A CLINICAL-DECISION TOOL TO IMPROVE THE STRATEGY OF MULTIPLE MYELOMA TREATMENT

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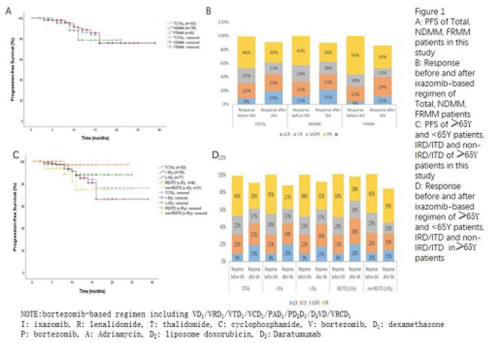
Background: Multiple myeloma (MM) is one of the most common hematologic malignancies with more than 30,000 cases diagnosed in the US alone. This incurable disease is characterized by a high heterogeneity and complex pathophysiology. A tremendous progress in our ability to treat this disease has been made in the last two decades by introduction of new therapeutic modalities. Today, there are dozens of interventions that include radiation therapy, cell therapy and drug combinations available. Unfortunately, direct head-to-head comparisons between treatment regiments in MM are often available due to the high cost and time-consuming nature of additional clinical trials.
Aims: Here we describe a method for prediction of several (clinical) parameters of responses to MM therapy that uses statistical and machine learning approaches.
Methods: Clinical data including names of treatment options, response rates, progressive-free survival (PFS) and other parameters were extracted from scientific publications that described results of clinical trials and real-world practice in the management of patients with MM. We used a very good partial response (VGPR) and PFS as outcomes for the prediction. The prognosis of VGPR was calculated as follows: 1) we calculated inverse percentages for each clinical study and treatment method, 2) added all inverse percentages for a given treatment method to get an average rate, 3) VGPR rates between the two treatment options were compared by using Odds Ratio (OR). The prediction of PFS is based on a machine-learning algorithm - random forests for survival which uses VGPR, line of therapy and stem cell transplantation as predictors. All statistical analyses were done using R version 3.6.0. and the "shiny", "epiR", "survminer", "survival", "ranger", "ggplot2" packages.
Results: More than 300 publications were identified by a systematic literature review and 100 treatment options with a total of 40334 patients with MM were selected. The data from this corpus of publications were analyzed using open-source R software, and visualized via an interactive web app. The functions of the app include: 1) calculation VGPR or better for selected treatment options, 2) therapy response comparison with calculation of statistical significance (OR, p-value), 3) PFS prediction with interactive graphs of survival curves (Hazard ratio, p-value). The Harrell's c-index for the model of PFS prediction is 0.81. The app is available at https://luchinin.shinyapps.io/MM_Therapy_Analyzer/. All treatment options are divided into two categories: "newly diagnosed MM" and "relapsed and refractory MM". Current version of the web app provides an additional reference point for making a decision about the treatment strategy in patients with MM. The tool also helps to estimate efficacy of the therapy in relation to another for categories of clinical cases.
Summary/Conclusion: We developed an interactive digital tool and web app to aid selection of strategy for multiple myeloma treatment. We used machine learning and general statistics to calculate and predict key outcomes of therapy in patients with MM based on a systematic review of 300+ clinical publications. To the best of our knowledge, this is the first publication describing this approach combined with a user-friendly publicly available tool. Future work will extend this approach and explore the potential for integration into hematology clinical decision-support systems.

PB1646 IN-CLASS TRANSITION FROM INTRAVENOUS TO ORAL PROTEASOME INHIBITOR AS LONG PROTEASOME INHIBITION IN NEWLY DIAGNOSED AND FIRST RELAPSED MULTIPLE MYELOMA PATIENTS IN CHINA: A REAL-WORLD STUDY

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Background: Bortezomib, as an intravenous proteasome inhibitor (PI) is important in the treatment of multiple myeloma (MM), but it always discontinued by adverse event (AE).
Aims: Assessing in-class transition (iCT) from intravenous bortezomib-based induction to all-oral ixazomib-based regimen is a good method for improving PI-based continuous therapy with efficiency, safety and convenience.
Methods: In this real-world retrospective study from Chinese seven hospitals during Oct, 2017-Jan, 2021, we analysed newly diagnosed multiple myeloma (NDMM) and first relapsed multiple myeloma (FRMM) patients without transplantation, who achieved at least partial response of bortezomib-based introduction and then received ixazomib-based regimen for 2 years or until progression/intolerant toxicity. Primary endpoint: progression-free survival (PFS). Key second endpoints included response rate, therapy duration and AE.
Results: 183 patients were enrolled in this study (NDMM 76%, FRMM 24%, median age 63 years; 42% ≥ 65 years; 10% ≥ 75 years; 51% male; IgG/IgA/IgD/light chain /non-secretory/others 50%/22%/2%/22%/1%/3%; ISS stage I/II/III 16%/37%/47%; R-ISS stage was estimated in 107 patients, stage I/II/III 9%/54%/37%). 48% high risk (HR,59/123) and 52% standard risk (SR,64/123) were tested by metaphase fluorescence in situ hybridization (M-FISH) according to Mayo clinic risk stratification.
183 patients received median 4 cycles (1-14) of bortezomib-based regimen, and median 4 cycles (1-20) of iCT regimen including I/ ID1/IRD1/ITD1/ ICD1. Median duration of total PI therapy was 10 months and of iCT regimen was 4 months. With 13 months median follow-up, 18 month PFS rate was 80% (95% confidence interval,67-93) from the start of bortezomib-based induction and 78% (95% confidence interval,70-94) from the start of iCT (Figure 1A), 66% patients remain on therapy at data cutoff. There's no significance in PFS between NDMM and FRMM, between HR and SR MM patients (P=0.419, P=0.105, Figure 1A, Figure 1C). Before iCT, ORR rate was 100% (sCR 9%; CR 22%; VGPR 22%; PR 47%) and 90% (sCR 19%; CR 25%; VGPR 19%; PR 27%) after iCT. There were 50 PR improved to more than VGPR (Figure 1B). ORR of HR and SR patients were 100% and 83%, 100% and 94%, before and after iCT, respectively (Figure 1D).
Among 113 patients who transited to IRD1/ITD1 regimen, medium duration of total PI therapy was 9 months and of iCT regimen was 3 months, 77% of patients remain on therapy (Figure 1C). ORR rate was 100% and 92% before and after iCT, respectively (Figure 1D). ORR of HR (23/52), of SR patients (29/52) patients were 100% and 96%, 100% and 86% before and after iCT, respectively. For those non-transplantation-eligible (NTE, ≥65 years old) patients, medium duration of total PI therapy was 9 months and of iCT regimen was 4 months (Figure 1E). PFS and ORR rate of IRD1/ITD1 group are better than non-IRD1/ITD1 group (P=0.023, Figure 1E; ORR rate still 98% after iCT, Figure 1F).
The ixazomib-safety profile was consistent with previous clinical trial data. 54% of patients had any grade AEs. In which, the most frequent grade <=2 AEs were peripheral neuropathy (PN) (37%, 50 patients began before iCT), nausea and vomiting (16%), diarrhea (13%). Grade 3/4 AEs were agranulocytosis (1%), rash (1%), pneumonia (1%), PN (1%). The most often treatment discontinued AEs is PN.



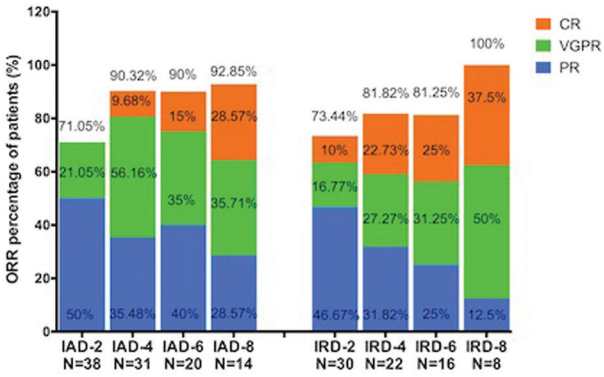
Summary/Conclusion: In real-world China MM population, NDMM and FRMM patients are sensitive to PI-based continuous therapy with satisfied response rate; iCT can permit prolonged PI-based therapy with promising efficacy and tolerated adverse events.

PB1647 EFFICACY AND SAFETY OF INDUCTION THERAPY WITH IAD VERSUS IRD REGIMEN IN FRAGILE ELDERLY PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA-RESULTS OF PROSPECTIVE MULTICENTER CLINICAL TRAIL

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Background: Fragile elderly patients with multiple myeloma(MM) have poor efficacy and low survival rate due to many factors including complications, poor tolerance and compliance, high rate of treatment discontinuation.
Aims: This is a prospective multicenter non-randomized controlled study, design to compare efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone versus ixazomib in combination with liposome doxorubicin and dexamethasone. (ClinicalTrials.gov number, chiCTR1900024917)
Methods: This multicenter trial was conducted in 13 hospitals. Inclusion criteria was patient age≥65 and IMWG geriatric scoring system (GA)≥2 points or Mayo geriatric vulnerability scoring system defined as vulnerable. No exclusion criteria. Scheme include: IAd regimen (Ixa 4mg d1,8,15, liposome doxorubicin 40mg d1, dexamethasone 20mg d1,8,15,22); IRd regimen (Ixa 4mg d1,8,15, lenalidomide 25mg d1-14, dexamethasone 20mg d1,8,15,22) 4 weeks a cycle. The assessment of response conducted post four 28-day cycles. The consolidation therapy of previous regimen recommended 2 cycles for ≥VGPR and 4 cycles for PR &MR. Id (Ixa 4mg d1,8,15, dexamethasone 20mg d1,8,15,22) regimen maintenance initiated until progression. Primary endpoint is overall response rate (ORR). The secondary endpoints are progression free survival (PFS), overall survival (OS), tolerability, toxicity, health-related Qol. This study is designed for 3 years, 120 patients in-total, 60 each group.
Results: From Oct 2019 to Jan 2021, 79 cases were enrolled without intervention, 29.1%(23/79) of them were aged≥75. 15.2%(12/79) cases with renal insufficiency, including 9 severe renal failure (eGFR<30mL/min), 2 dialysis. 7 cases were complicated with paraplegia. Efficacy could be evaluated in 68 cases, 11 cases could not be evaluated, of them, 4 had not completed a cycle chemotherapy, 5 had given up, and 2 died in the 1st treatment course. Most if not all cases with renal failure, bedridden and thrombosis enter the IAd group. The total ORR was 82.35%, with 84.21% (32/38) in the IAd and 80.0% (24/30) in the IRd group, $p>0.05$. 53 cases (77.9%) completed 4 cycles (IAd group of 31, the IRd group 22); 22 cases (32.4%) completed 8 cycles (IAd group of 14, the IRd group 8).16 cases (23.5%) are in maintenance treatment (10 of IAd group, the IRd 6). The median follow-up period was 8 months (1-16m), the median PFS and OS were not achieved either, with OS of 85.7% at 12th months. According to IMWG risk stratification, OS in high-risk group was significantly shorter than that in standard risk group,14.0m vs not reached, respectively ($p=0.022$).
To date, 15 death occurred, including 4 early deaths within 60 days, 7 by disease progression, 3 individually gave up and 1 unexplained sudden death. During induction chemotherapy,11.8% (8/68) of cases experience hematology above grade 3, 11(16.2%) cases with pneumonia (8 of IAd and 3 of IRd), 13(19.1%) cases developed gastrointestinal AE above grade 3 (10 cases in the IAd group and 3 cases in the IRd group), among which 4 cases developed AE above grade 4.



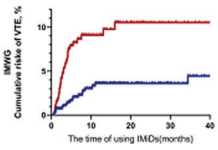
Summary/Conclusion: The results showed in the interim observation, both three-drug combination regimen of ixazomib was effective, with overall response rate of 82.35% and 12-month OS of 85.7%. The adverse reactions were tolerable. As AE rate and the interim mortality rate are comparably high in fragile elderly MM patients, it is still a challenge for treatment. Drugs and regimens with low toxicity and high efficacy are needed to continuously explore.

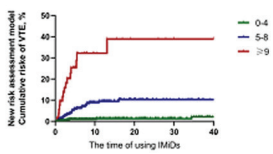
PB1648 RISK ASSESSMENT MODEL FOR IMMUNOMODULATORY DRUG-ASSOCIATED VENOUS THROMBOSIS AMONG PATIENTS WITH MULTIPLE MYELOMA IN CHINA

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Background: Venous thromboembolism (VTE) is a significant complication for patients with multiple myeloma (MM) receiving immunomodulatory drugs (IMiDs). The International Myeloma Working Group (IMWG) developed guidelines recommending primary thromboprophylaxis in those identified to be at high risk of VTE according to the presence of risk factors. However, these guidelines lack validation and do not take ethnic differences into account. There is no validated clinical model predicting VTE in this population in China.
Aims: This study aimed to assess the frequency of VTE and associated risk factors and derive a new risk assessment model for IMiD-associated VTE in Chinese MM patients.
Methods: Patients with MM receiving IMiDs were selected from 16 centres in China between 2010 and 2020. We assessed the incidence of VTE and the associated clinical parameters. The primary endpoint was the rate of symptomatic VTE. Secondary endpoints were associations between VTE and clinical factors, including age, sex, disease characteristics and duration, history of VTE, immobilization, comorbidities, treatment regimens, and laboratory parameters.
A multivariable cause-specific Cox regression model was used for model development.
Results: A total of 1137 myeloma patients were followed up for a median of 8.51 months (range 0.46-180.01 months), and 52 (4.6%) developed VTE, which was lower than the rate found in Western countries. In addition, 41 patients developed VTE within 6 months of treatment with IMiDs. The sites for VTE included the lungs (6%), lower extremities (71%), upper extremities (11%), and central venous catheter (12%). Thromboprophylaxis with aspirin or warfarin did not reduce the risk of VTE; the rates of VTE with or without aspirin or warfarin treatment were 5.2% and 4.1% (p=0.377), respectively. Multivariate analysis determined that an ECOG score≥2, history of VTE, D-dimer>2.42 mg/L, use of IMiDs during induction therapy, diabetes and the use of lenalidomide, dexamethasone, anthracyclines or erythropoietin were significant risk factors for VTE. We derived a new risk assessment model that included these 9 clinical variables. The model stratified approximately 32.1% of patients as high-risk. In contrast, the IMWG stratification method only classified 9.1% of patients as high-risk. A high-risk group for VTE among MM patients receiving IMiDs was identified, and a larger study is needed to confirm these findings.





Summary/Conclusion: The new risk assessment model score outperformed the current IMWG guidelines in the risk stratification of patients with MM receiving IMiD therapy in China. A high-risk group for VTE among MM patients receiving IMiDs was identified, and a larger study is needed to confirm these findings.

PB1649 REAL-LIFE DATA ON THE SAFETY AND EFFICACY OF CARFILZOMIB AND LENALIDOMIDE PLUS DEXAMETHASONE (KRD) IN 149 PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: A RETROSPECTIVE ANALYSIS OF GEMMAC GROUP.

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Background: Carfilzomib, a second-generation proteasome inhibitor, in combination with lenalidomide plus dexamethasone (KRD) is approved for the treatment of patients with relapsed/refractory multiple mm (RRMM) after 1-3 prior lines.
Aims: Our objective was aimed to analyse the efficacy and safety of KRD in a real-life cohort in eleven hospitals from Catalonia.
Methods: A real-life retrospective analysis of RRMM patients treated with KRD at hospitals in GEMMAC group from January 2016 until May 2020. KRd was administrated at standard schedule (carfilzomib 27mg/m2, d1,2,8,9,15,16; lenalidomide 25mg/d,d1-21 (adjusted by renal clearance); dexamethasone 20-40mg,d1,8,15, 22). Response rate was assessed using IMWG criteria. Progression free survival (PFS) and overall survival (OS) were calculated from the start of KRD treatment using Kaplan-Meier method. Cytogenetic high-risk (HR) included t(4;14), t(14;16) or del(17p) vs. Standard risk (SR).
Results: We included 149 patients with a median age of 66 years (range:40-88); 56% were male. Forty-four (29%), 57(38%) and 42(28%) patients were ISS1, ISS2 and ISS3, respectively. Ninety-seven (65%) patients had cytogenetic information by FISH at diagnosis, thirty-six (37%) of them had HR cytogenetic. Median prior lines of therapy were 1 (range: 1-4), 120(80%) patients had received only one prior line. All patients had previously received bortezomib and 61(41%) thalidomide. Seventeen (11%) patients had been exposed to lenalidomide previously. The overall response rate (ORR) was 75% (53% ≥VGPR, 38% ≥CR) with a median time to best response of 4 months. Median time on treatment was 6 (1-46) months. One hundred one (68%) patients discontinued treatment, mainly due to progression and toxicity: 49 (33%) and 17(11%) patients, respectively. Twenty-one (14%) patients received consolidation with autologous transplantation (ASCT) and 7 (5%) patients with allogeneic transplantation (AlloSCT). After a median of 18 months of follow-up, median PFS and OS were 26 (95% CI, 20-33) and 42 (95% CI, 34-50) months, respectively. Median PFS and OS at 1st, 2nd and subsequent relapse were 28 (95%CI, 22-34), 22 (95%CI, 1-46) and 1 (95%CI,1-4) months (p=0,004) and 50 (95%CI, 30-70), 37 (95%CI, 0-79) and 4 (95%CI, 0-8) (p=0,014) months, respectively. PFS was shorter in HR cytogenetic group patients but did not achieve statistically significance (HR: 12 [95%CI, 1-27] months vs SR: 25 [95%CI, 15-34] months, p=0.15). OS was either not significantly different in this group (OS: HR: not reached vs SR: 50 months, p=0,15). Median PFS and OS in a subgroup of patients who consolidated with ASCT or AlloSCT (28 [19%]) were longer [PFS: not reached vs 20 (95%CI,9-31) months, p=0.001; OS: not reached vs 42 (95%CI,29-55) months, p=0.007]. The most common adverse effects (incidence >10%) were hematological [anemia (41%), leukopenia (36%) and thrombocytopenia (34%)], infection (32%), asthenia (25%), gastrointestinal (19%) and cutaneous (10%). Fifteen (10%) patients discontinued carfilzomib due to toxicity, 6 (4%) of them by cardiovascular toxicity.
Summary/Conclusion: Our cohort shows that KRD is especially effective (ORR: 82%) in patients at first or second relapses after bortezomib- or thalidomide-based regimen. In patients who were candidates for transplantation (ASCT or AlloSCT) KRD was an effective salvage treatment. The most frequent toxicities were haematological and infectious complications. Cardiac toxicity, even not frequent, was the main cause of carfilzomib discontinuation. In conclusion, this data shows that KRD is an effective and safe regimen in patients with RRMM.

PB1650 HIGH LEVELS OF GALECTIN-3 AND IMMUNOGLOBULIN LIGHT CHAINS AS MARKERS OF THE RISK OF PROGRESSION OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE IN RESIDENTS OF GOMEL REGION OF BELARUS

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Background: Monoclonal gammopathy of undetermined significance (MGUS) is asymptomatic in most cases, but there is an increased risk of developing multiple myeloma (MM) or other lymphoproliferative disorders. There is very little information about the markers that lead to the development of MM.
Galectin-3 (Gal-3) is one of the members of lectin family expressed in the human body. It plays an important role in many biological processes, it is involved in the suppression of apoptosis and proliferation processes.
We presented the results of a study of Gal-3, immunoglobulins, and other blood indicators and their impact on the MM progression in MGUS patients of Gomel region, Belarus.
Aims: To study risk markers of MGUS progression in residents of Gomel region, Belarus.
Methods: The study included 22 MGUS patients who underwent examination in the period 2020-2021 in RRCRM&HE, Gomel (Belarus) The diagnosis was confirmed by the presence of abnormal immunoglobulin in the blood and/or urine and the tumor immunophenotype of the plasma cells of the bone marrow. All patients underwent assessment of renal function (study of creatinine clearance and estimated glomerular filtration rate). Determination of the level of Galectin-3 in blood serum was carried out by the CMIA method on ARCHITECT 12000SR analyzer. Results were assessed at the time of detecting MGUS and after 8 months of the study. The number of clonal plasma cells in the bone marrow averaged 2.4%. MGUS was more common in women (72.2%). The median age was 60 years.
Results: At the first stage, we examined immunoglobulins and renal function, and then the level of Gal-3 and B2-microglobulin.
Pathological protein in patients was represented by IgG (22.7%), IgA (22.7%), IgM (9%), two Ig (18.2%), and light chain secretion (27.4%).
An increase in the level of B2- microglobulin was detected in 16 patients (72.2%) (in 2 patients it was not associated with impaired renal function). Renal dysfunction was detected in 6 patients (27.4%), an increased Gal-3 level was found in 4 patients (18.2%).
The study revealed a significant excess of the Gal-3 level in patients with secretion of immunoglobulin light chains ($p = 0.0001$).
In our study, high levels of B2-microglobulin were revealed in patients with renal dysfunction and a high level of Gal-3. It is 1.52 times more frequent than in patients with normal Gal-3 levels ($p = 0.051$).
During the follow-up period, MM developed in two patients with secretion of light chains, high Gal-3 levels, renal dysfunction, and high levels of B2-microglobulin.
Summary/Conclusion: Despite a very short follow-up period and a small number of cases, our study identified patients with a high Gal-3 level, the presence of immunoglobulin light chains, a high level of B2-microglobulin, and kidney damage that progressed within a year. We supposed that these indicators as a whole at the initial stage of diagnosis can be considered as unfavorable prognostic markers with a high risk of developing MM in MGUS patients.

PB1651 ANALYSIS OF DELAY IN THE DIAGNOSIS OF MULTIPLE MYELOMA IN A SANITARY REGION OF SOUTHERN SPAIN.

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Background: Multiple myeloma (MM) is a bone marrow neoplasm that accounts for 1% of all cancers. Besides, it also constitutes a 10% of haematological malignancies. Nowadays, MM continues to be an incurable disease that affects the elderly. It is not a well-known disease by general practitioners and its symptoms are also common in many other conditions which make it difficult to suspect MM as the underlying cause. Longer time to diagnosis is associated with more complications and irretrievable consequences.
Aims: Assessing the delay in the diagnosis of MM, number of visits in different health units, reasons for consultation and possible consequences.
Methods: We have carried out a retrospective study and we have analysed all new diagnoses of MM patients between 1st January 2017 and 31th December 2020 in our centre. Patients with monoclonal gammopathy of undetermined significance (MGUS), previous or another centre diagnosis were excluded. We define "delay in diagnosis" as the time that elapses from the first consultation of the patient for any symptom or sign related to the disease until the final diagnosis of MM by bone marrow aspiration.
Results: In total, 61 patients were diagnosed as de novo MM, between 2017 and 2020. Median age was 68 years (range 30-85 years). 41% (25 patients) were females and 59% (36) were males. IgG was the most frequent type of MM (47.5%) and more than a half of patients were stage two by MM international staging system (ISS). Characteristics of patients are in table 1A and the results of sample in table 1B.
The average delay in diagnosis was 81 days (range 2-321 days) and in 27 patients (44.3%) the retardation between the first claim for a MM symptom and diagnosis was equal or less than 60 days. However, 11 patients (18%) were diagnosed within more than two months and equal or less than four months and the delay was more than 120 days in 23 patients (37.7%). Besides, almost 20% of patients waited for more than 6 months to be diagnosed.
The first consultation for any sign or symptom was in primary care centres (49.2%), emergency services (37.7%) or another specialist hospital consultation (17%) and low back pain was the reason in almost half of the patients (45.9%).
Two visits (range 0-12) were the median in care centres but 40.9% of patients needed more than two and 9 people (14.7%) went more than five times. Also, the median was two visits (range 0-7) in emergencies, although 42.5% of patients were three times or more. In consultation with another specialist (nephrology, traumatology, internal medicine…) median of visits was one (range 0-4).
Twenty-five patients (41%) were admitted without diagnosis to the hospital by internal medicine. At diagnosis, anemia was presented in 67.2% of patients, kidney failure in 42.6%, hyperkalaemia in 13.1%, bone fractures in 37.7% and 6.6% of patients had spinal cord compression.

Table 1A: Characteristics of patients

Sex	41% (25) Females /59% (36) Males
Age	Median: 68 years (range 30-85 years).
Multiple Myeloma type	IgG: 47.6% (29) Light chains: 24.6% (15) IgA: 26.2%(16) IgD: 1.6% (1)
Serum monoclonal protein	Mean: 2.85 g/dl (range 0 – 7.06 g/dl)
Urinary monoclonal protein	Mean: 1147 mg per 24h (range 0 – 12850 mg per 24h).
Serum free light chain ratio	Mean: 242.14 [0.01 – 1869.05].
Bone marrow plasma cells	Mean: 30.9% [range 10 - 95%]
ISS	I: 8.2% (5) II: 52.5% (32) III: 24% (39.9%)

Table 1B: Results

Diagnostic delay Median: 81 days (range 2 – 321 days).	≤ 60 days (2 months): 44.3% (27) ≤ 120 days (4 months): 18% (11) ≤ 180 days (6 months): 18% (11) ≤ 240 days (8 months): 11.5% (7) ≤ 300 days (10 months): 6.6% (4) > 300 days: 1.6% (1)
First consultation for any reason caused by multiple myeloma	
Where?: Primary care center: 49.2% (30) Emergency department: 37.7% (23) Medical specialist consultation: 13.1% (8)	**Why?:** Low back pain: 45.9% (28) Other bone pain:11.5% (7) Renal failure: 9.8% (6%) Anemia: 14.8% (9) Lesions on imaging test: 3.3% (2) Other sign/symptom: 14.8% (9)
Number of consults:	Primary health care center. Median: 2 (range 0-12) Emergency unit. Median: 2 (range 0-7) Medical specialist consultation. Median: 1 (range 0-4)
Hospitalization without diagnosis	Yes: 41% (25) / No: 31.1% (19)
Signs at diagnosis	Anemia: 67.2% (41) Renal failure: 42.6% (26) Hypercalcemia: 13.1% (8) Bone fractures: 37.7% (23) Spinal cord compression: 6.6% (4)

Summary/Conclusion: We believe that there is a significant delay in the diagnosis of patients with MM. There are probably many reasons for this, but we think that one of the most important is the lack of knowledge about this pathology outside the haematology units. Based on these data, we are going to implement a protocol for the early diagnosis of myeloma, in collaboration with the emergency department, other hospital specialties and the primary care centres in our health area. The protocol is already written and it is approved by the hospital's medical management. With the implementation of the protocol, our objective is to reduce the delay in the diagnosis of these type of patients.

PB1652 REAL-WORLD EVIDENCE OF CARFILZOMIB USE AMONG MULTIPLE MYELOMA PATIENTS WITH AT LEAST ONE PRIOR THERAPY ACROSS 4 COUNTRIES IN CENTRAL EASTERN EUROPE AND ISRAEL

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Background: Carfilzomib (K) was approved in combination with dexamethasone (d), i.e. Kd, or with lenalidomide (R) and d, i.e. KRd, in Europe during a large, prospective, observational study (NCT03091127) that included 701 patients (pts) with relapsed or refractory multiple myeloma (RRMM) across 10 European countries and Israel.
However, in participating Central Eastern European (CEE) countries and Israel, usage of K-based regimens was restricted in routine practice: in Bulgaria and Romania, Kd was reimbursed for use in second line of therapy (LoT) and KRd access was limited by R availability for private purchase; in Czech Republic (CZ), only KRd was reimbursed. In Israel, KRd was reimbursed in second LoT, and Kd in third LoT.
Aims: To understand effectiveness, safety and usage of K-based regimens according to routine practice in selected CEE countries and Israel during study NCT03091127.
Methods: Adults with ≥1 prior LoT (pLoT) and ≥1 K dose received in routine care were eligible. Data were collected and analysed as previously described (Terpos et al., *Blood* 2020. 136 [Suppl_1]: 38-39).
Results: Of the 144 pts enrolled in CEE and Israel, 63% received Kd and 32% KRd. The remaining 5% received other K-based triplets (Kd+cyclophosphamide, Kd+thalidomide) not further described here. Pts characteristics and results are summarized in Table. Across countries, Kd was mainly used, except for CZ (KRd only). Median pts age was comparable in Kd and KRd cohorts (64 vs 63 years).
Kd pts had received a median of 2 pLoTs, 36% had a prior autologous stem cell transplantation (ASCT). Nearly all Kd pts were exposed to bortezomib (V) in a pLoT and over half (53%) of them were V-refractory. Over one-fifth (23%) were exposed to R and 81% of these were R-refractory.
KRd pts had received a median of 1 pLoT and 72% had a prior ASCT. All KRd pts had a prior V-exposure with one-third being V-refractory. Prior R-exposure was reported in 22% of pts, of whom 40% were R-refractory. In this population, overall response rates (ORRs) were high regardless of K-based regimen (Kd: 80%; KRd: 87%).
The mean K dose intensity received relative to EU label for Kd (20/56 mg/m^2 twice weekly [Q2W] for K) and KRd (20/27 mg/m^{2}Q2W for K) was 81% and 83%, respectively. The Kaplan-Meier median estimate of treatment duration was 9.7 months (95% CI: 7.2, 12.0) for Kd and 13.6 months (95% CI: 8.8, 16.6) for KRd.
Treatment-related adverse events (TRAEs) of grade 3 or above (Gr3+) were reported in 13% of Kd and 35% of KRd pts, including 9% and 13% of serious TRAEs, respectively. The most frequent Gr3+ TRAEs were blood cytopenias (2% Kd, 24% KRd), infections (3% Kd, 11% KRd), respiratory and vascular disorders (2% Kd, 4% KRd). Of the fatal events (8 Kd and 1 KRd), none were considered treatment related.

Table: Patient Characteristics at K initiation and Response by Planned K Regimen

	Kd (N=91)	KRd (N=46)
Distribution of K-based regimens by country[a], n (%) (n=144)		
Bulgaria (n=22)	17 (77)	4 (18)
Czech Republic (n=27)	0 (0)	27 (100)
Israel (n=18)	11 (61)	3 (17)
Romania (n=77)	63 (82)	12 (16)
Median (IQR) age at K initiation, years	64 (59, 70)	63 (55, 68)
ISS stage, n (%)[b]	***N=46***	***N=21***
I	17 (37)	9 (43)
II	13 (28)	7 (33)
III	16 (35)	5 (24)
Derived frailty score, n (%)[b]	***N=74***	***N=39***
Fit	6 (8)	11 (28)
Intermediate	29 (39)	16 (41)
Frail	39 (53)	12 (31)
Cytogenetic risk, n (%)		
High risk	2 (2)	4 (9)
Normal/intermediate risk	4 (4)	16 (35)
Unknown/missing/not done	85 (93)	26 (57)
Previous therapies of interest, n (%)		
ASCT	33 (36)	33 (72)
Bortezomib	91 (100)	45 (98)
Lenalidomide	21 (23)	10 (22)
Monoclonal antibodies	6 (7)	3 (7)
Patients with evaluable best response, n (%)[b]	***N=88***	***N=45***
ORR [95% CI]	**70 (80)** [69.6, 87.4]	**39 (87)** [73.2, 94.9]
CR or better	15 (17)	17 (38)
VGPR	36 (41)	12 (27)
PR	19 (22)	10 (22)
Adverse events of Grade 3 or above, n (%)		
Overall adverse events	29 (32)	23 (50)
TRAEs	12 (13)	16 (35)
Serious TRAEs	8 (9)	6(13)
Fatal TRAEs	0 (0)	0 (0)

[a]Percentages of Kd and KRd are listed, other K-based triplets account for those missing to total number of patients in the respective country/region. [b]Percentages based on reported data

ASCT, autologous stem cell transplantation; CI, confidence interval; CR, complete response; IQR, interquartile range; ISS, international staging system; K, carfilzomib; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone; ORR, overall response rate (partial response or better); PR, partial response; TRAEs, treatment-related adverse events; VGPR, very good partial response

Summary/Conclusion: In CEE and Israel, usage of K-based regimens (32% KRd, 63% Kd) differed from that in the overall study population (55% KRd, 39% Kd) probably due to country-specific reimbursement regulations at time of study. Compared with the overall study population, pts enrolled in CEE and Israel were generally younger (Kd: 64 vs 68; KRd: 63 vs 65) and Kd was used in earlier lines (median number of pLoTs: 2 vs 3). Irrespective of K-based regimens, high response rates (over 80%) and deep responses (≥VGPR: Kd 58%, KRd 64%) were achieved over long treatment durations. K-based regimens were well tolerated (TRAE G3+: 13% Kd, 35% KRd).

PB1653 MODIFIED DELPHI CONSENSUS ON THE RELEVANCE OF MINIMAL RESIDUAL TESTING IN MULTIPLE MYELOMA IN THE CLINICAL PRACTICE

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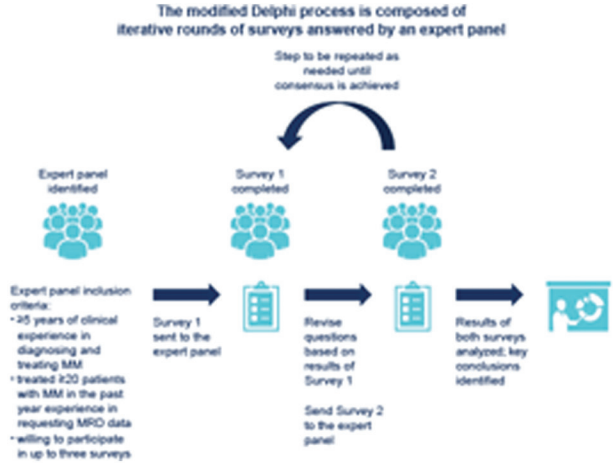
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Background: Results from clinical trials in patients newly diagnosed with multiple myeloma (MM) or those with relapsed/refractory MM (including trials investigating add-on monoclonal antibodies to standard of care regimens), as well as retrospective analyses from clinical practice, have demonstrated a consistent association between minimal residual disease (MRD) negativity in MM and sustained clinical response to therapies. In these studies, depth of clinical response as measured by MRD predicted progression-free survival and overall survival. While these data indicate that MRD status is prognostic in clinical practice and may represent a valuable surrogate efficacy endpoint in clinical trials, to date, results from large-scale randomized clinical trials of MRD-directed therapy are lacking. In the absence of these data, a Delphi survey to establish consensus regarding the clinical practice utility of MRD in MM may serve as a bridge to help close this knowledge gap. Here we describe the interim results of a modified Delphi analysis conducted among representative experts in the field of MM across Europe.

Aims: To establish whether there is consensus on the relevance of determining MRD status in MM clinical practice in assessing and confirming response to therapy, and to assist physicians in implementing MRD assessment in the management of patients with MM.

Methods: The modified Delphi process is composed of two or more rounds of surveys answered by an expert panel. The expert panel comprises invited, currently practicing, hematological oncologists who fit all inclusion criteria (see Figure). A panel of 11 advisors across 8 European countries developed the questionnaires, identified and invited expert panel members, completed the surveys, and analyzed the results. Questions from Survey 1 were divided into 6 categories: screening and respondent demographics; perceptions regarding the potential use of MRD in clinical practice; actual use of MRD; barriers to routine MRD assessment; guidelines concerning the use of MRD; and educational needs concerning the use of MRD in MM. Advisors defined consensus *a priori* as 75% agreement or disagreement by the expert panel. Participants' contact details and survey data were handled in accordance with local regulatory requirements. This analysis focuses on the results from the categories on guidelines and educational needs concerning the use of MRD in MM (as stated in the categories above).

Results: Sixty-one experts (11 advisors; 50 invited) from 16 Western European countries completed Survey 1. Half (50%) reported that MRD was covered in either the prognostic, treatment, or both guidelines that they used. 64% felt suitably informed regarding the use of MRD in MM and were confident using it in a variety of clinical situations, while only 16% felt other clinicians in their country were suitably informed. There was consensus among the experts that clinicians in their country would benefit from education/resources in the use of MRD in informing treatment decisions (92%), and guidelines on the use of MRD in MM (75%).



Summary/Conclusion: As the treatment of MM continues to evolve, guidelines on using MRD in the clinic are increasingly necessary. Results from a Delphi survey of expert MM clinicians suggest a lack of MRD practice guidelines, and consensus that clinicians across Europe were not suitably informed regarding the clinical use of MRD in MM. These preliminary results highlight the importance of establishing guidelines and providing education on MRD in MM; final Delphi results will provide areas of expert consensus on MRD utility in clinical practice.

PB1654 A RETROSPECTIVE TWO-CENTRE COHORT STUDY OF THE EFFICACY AND SAFETY OF DARATUMUMAB WITH BORTEZOMIB AND DEXAMETHASONE THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA

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Background: Daratumumab, bortezomib and dexamethasone (DVd) is a therapy that has demonstrated significant clinical activity in relapsed/

refractory multiple myeloma (RRMM). In April 2017, DVd was approved by the European Medicines Agency (EMA). In June 2020, subcutaneous (SC) daratumumab gained EMA approval.
Aims: To analyze the clinical characteristics, response rates and treatment emergent toxicity of DVd combined therapy in two European centres.
Methods: This two-centre retrospective study includes 25 RRMM patients who started DVd therapy between July 2018 and November 2020 at Guy's Hospital (London) or Hospital Principe de Asturias (Madrid). The patients' data were reviewed using electronic records. Response outcomes were assessed for patients who received ≥1 cycles.
Results: The median age at the start of therapy was 62 (range 42-86), with 15 (60%) male patients. Clinical characteristics are shown in Table 1. Twenty (80%) patients had 1 previous line of therapy: 5 (25%) VMP (bortezomib, melphalan, prednisone), 5 (25%) VTd (bortezomib, thalidomide, dexamethasone), 3 (15%) VCd (bortezomib, cyclophosphamide, dexamethasone), 1 (5%) Vd (bortezomib, dexamethasone), 1 (5%) CRd (carfilzomib, lenalidomide, dexamethasone) and 4 (20%) a clinical trial. Five (20%) patients had 2 prior lines. Fourteen (56%) had undergone autologous stem cell transplant. Overall, 21/25 (84%) patients had been exposed to bortezomib: overall response rate (ORR) was 90.5% and 1 (4.8%) was bortezomib-refractory in 1st line. Median progression free survival (PFS) was 43.1 months (m) and median treatment-free interval was 33.2 m.
All patients had disease progression and 1 (4%) extramedullary disease prior to starting DVd. Median time on treatment was 9.6 m (0.2-29.4), with a median number of cycles of 12 (2-33). Seven (28%) patients discontinued therapy: 5 (71.4%) due to progressive disease, 1 (14.3%) for patient's choice and 1 (14.3%) died on treatment (due to SARs-CoV2-related pneumonia).
At a median follow-up of 11 m (1.8-29.4), 24 (95.2%) patients have completed ≥1 cycles. ORR is 83.3%, with very good partial response (VGPR) in 10/24 (41.7%) patients; only 2 (8.3%) patients had no response. The patient who was bortezomib-refractory in 1st line has a partial response (PR) so far. Median time to PR in the population is 36 days (15-120). PFS and overall survival (OS) rates are 73.7% and 90% at 11 m.
Daratumumab administration was SC in 6 (24%) patients, and was switched from intravenous (IV) to SC in 8 (32%) patients. Eight (32%) patients had a first-dose infusion related reaction (IRR) with daratumumab, in all cases being IV. In 3 (12%) it had grade 3 (hypertension) and infusion could be resumed.
Common (≥15%) AEs were: lymphopenia (76%), anaemia (64%), thrombocytopenia (60%), neutropenia (20%), peripheral sensory neuropathy (32%) and infections (36%), most of them SARs-CoV2 related (44.4%).
Grade ≥3 AEs occurred in 12 (48%) patients. Three (25%) developed thrombocytopenia, 1 (8.3%) anaemia, 3 (25%) neutropenia and 6 (50%) lymphopenia. Moreover, 3 (25%) patients had SARs-CoV2-related pneumonia (in 1 leading to death), 1 (8.3%) neutropenic sepsis secondary to pneumonia (causing death), 1 (8.3%) sepsis secondary to jaw infection and 1 (8.3%) non-pneumonic respiratory tract infection.

Table 1. Clinical characteristics of the population.

Characteristics (n=21)		Overall data (%)
MM type	- IgG	16/21 (76.2%)
	- IgA	2/21 (9.5%)
	- Bence-Jones	2/21 (9.5%)
	- Non-secretory	1 (4.8%)
ISS stage at diagnosis	- I	11/21 (52.4%)
	- II	6/21 (28.6%)
	- III	4/21 (19%)
ISS-R stage at diagnosis	- I	6/21 (28.6%)
	- II	7/21 (33.3%)
	- III	2/21 (9.5%)
	- Unknown	6/21 (28.6%)
Cytogenetics at diagnosis*	- Non-high risk	15/21 (71.4%)
	- High risk	1/21 (4.8%)
	- Unknown	5/21 (23.8%)
ECOG performance scale ≤2		21/21 (100%)

Abbreviations: MM: Multiple myeloma. ISS: International Staging System. ISS-R: Revised International Staging System. ECOG: Eastern Cooperative Oncology Group. *High risk cytogenetics at diagnosis: t(4;14), del(17/17p), t(14;16).

Summary/Conclusion: Daratumumab combined with bortezomib and dexamethasone as salvage therapy in MM demonstrates encouraging outcome results in our population, similar to those exposed in the analysis of the phase III CASTOR study. It shows an acceptable safety profile, with no IRRs to the moment since the introduction of SC daratumumab.

PB1655 LIGHTHOUSE (OP-108): A PHASE 3 STUDY OF MELFLUFEN IN COMBINATION WITH DEXAMETHASONE AND DARATUMUMAB VS DARATUMUMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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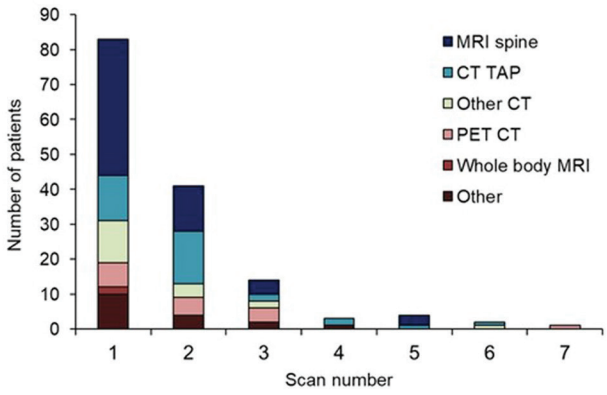
Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and thereby delivers and rapidly releases alkylating agents inside tumor cells. In the phase 2 HORIZON study, melflufen plus dexamethasone showed clinical efficacy and was well tolerated in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM; Richardson et al. *J Clin Oncol.* 2020 Dec 9 [Epub]). The ongoing phase 1/2 ANCHOR study (OP-104) established the optimal dose for melflufen plus dexamethasone and daratumumab, showing meaningful clinical activity and manageable safety at both melflufen doses tested in patients with RRMM (Ocio et al. ASH 2020. Oral 417).
Aims: LIGHTHOUSE (OP-108; NCT04649060) is a randomized, open-label, multicenter, phase 3 study designed to evaluate the efficacy and safety of melflufen plus dexamethasone and daratumumab vs daratumumab alone in patients with RRMM previously treated with an IMiD and a proteasome inhibitor (PI).
Methods: Patient enrollment has begun, with N=240 patients planned for enrollment. The patient population is similar to that of the indication for daratumumab monotherapy. Key inclusion criteria are age ≥18 years, double refractory to (or intolerant of) an IMiD and a PI or having had ≥3 prior lines of therapy including an IMiD and a PI, have measurable disease, and Eastern Cooperative Oncology Group performance status ≤2. Patients with primary refractory disease and refractoriness to an anti-CD38 antibody are excluded. Patients will be randomized 1:1 to open-label melflufen plus dexamethasone and daratumumab (Arm A) or single-agent daratumumab (Arm B) and stratified by number of prior lines of therapy. Patients will receive therapy until progressive disease (PD) or unacceptable toxicity. In Arm A, patients will receive melflufen 30 mg intravenously on day 1 of each 28-day cycle; dexamethasone 40 mg weekly orally (20 mg if aged ≥ 75 years); daratumumab 1800 mg subcutaneously on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 of cycles 3-6, and day 1 of cycles 7+. In Arm B, patients will receive daratumumab at the same dosage as in Arm A. Patients in Arm B with PD can opt to receive triplet therapy as in Arm A.
The primary objective of the study is to show superiority of progression-free survival (PFS) in patients treated with triplet therapy vs daratumumab alone (*P* value from the 2-sided statistical test <0.05; upper limit of the 2-sided 95% CI for the hazard ratio <1). An estimated sample of 240 patients with 160 expected events (PD or death) and 15% assumed dropout rate would provide 90% power at a 2-sided log rank test at 5% significance level to detect a hazard ratio for death of 0.6. Key secondary endpoints are overall response rate (ORR; ≥ partial response [PR]), duration of response, and safety. Response will be assessed by a blinded independent review committee based on International Myeloma Working Group response criteria. Other secondary endpoints include clinical benefit rate (≥ minimal response), time to response, time to progression, time to next treatment, and overall survival. Exploratory endpoints include minimal residual disease in patients achieving ≥ very good PR, PFS following next line of treatment (PFS-2), patient-reported outcomes, pharmacokinetics, translational biomarkers, response rate in patients with extramedullary disease, and efficacy (including ORR) in patients in Arm B who receive triplet therapy as in Arm A after PD.
Results:.
Summary/Conclusion:.

PB1656 WHOLE BODY MRI IS A FEASIBLE AND COST-EFFECTIVE IMAGING MODALITY FOR WORK-UP OF SUSPECTED OR NEWLY DIAGNOSED MULTIPLE MEYLOMA: A RETROSPECTIVE, SINGLE CENTRE COHORT STUDY

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Background: The detection of bone disease has important prognostic implications in multiple myeloma and can influence the diagnostic classification and the urgency of instituting treatment. Whole body magnetic resonance imaging (WB-MRI) is the most sensitive imaging technique and there are a number of advantages over other modalities. WB-MRI is able to detect axial and extra-axial disease, other solid organ malignancies, and has superior resolution and sensitivity for focal bone lesions. However, its use is restrained by a lack of local availability, paucity of radiological expertise in reporting, long acquisition time, and other factors. In this study, we hypothesised that more widespread use of WB-MRI would decrease the total number of scans, improve the patient journey and be cost effective.
Aims: The primary aim was to ascertain the feasibility, service impact and potential for cost-saving of instituting WB-MRI as the first-line skeletal imaging technique for patients with suspected or proven multiple myeloma in a large teaching hospital.
Methods: Electronic records of 88 consecutive patients with newly diagnosed multiple myeloma in the University Hospitals North Midlands NHS trust between 1st November 2018 and 31st October 2020 were studied. For the purposes of our analyses, a label of suspected myeloma was assigned when an abnormal protein electrophoresis or serum free light chain result was available. Confirmed myeloma was assigned when results of bone marrow showing >10% plasma cells was available. Data were anonymised and stored using Microsoft Excel on password-protected trust computers.
Results: 83 (94%) patients had imaging performed, with a total of 213 imaging procedures during the time period. Diagnostic imaging is summarised in figure 1 which includes all imaging performed prior, and up to, the achievement of a formal diagnosis of multiple myeloma (not follow-up scans). 43/83 (52%) had focal skeletal disease. Imaging triggered upstaging from smouldering myeloma to multiple myeloma in 7 (8%) patients. Where scans were performed for suspected or confirmed myeloma, 18 patients had in total 28 scans that could have been avoided if we had performed at the earliest realistic opportunity, 70 WB-MRI instead of 43 MRI whole spine, 12 computed tomography (CT) thorax, abdomen, and pelvis, 4 other CT scans, 8 positron emission tomography (PET) CT scans, and 3 other MRI scans. This equates to a direct cost saving of £11,428 (€13,177) over two-year period - a cost saving of £130 (€149) per patient – and the opportunity to redirect valuable scanner time for other cases.



Summary/Conclusion: As myeloma is a rare disease, patients arrive at the diagnosis through a variety of circuitous routes. It is therefore not feasible to perform WB-MRI in all patients as firstline imaging. However, it is reasonable to perform WB-MRI where myeloma is suspected or confirmed in place of other imaging. We have calculated direct cost savings but there are likely to be myriad benefits for the patient journey relating to improved diagnostic sensitivity and speed, fewer hospital visits, decreased exposure to radiation, and timely access to treatment where appropriate. Our findings support UK recommendations for WB-MRI as the first-line imaging modality. Radiology services should focus on expanding expertise in the delivery of this service and identifying patients who can benefit. Clinicians should be encouraged to utilise WB-MRI wherever possible.

PB1657 AL AMYLOIDOSIS SURVIVAL EVOLUTION IN NEW AGENTS ERA: A REAL LIFE EXPERIENCE

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Background: Light chain amyloidosis (AL) is a rare but severe disease due to deposition of misfolded protein in tissues leading to progressive organ failure. Its prognosis is mostly due to the degree of cardiac involvement at diagnosis. In the past years, thanks to the introduction of new agents, such as Daratumumab, a huge improvement of the prognosis has been observed due to better efficacy and less toxicity as well.
Aims: This retrospective review aimed to evaluate the reported improvement in a real life population. For this purpose, we looked at our entire AL patients population during the past 15 years.
Methods: We collected the data of 42 AL patients from two hospitals in Brussels from 2006 until 2019 and separated them into two cohorts: 2006-2015 and 2016-2019, before and after the introduction of Daratumumab. We looked into and then compared baseline characteristics, treatments, overall survival (OS), response rate, toxicities but also time from first symptoms to diagnosis between the two cohorts.
Results:
The median age at diagnosis was 62.3 62 (58-72) years, 45% were females, and 23% of patients had an ECOG performance status ≥ 3. Basics characteristics of the two groups were comparable no difference regarding the number of organ involvement and their severity (stage 4 revised Mayo Clinic 23 vs 25% respectively, p=1). No improvement concerning the time to establish the diagnosis from first symptoms described by patients was observed (109,5 months versus 181 months, p=0.3) between the two periods of time. In the second cohort, an increase of Bortezomib-based regimens use was observed (71 vs 59%) and 12 patients were treated by Daratumumab in the relapse setting. The hematological overall RR was 65%, with high-quality response (≥ very good partial remission)in 41% of the patients. There was no difference in the RR between the two periods. Median OS was 33 months for the whole cohort. However, an improvement in overall survival is neat between the two cohorts with median OS (mOS) of 7 months for the first period of time compared to a mOS that was not reached yet in the second cohort (p=0.01). As expected, concerning the whole population, the mOS was significantly and hugly better in patients with PS 0-2 comparing to those with PS 3-4 (116 vs 8,9 months; p=0,009.). Moreover, median mOS according to stage of Mayo Clinic was 55,1 months for stage 1-2 and 32,1 months for stage 3-4 (HR 0.58). Within the specific population treated by Daratumumab(N=12), we described a significant improvement of mOS compared to other treatments (7 months versus not reached; p=0,01). Moreover, less toxicities were described with 25% of infectious and 17% of haematological complications of > grade 2.
Summary/Conclusion: We observed a significant improvement in overall survival as described in other recent and larger publications. These encouraging results are mostly due to the introduction of new agents, especially Daratumumab in the relapse setting. Also, new guidelines recommending to switch treatment quickly if no satisfactory response is reached, are part of this success. However, even if a massive effort has been done in the recent past years by scientific authorities to improve the time to diagnosis (recommendation of MGUS screening i.e.), no difference was observed in the time needed to establish the diagnosis and hence, in the amount of severe cases at diagnosis between the two periods of time.
Finally, according to recent studies, Daratumumab is well tolerated and extremely efficient in AL amyloidosis.

PB1658 RECOMMENDATIONS FOR VACCINATION GIVEN TO PATIENTS WITH MULTIPLE MYELOMA IN REAL-WORLD CLINICAL PRACTICE AND PATIENTS` COMPLIANCE WITH THEM

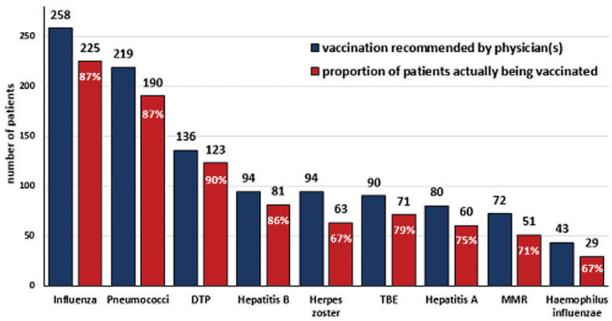
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Background: Infections are the second leading cause of death in multiple myeloma (MM). All available measures to curb this complication should be exploited, including vaccination against several bacteria and viruses.

Aims: In this study, we examined the recommendations for vaccination given to patients (pts) with MM in real-world clinical practice and pts' compliance with them. We also analyzed the incidence of infections before and after diagnosis, and pts' willingness to be vaccinated against COVID-19.
Methods: 335 pts with MM from Germany, Switzerland, and Austria participated in this survey. A questionnaire was designed in cooperation with pts groups to assess the vaccination recommendations given to them from their treating physicians, to evaluate their compliance with the advice received, to capture the infection rate of pts in the year before and the first six months after start of therapy, and to assess pts' willingness to be vaccinated against COVID-19. The invitation to participate in this electronic survey was distributed by 31 participating myeloma support groups. In addition, 500 hardcopy questionnaires were mailed directly to pts, reaching out to approximately 2,000 pts.
Results: Pts' median age was 65 years; 23.0% had 1, 34.8% 2-3, and 42.3% ≥ 4 lines of prior treatment. Pts' responses were similar between respondents to the online and printed version of the questionnaire. The number of pts who received recommendations for the various vaccinations and the proportion of pts who actually received the vaccine is shown in Figure 1. Influenza was the most frequently recommended vaccine (77.0%), followed by pneumococci (65.4%). Pts' compliance with their physicians' advice varied between 67% and 90%.
At least one infectious period in the year preceding the diagnosis of MM was reported by 51.9% of the 322 responding pts, and by 42.4% of the 314 responding pts during the first six months after initiation of first-line therapy. Eighty-three percent of pts declared their willingness to be vaccinated against COVID-19, while 17% stated that they objected to it. Reasons for refusing SARS-CoV-2 vaccination were lack of long-term experience (76.6%), concerns regarding late effects (60.9%), insufficient confidence in the pharmaceutical industry (26.7%), and concerns that the vaccine will not be protective (15.6%).

Figure 1: Types of vaccinations recommended, number of pts with vaccination advice, and proportion of patients who actually received the vaccine



DTP – diphtheria, tetanus, pertussis; TBE – tick borne encephalitis; MMR – measles, mumps, rubella

Summary/Conclusion: The vaccination recommendations varied widely depending on the type of vaccine, but compliance with these recommendations was remarkably high (>80%) for influenza, pneumococci, hepatitis B, and DTP. The high rates of recommendations for influenza and pneumococci seem to reflect the high prevalence of upper and lower respiratory tract infections in MM. Of note, 51.9% of pts reported a least one infectious episode in the year before, and 42.4% during the first six months after initiation of treatment. As 75.4% of pts did receive prior ASCT, vaccinations with DTP and MMR were recommended to substantial pt numbers. In contrast, fewer than expected pts were advised to get vaccinated against VZV (28%) and against Haemophilus influenzae (12.8%). Tick borne encephalitis is endemic in the some areas of the participating countries, which possibly explains the high compliance rate (78.8%) in the 26.8% of pts who were advised to be vaccinated.
The high readiness of MM pts to get vaccinated with a SARS-CoV-2 vaccine (83%) seems remarkable and much higher than that of the general population. A possible explanation for this proactive attitude is the preferential participation of well-informed pts in this study.

PB1659 COVID-19 MORTALITY IN CONCURRENT MULTIPLE MYELOMA (MM) – A PROSPECTIVE AND COMPARATIVE CASE SERIES THROUGH THE FIRST AND SECOND WAVE OF THE SARS-COV-2 PANDEMIC IN A UK TERTIARY HAEMATOLOGY CENTRE

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Background: The Sars-CoV-2 pandemic has markedly disrupted haemato-oncology services in the UK in balancing Covid-19 infection risk with MM management. New light has been shed on risk factors for mortality in hospitalised Covid-19 patients with concurrent MM. However, reported mortality rates for Covid-19 in MM patients show significant heterogeneity between countries, and do not examine for changes to mortality despite huge shifts in Covid-19 management throughout the pandemic.
Aims: 1) Record patient demographics and medical risk factors of all MM patients hospitalised with Covid-19 between March 2020 to January 2021 in the NCA (catchment population of ~1,000,000 patients), UK.
2) Compare patient factors and outcomes between the first and second wave of the Sars-CoV-2 pandemic to characterise more currently reflective demographic and outcome data for Covid-19 in MM patients.
Methods: All patients with a previous diagnosis of MM who were admitted Covid-19 treatment were included. Covid-19 diagnosis was defined as a positive nasopharyngeal PCR swab 7 days before or after admission. Admissions during the 01/03/2020 to 30/06/2020 and 01/07/2020 to 07/01/2021 were included, and classified as the first and second wave, respectively. Patient demographics, myeloma therapy before admission, medical co-morbidities, and 28-day mortality from Covid-19 test positivity was recorded and analysed. Statistical comparison of mortality rate was applied between the first and second wave.
Results: 6 patients were admitted in the first wave of whom 6 (100%) died. 6 patients were admitted in the second wave, of whom 2 (33.3%) died. The change in mortality between waves approached, but fell short of, statistical significance (p=0.061). The average age in both waves was 79 and both had heterogeneous but comparable medical co-morbidities. Gender did not correlate to mortality, and gender ratios were comparable between both groups. 10 of 12 patients had medical therapy for MM prior to their admission, 7 of which were bortezomib based, two lenalidomide-Ixazomib based, and one receiving pomalidomide monotherapy. No correlation was detected between specific MM therapy or therapy line, on pandemic wave or mortality.
Summary/Conclusion: This study seeks to define more up to date Covid-19 outcomes in MM patients compared to previous outcome data which uses both early and current Covid-19 outcome data, homogenously. Our findings are strictly limited by sample size and power but display a large difference in Covid-19 mortality rate between the first and second wave in the NCA. Due to comparable patient and medical characteristics, and near statistical significance, these findings suggest a significant reduction in mortality of Covid-19 in MM patients between the first and second Sars-CoV-2 wave in the UK and is a novel finding which warrants further study to confirm or refute this. A more representative set of outcome statistics for Covid-19 infection in MM patients would represent today's pandemic and may shed light on the impact of previously implemented changes in MM management as well as advances in Covid-19 inpatient care. Finally, an accurate representation of today's Covid-19 outcomes in MM patients would set the benchmark for comparing interventional outcomes going forward.

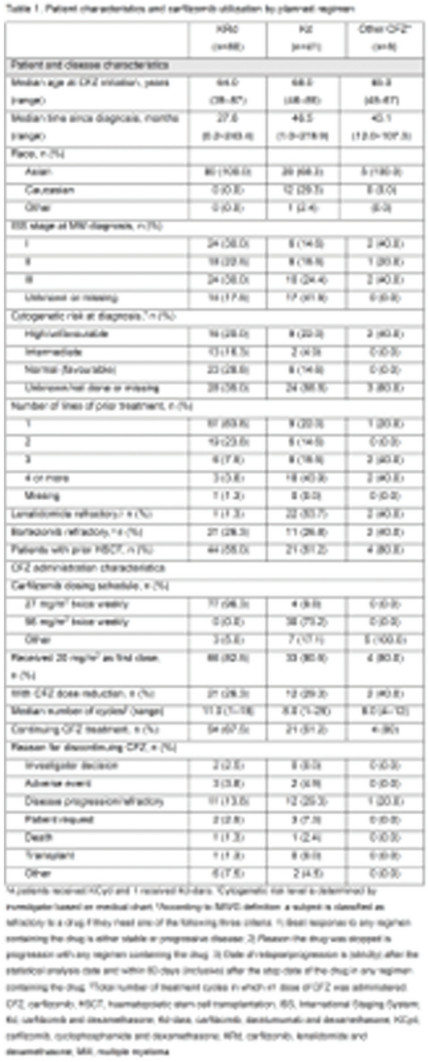
PB1660 CARFILZOMIB USE AMONG PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA IN THE ASIA PACIFIC REGION: AN INTERIM ANALYSIS FROM A PROSPECTIVE, REAL-WORLD STUDY

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Background: Carfilzomib (CFZ) is a next-generation proteasome inhibitor currently approved in combination with lenalidomide and dexamethasone (KRd) or with dexamethasone alone (Kd) for treatment of multiple myeloma (MM) patients with at least one prior line of therapy in the Asia Pacific (APAC) region. Real-world evidence is crucial to understanding how CFZ-based regimens are used in practice.
Aims: To describe utilization of KRd and Kd in routine clinical practice in APAC, including treatment patterns, patient profile and reasons for discontinuation.

Methods: This prospective, single-arm cohort study recruited adults with relapsed or refractory MM who received ≥1 dose of CFZ in either a combination or monotherapy regimen and had received ≥1 prior line of MM treatment prior to CFZ initiation. Between July 2019 and June 2021, approximately 300 patients are anticipated to be enrolled in this study, with 25–100 patients from each included country/region. Medical history, patient characteristics and clinical data will be collected at baseline and throughout the 2-year observation period or until death, withdrawal of consent or loss of follow-up. Follow-up data will be collected through chart reviews every 3 months. Adverse events (AEs) leading to treatment discontinuation will be collected. The last patient record for the analysis will be collected no later than Q1, 2023.
Results: The first patient was enrolled on 10 July 2019. As of 10 September 2020, 126 patients have been included from five countries/regions: Australia (n=15), Hong Kong (n=2), Korea (n=95), Singapore (n=10) and Taiwan (n=4). To date, the regimens prescribed were KRd (63%), Kd (33%) and other CFZ-based regimens (4%), including triplet combinations with cyclophosphamide (n=4) and daratumumab (n=1). Overall, 29% of patients reported a history of hypertension, 9% of cardiac disorders, 8% of diabetes mellitus and 1% of pulmonary embolism, prior to CFZ initiation. On average, patients prescribed KRd were slightly younger than patients prescribed Kd. The majority of KRd patients (63.8%) had received one prior line of treatment, whereas nearly half of Kd patients (43.9%) had received ≥4 lines of prior treatment. Similar proportions of KRd (26.3%) and Kd (26.8%) populations were bortezomib refractory; 53.7% of Kd patients were lenalidomide refractory. For nearly all KRd patients (96.3%) and almost three-quarters of Kd patients (73.2%), the initial prescribed therapeutic CFZ dose was in accordance with the local product information: 27 and 56 mg/m^2 twice weekly, respectively. As of September 2020, 67.5% and 51.2% of KRd and Kd patients, respectively, remained on CFZ treatment. The most common reason for CFZ discontinuation was disease progression/refractory disease (See Table). Overall, only five patients discontinued CFZ for treatment-related AEs.



Summary/Conclusion: This study investigates the real-world use of CFZ for relapsed/refractory MM in a predominantly Asian patient population from across the APAC region. Interim results confirm that the standard dosing schedules for KRd and Kd are well tolerated in real-world practice and suggest a very low rate of discontinuation due to CFZ-related AEs, even in the very late stages of MM. Further prospective data collection of patients in routine practice is ongoing to assess patterns of longer-term patient management, response, survival outcome and AEs, which will inform optimal use of CFZ.

PB1661 BCMA-DIRECTED THERAPY IN MULTIPLE MYELOMA: EFFECT OF ONLINE EDUCATION ON CLINICIAN KNOWLEDGE AND CONFIDENCE

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Background: BCMA-directed modalities including CAR T-cell therapy, bispecific antibodies and antibody-directed cytotoxic agents are potentially transformative next steps in managing patients with multiple myeloma. However, beyond expert centres physicians have little experience of such agents to date.
Aims: This study aimed to determine whether online continuing medical education could improve the knowledge and confidence of clinicians in their understanding of the rationale for and clinical aspects of different BCMA-directed therapies
Methods: Three educational activities were launched for physicians outside the USA during 2020 to a target audience of hematologist/oncologists and ophthalmologists. Activities comprised a 30-minute video lecture, a 15-minute video collegial discussion, and a 30-minute online video panel discussion. Data were collected March to June 2020. For each activity educational effect was assessed with repeated-pairs pre-/post-activity, where individual participants served as their own control. 3 multiple-choice, knowledge questions and 1 self-efficacy, 5-point Likert scale confidence question were analyzed. Data were subsequently combined and analyzed to provide a summative overview of the effect of the education across the combined knowledge-based learning objectives and confidence questions from the three programs. A McNemar's test was conducted to assess statistical significance of changes from pre- to post-assessment.
Results: Between 66 and 103 hematologist/oncologists (combined total n=259) and 39-41 ophthalmologists (combined total n=121) completed pre- and post-activity questions. A statistically significant effect was observed for hematologist/oncologists across all 3 learning objectives (P<0.05-P<0.001) with a relative improvement in % of correct responses ranging from 10-44%. Furthermore, there was an overall improvement in confidence, with a 72% gain in confidence in those reporting increased confidence. The education had less impact on ophthalmologists; while some improvements were noted in individual activities, in the summative overview the greatest improvement was noted in knowledge of AEs associated with BCMA-directed therapies. The summative overview revealed that hematologists/oncologists demonstrated improvements in knowledge across the 3 learning objectives: 10% (P<0.05) regarding rationale and types of BCMA-directed therapies, 44% (P<0.001) regarding AEs associated with BCMA-directed therapies, and 29% (P<0.001) regarding BCMA clinical trials data. Ophthalmologists showed knowledge changes of -2% (NS) regarding knowledge of clinical data and the rationale and type of BCMA-directed therapy, and a 41% (P<0.05) improvement in knowledge of BMCA-therapy associated AEs. In combined self-assessed confidence questions, 51% of hematologist/oncologists had a measurable increase in and 46% maintained confidence. Thirty-three percent of ophthalmologists had a measurable increase in and 59% maintained confidence. All changes in confidence were significant (P<0.01 or P<0.001). At the individual activity level, ~50% of all participants stated that they would modify treatment plans and ~90% were committed to those changes.
Summary/Conclusion: These three educational activities resulted in a considerable educational impact, particularly for hematologist/oncologists. Online medical education is valuable in improving knowledge and confidence, as well as identifying areas of continued educational need and potentially improving patient outcomes, of particular importance during the COVID-19 pandemic where in-person conference learning is inaccessible.

PB1662 A DESCRIPTIVE COST-ANALYSIS OF MYX.1/MCRN003 - A PHASE 2 CLINICAL TRIAL EVALUATING HIGH-DOSE WEEKLY CARFILZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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Background: The prevalence of multiple myeloma is increasing and there is a need to evaluate the associated escalating therapy costs(1). The MYX.1 phase II trial showed that high-dose weekly carfilzomib, cyclophosphamide, and dexamethasone (wKCD) is efficacious in relapsed and refractory disease (2,3). We conducted a descriptive cost analysis, from the perspective of the Canadian public healthcare system, using trial data.
Aims: The goal of this secondary analysis was to determine the total cost of wKCD per patient with a description of per cycle costs and estimated annual costs.
Methods: The primary outcome was the mean total cost per patient. Resource utilization data were collected from all 75 patients enrolled in the MYX.1 trial over a trial time horizon. Costs are presented in Canadian dollars (2020).
Results: The cost of treatment was calculated from the time of patient enrollment until the time of the second data lock in June 2019. The mean total cost per patient was $203,336.08 (range $17,891.27 – $505,583.55) Canadian dollars (CAD, where 1 CAD = 0.65 Euro (EUR)). The median number of cycles was 15. The mean cost per patient per cycle was $14,081.45. The predominant cost driver was the cost of chemotherapy accounting for an average of $179,332.78 per patient or $12,419.17 per patient per cycle. Carfilzomib acquisition accounted for the majority of chemotherapy costs – $162,471.65 total per patient or $11,251.50 per patient per cycle. Fifty-six percent (56%) of patients had at least one hospitalization during the trial period with an average cost of $12,657.86 per hospitalization. The average cost to treat each patient with thrombotic microangiopathy (TMA) was $18,863.32 including the cost of hospitalizations and therapeutic plasma exchange.
Summary/Conclusion: High-dose wKCD is an active triplet regimen for RRMM associated with reduced total cost compared with twice weekly regimens.

PB1663 RACIAL DISPARITIES OF OUTCOME IN MULTIPLE MYELOMA COMPARATIVE ANALYSIS OF VARIED ETHNIC GROUPS IN GALILEE, ISRAEL

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Background: Multiple Myeloma is a malignant bone marrow disorder with plasma cell proliferation. The average survival is about 4 years. There are 19,900 new cases of Multiple Myeloma (MM) every year in the United States and 10,700 deaths from the disease annually. Multiple myeloma is about 1% of all cancers and about 10% of the hematologic malignancies. Monoclonal gammopathy of undetermined significance (MGUS) is the most common form of the pre-cancerous stage of MM. MGUS is characterized by the absence of clinical symptoms and low fraction of a monoclonal antibody (less than 3 g/dl) In addition less than 10% of the plasma cells in the bone marrow.MGUS prevalence is 2-3 times higher in Afro-Americans. There are differences in disease presentation and epidemiology of MM and MGUS between patients from different ethnic groups (Caucasian, Afro-Americans and Asian.). the difference between the incidence of phenomena in different ethnic groups implies a genetic basis for the disease. In Israel it is estimated that 400 to 500 new cases of MM are diagnosed annually.
Aims: Various studies have been conducted around the world examining the relationship between ethnic origin and the prognosis of multiple myeloma by comparing different indicators such as the survival index. The survival index differs among MM patients depending on their ethnic origin. Thus, the treatment of multiple myeloma may be tailored based on their background and ethnicity. For instance, studies conducted in the United States compared Caucasians to African Americans and other ethnic groups such as Asians and Hispanics. These studies indicate that the prognosis differs between populations and show a relationship between survival rates and patients' ethnicity. The aim of this study is to assess the relationship between ethnic origin and the prognosis of MM among various populations in Israel, particularly in the Galilee region
Methods: A retrospective study was performed in order to analyze the medical records of MM patients treated in the Galilee region, exploring the relationship between prognosis and ethnicity. For this purpose, data was collected from medical files of MM patients treated at Ziv medical center and Galilee Medical center between 2008-2018.Patients were divided according to their ethnicity and survival was compared between different ethnic groups. Statistical analysis: Statistics are described using averages and standard deviations, median, and range. Qualitative data was described through prevalence and percentages. Differences in measures between the ethnic groups were thought of by the T or ANOVA tests. Results with $p<0.05$ were considered statistically significant
Results: A mortality rate of 48.9%, was found in the study, regardless of population origin. There was no difference in PFS (progression free survival) and OS (overall survival) between the different ethnic groups. The stage of the disease at the time of diagnosis is lower in Jews compared to patients of Arab origin with statistical significance ($p\leq0.008$),34% of the patients were diagnosed in Stage I, 70.6% of them were Jewish compared to 29.4% of patients of Arab origin. 51.4% of patients were diagnosed in advanced stage III disease were from Arab ethnicity versus 39.4% of all patients
Summary/Conclusion: There was no statistically significant difference in survival between populations of different ethnicity. A difference was found in the stage of the disease at the time of diagnosis. The patients of Arab origin were diagnosed at a more advanced stage than the patients of Jewish origin

PB1664 TREATMENT FOR NEWLY DIAGNOSED, FIT AND YOUNG PATIENTS WITH MULTIPLE MYELOMA: "ONE SIZE FITS ALL" OR PERSONALIZED TREATMENT APPROACHES SHOULD BE CONSIDERED?

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Background: Multiple myeloma (MM) is considered a disease of elderlies with only 15% of cases occurring in patients (pts) ≤55 years (ys) old. Despite the improvements on response and survival rates after treatment with the novel agents combinations, the disease still remains incurable. Focusing on younger pts, although they succeed better outcomes, a considerable number of them (25-35%) succumb to MM, within 5 years after diagnosis. Therefore, even in the novel agents era, an efficient treatment approach for young and fit pts remains a goal to be fulfilled.
Aims: In this retrospective study we evaluated the overall survival (OS) and the potentially related risk factors, in newly diagnosed MM pts aged ≤55 years. We also designed a scoring system with predictive value on their long-term outcome.
Methods: We reviewed the medical records of 122 pts who were treated in our center from 2010-2020 and received either combinations with 2 (n=21) or 3 (n=91) agents of Velcade, Cyclophosphamide, Thalidomide, Lenalidomide and Dexamethasone, or other regimens (n=10), and had also adequate data regarding their age, disease stage (according to ISS), response to the treatment (according to the latest IMWG criteria) and long-term outcome. Pts diagnosed with amyloidosis or smoldering MM were excluded from the study. Student's t-test, Kaplan-Meir and Cox regression methods, were used for the statistical analysis.
Results: Based on the whole cohort's median age (55 ys, range, 38-80), we divided our pts in two groups: those of ≤55 ys (group A, n=63) and those of >55ys (group B, n: 59). Cytogenetic analysis was feasible in 75 (60%) and only 7/75 pts found to have high risk features. No significant differences were noticed between the two groups in terms of disease stage, cytogenetic abnormalities and response rates after induction remission treatment. Autologous stem cell transplantation (ASCT) was performed in 69 pts [51 (81%) from group A and 18 (30%) from group B, p< .001]. After a median follow up of 28 months, the 10-year OS was better for group A

(75% vs 50%) and the median OS was not reached in group A vs 6,5 ys in group B (p: 0,01). With regard to younger pts, we observed that approximately 25% died within 5 years after MM diagnosis, even if combinations of novel agents plus ASCT (either as induction or as salvage treatment) had been used. Three factors adversely affected the outcome of group A pts: advanced stage, less than VGPR achievement after induction treatment and presence of extramedullary disease at diagnosis. Based on these 3 factors we created an easily applicable scoring system. Due to the insufficient number of pts with chromosomal analysis, the cytogenetic abnormalities were not incorporated in the scoring system. Pts with 0-1 factors had significantly better prolonged OS rates as compared to those with 2-3 factors (82% vs. 55% p=0.02). Also, in multivariate analysis, our proposed scoring system was found to be independent risk factor for prolonged survival.
Summary/Conclusion: The heterogeneity in the outcomes among the MM pts, denotes that the "one size fits all" approach, probably is not efficient enough at least for selected young pts with adverse disease features. Currently, the plethora of the available novel treatment agents, highlights the unmet need to establish appropriate criteria for personalized and more efficient treatment approaches for MM pts, especially for the younger ones. In this study, using an easily applicable scoring system, we were able to identify pts ≤55 ys who might need more intensive treatment approaches aiming at prolonged survival rates.

PB1665 MULTIPLE MYELOMA TREATMENT DECISIONS FROM THE PATIENT PERSPECTIVE

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Background: Multiple myeloma (MM) is an incurable hematological malignancy, and during the illness course, patients face a range of disease symptoms and treatment side effects, making therapeutic management a challenging process. There is currently a shortage of data on the treatment decision-making process from the patient perspective, and published literature and patient-reported information (PRI) shared on social media could be a potential source for this evidence.
Aims: A combined research methods approach using a review of published literature and social media posts was conducted to better understand treatment decisions associated with MM from the patient perspective.
Methods: Targeted searches of PubMed and PsycINFO were conducted from 2010 to November 2020 to identify articles covering the patient voice of the burden and treatment of MM. Titles and abstracts were screened for relevance by 2 experienced reviewers with the most relevant full-text articles selected for inclusion in the review. To supplement this, searches for PRI were conducted of relevant patient advocacy websites (e.g., Patient Power, The Patient Story, Cure Today) and YouTube. Posts were included for review if shared by adults with a self-reported diagnosis of MM and had content relating to the patient experience of MM and its treatment. Demographic and disease characteristics at the time of the post were recorded where available.
Results: From a total of 374 articles identified in the literature search and 2,575 posts identified in the social media search, 27 articles and 138 posts were included in the review. Of these, 3 articles and social media posts from 19 patients reported information on patient views regarding treatment decision making. Patients with newly diagnosed MM (N = 7) reported feeling that their life and independence were being taken away and expressed shock at the number of therapeutic decisions. Evidence from the literature (3 articles) stated that a high percentage of patients expressed a desire to be included in treatment decisions but results from the social media posts (N = 5 patients) showed that some felt that they were not consulted by the treating physician before being assigned therapy. In the literature, patients (all treatment lines) reported that finding the most capable specialist and having trust in their health care provider was key (2 articles). From the PRI sources, patients receiving later lines of therapy (N = 10) stated that communication of comprehensive information was important and valued engagement in shared decision making; in this group, treatment effectiveness had the greatest influence on choice. Side effects were a lower concern for patients who had been on therapy for a long time versus patients receiving induction therapy (1 article). Despite this, patients on social media (N = 2 patients) valued the flexibility of being able to decide when to start or break from treatment to fit in with other life events such as holidays or important family occasions.
Summary/Conclusion: The patient perspective on participation in treatment decisions is an important factor in the MM patient journey, and our research showed that, in published literature and on social media, patients appreciate involvement in deciding treatment options. Our review highlights the importance of further understanding patient perspectives on their role and input into treatment decision making with the health care professional; patients value inclusion in the process, and this is an area that is important for improving the overall quality of care for the patient.

PB1666 BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (VRD) AS FIRST LINE THERAPY IN MULTIPLE MYELOMA PATIENTS. REAL LIFE EXPERIENCE IN A SINGLE INSTITUTION.

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Background: Achieving and maintaining high-quality response is the treatment goal for patients with newly diagnosed multiple myeloma (NDMM). Nowaday different schedaules of bortezomib, lenalidomida and dexamethasone are using. The phase 3 PETHEMA/GEM2012 study, in ≤ 65 years old with NDMM, is evaluating bortezomib (subcutaneous) + lenalidomide + dexamethasone (VRD) for 6 cycles. The ≥ very good partial response rates were 70.4% after induction. The complete response rate of 33.4% after induction in the intent-to-treat (ITT) population. Rates of undetectable minimal residual disease (median 3 × 10–6 sensitivity) in the ITT population was 28.8%.
Aims: We want to know the efficacy and safety of the induction therapy with VRD schedule in frail and fit NDMM patients in our institution.
Methods: we reported 34 NDMM patients who received VRD induction therapy since september 2015 until november 2020. All patients received first line treatment with VRD, which consisted of bortezomib 1.3 mg/m2 (subcutaneous) on days 1, 4, 8, and 11 of each cycle; lenalidomide 25 mg/day on days 1 to 21; and dexamethasone 40 mg on days 1 to 4 and 9 to 12 at 4-week intervals for 6 cycles (maximum or until better response). Thromboprophylaxis with low molecular weight heparin was mandatory. Antiviral prophylaxis was also required. MRD (median limit of detection, 3 × 10–6) was analyzed after induction using next generation flow following EuroFlow standard operation protocols as defined by the IMWG. Demographic characteristics are shown in Figure 1.
Results: Results of efficacy and safety are shown in Figure 1. High-risk cytogenetics, defined as t(4;14), t(14;16), gain 1p, and/or del(17p) (p53 deletion), were reported in 9 patients.

N= 34 (evaluable 31)	Follow up median 20 months (5-66)
Age (median)	62 (39-80) > 75 years old (29%) >70 years old (34%)
High risk Cytogenetic*	9 (26%)
Received Cycles (median)	4 (2-6)
Overall response	100%
Response	MRD—^ 6 (27 %) (after induction therapy) Very Good partial response (VGPR) 9 (29%) Complete response (CR) 22 (71%)
Progression free survival (PFS)	High Risk: 13 months (7-26 m) Overall: no reached (NR)
Dose Modifications	5% cycles (Peripheral neuropathy G3, Neutropenia G4, Diarrhea, infection, thrombosis)

Summary/Conclusion: 1) VRD is an effective and well-tolerated regimen for induction in NDMM with deepening response throughout induction.
2) VRD was well tolerated in transplant-ineligible patients.
3) High risk cytogenetic patients responded to treatment, but they need a long time better strategy.

PB1667 THE IMPACT OF COVID-19 ON PATIENT DISEASE EXPERIENCE: INSIGHTS FROM SOCIAL MEDIA POSTS CONTRIBUTED BY PATIENTS WITH MULTIPLE MYELOMA

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Background: Coronavirus disease 2019 (COVID-19) is rapidly spreading; high infection and mortality rates have resulted in extreme restrictions on individuals' liberties and freedom of movement, which are particularly salient for individuals with pre-existing conditions affecting health related quality of life. Patient-reported information (PRI) shared on social media provides an opportunity to access real-time data to better understand patients' perspectives outside the formal research context.
Aims: The aim of this study was to explore the impact of COVID-19 on patients, focusing on analyzing relevant social media posts to better understand the patient experience of multiple myeloma (MM) during the COVID-19 pandemic.
Methods: Searches were conducted of two patient advocacy websites (Patient Power, Myeloma Crowd) and YouTube to identify individual social media posts. English-language posts were reviewed if shared by adults with a self-reported MM diagnosis, with content relevant to the impact of COVID-19 on their experiences of MM. A pragmatic literature review was also conducted to identify articles on the impact of COVID-19 on general patient disease experience and use of social media for research during the pandemic.
Results: Six social media posts (9 individuals [4 male/5 female]) were identified that met the review criteria (7 individuals provided >1 source of data). Four articles were identified as pertinent to humanistic challenges associated with disease management and use of social media for research during the pandemic. Patients with MM encounter additional challenges associated with the pandemic. The PRI data highlighted exacerbation of the psychosocial impact of MM by the pandemic; patients expressed concern about increased vulnerability to infection due to previous treatment toxicities, plus fear and anxiety regarding possible virus transmission. PRI data reported that patients with MM took additional precautions to limit physical contact while attempting to maintain social interactions; already restricted by MM. Both data sources identified that patients encountered disruption/delays to their medical management and treatments. Although the pandemic has been a catalyst for development of telemedicine strategies to provide efficient management, delays/restrictions on treatments (e.g., transplants for MM) and suspension of development of innovative treatments may have deleterious effects for disease management. However, COVID-19 has also provided positive opportunities. Patients' previous experience of MM treatment–related immunosuppression had provided preparation for dealing with COVID-19. Articles reporting on patients' experiences in general noted that medication adherence during the pandemic has reportedly improved for patients with respiratory conditions. Social media has been utilized as a strategy for patient research during the pandemic, resulting in the formation of research groups—i.e., the COVID-19 Global Rheumatology Alliance—as a way of studying the effects of COVID-19 on patients with rheumatic disease.
Summary/Conclusion: PRI can provide timely access to preliminary information on changes to the patient disease experience not easily accessed by traditional research methods. Findings from the targeted search of patients in general and social media posts from patients with MM illustrated that patients with pre-existing diseases encounter challenges due to COVID-19 that can further disrupt their daily lives (e.g., social functioning, medical management) and impact their psychological well-being (e.g., anxiety, fear).

PB1668 THE PATIENT EXPERIENCE OF MULTIPLE MYELOMA: SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE

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Background: Patients with multiple myeloma (MM) report considerable disease- and treatment-related impacts on their health-related quality of life (HRQOL) despite improvements in treatment strategies over the past 5 years. Patient-reported information (PRI) shared on social media provides a unique opportunity to explore unsolicited patient data to understand patients' perspectives outside of the formal research context.
Aims: A combined research methods approach was conducted of a review of published literature and social media posts to better understand the MM patient disease and treatment experience.
Methods: Targeted searches of PubMed and PsycINFO were conducted from 2010 to November 2020 to identify articles describing the humanistic burden of MM and its treatment from the patient perspective. Titles and abstracts were screened for relevance by two experienced reviewers, with relevant articles included in the review. In parallel, PRI derived from social media posts from five patient advocacy websites and YouTube were included. English-language posts were reviewed if shared by adults with a self-reported MM diagnosis and content was relevant to patient MM and treatment experience. Patients' demographic and disease characteristics were extracted from posts (where available), and the posts were analyzed thematically.
Results: A total of 27 articles and 138 posts were included in the final review (79 videos/58 blog posts/1 podcast). The review included PRI from 76 individuals (38 males/38 females). Seven contributors provided more than one source of data (i.e., blog and/or video). Key symptoms reported by the PRI: pain (n = 24), fatigue (n = 10), fractures (n = 9), and infections (n = 6). Substantial impairments to patients' HRQOL were reported in terms of patients' physical functioning (n = 11), emotional and psychological well-being (n = 26), relationships (n = 13), and work (n = 8). Patients with MM tend to experience multiple treatments during their MM journey in pursuit of remission. Patients reported that the impact of their MM treatments can often be more detrimental to their HRQOL than the disease itself (n = 2). Patients can experience a range of long-lasting and durable side effects from their different MM treatments, including neuropathy (n = 3), fatigue (n = 3), nausea (n = 2), and cognitive dysfunction (n = 2). Steroids (n =7) were particularly burdensome for patients due to the numerous and sometimes severe side effects, including sleep disturbances, weight gain, and the detrimental effect on patients' mood. Treatment expectations were reported by 6 patients in the PRI: hopes and expectations of delaying disease progression and prolonging life are often counterbalanced by the negative consequences and burden of therapies (e.g., side effects/social isolation/financial impact).
Summary/Conclusion: The combination of published literature and PRI provided valuable and rich information on the patient experience and perceptions of MM and its treatment. Frequently reported themes in PRI included the symptom burden and HRQOL impact of MM as well as the burden associated with treatment. These key issues were also illustrated by results of the literature review. The data highlighted that the MM patient journey is multifaceted; patients' HRQOL is impeded not only by the disease but also by the treatment-related side effects, which can have a substantial and long-lasting impact on patients' lives.

PB1670 PHASE 2 MARCH STUDY OF ORAL ATG-010 PLUS LOW DOSE DEXAMETHASONE IN CHINESE PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA PREVIOUSLY EXPOSED TO AN IMMUNOMODULATORY AGENT AND A PROTEASOME INHIBITOR

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Background: ATG-010 (Selinexor) is a novel, oral selective inhibitor of nuclear export inhibiting exportin 1. In preclinical and clinical studies, ATG-010 has demonstrated activity against multiple myeloma (MM). ATG-010 (80 mg biweekly) plus dexamethasone (20 mg biweekly) (Sd) was approved by US FDA for treatment of patients(pts) with penta-refractory MM in 2019 based on the STORM study. MARCH is a single arm, Phase 2 study to assess efficacy and safety of Sd in Chinese pts with relapsed/refractory MM (RRMM) (NCT03944057).
Aims: To evaluate efficacy and safety of oral ATG-010 plus low dose dexamethasone in Chinese pts with RRMM.
Methods: Enrolled pts have been previously treated with and refractory to proteasome (PI), immunomodulatory agent (IMiD), and the last line of therapy. Sd is administered in 4-week cycles. Primary endpoint

is overall response rate (ORR) per independent review committee. The total planned enrollment of 82 pts provides ~80% power to test against H_0 of 15% ORR at one-sided α of 0.025. This abstract provides data from a planned analysis of the first 60 treated pts.
Results: As of 13 Oct 2020, 18 (30%) of the 60 pts were on treatment. Median follow-up was 9.5 months (mo) (range: 1.9-12.8).
Median age was 61 years (range 43-82; 42% > 65). Pts had received a median of 5 (range 1-16) prior MM regimens, with following baseline risk factors: 72% R-ISS II/III, 70% cytogenetic abnormalities, 22% del (17p13),20% renal impairment, 15% prior CAR-T therapy, and 25% pre-treated with daratumumab (considered 'triple-class exposed').
ORR was 26.7% (95% CI: 16.1, 39.7). Median DOR was 4.6 mo (95% CI: 1.42, NE). Median PFS was 3.7 mo (95% CI: 1.92, 4.66). Median OS was not reached; 9-mo OS rate was 68.5%. ORR was 33.3% in triple-class-exposed pts, and 44.4% in pts with prior CAR-T. ORR was generally consistent across subgroups.
Common TEAEs of any grade included: thrombocytopenia (87%), nausea (87%), leukopenia (85%), anemia (85%), lymphopenia (78%), neutropenia (73%), weight loss (72%), hyponatremia (65%), decreased appetite (63%), asthenia (62%)/fatigue (17%), hyperglycemia (53%), vomiting (52%), hypocalcemia (38%), hypokalemia (30%), diarrhea (30%), pneumonia (27%). Common TEAEs of Grade ≥ 3 included: anemia (60%), thrombocytopenia (55%), leukopenia (42%), lymphopenia (42%), neutropenia (38%), hyponatremia (28%), and pneumonia (23%). Thirty pts (50%) had TESAEs, including (>3%): thrombocytopenia (15%), pneumonia (15%), anemia (6.7%), hyponatremia (3.3%). Eight pts (13.3%) had TEAEs leading to treatment discontinuation, including (>2%): thrombocytopenia (5%) and pneumonia (3%). Three fatal TEAEs were pneumonia, intracranial hemorrhage and sudden death (1 each).
Summary/Conclusion: In Chinese RRMM pts refractory to both IMiD and PI, with a highly unmet medical need, MARCH confirms the efficacy of Sd as a promising new oral therapeutic option with a manageable safety profile, which is consistent with STORM.

PB1671 VALIDATION OF THE MYRADS REPORTING CRITERIA USING DATA FROM A PROSPECTIVE IMAGING STUDY IN PLASMA CELL DYSCRASIAS (LOOMIS).

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Background: Cross-sectional MRI imaging has a growing importance in the classification of plasma cell dyscrasias, and in the definition of multiple myeloma (MM) response or progression (Dimopoulos 2015, Chantry 2017). High sensitivity of a diffusion-weighted whole body MRI (DW-WBMRI) in the early detection of bone marrow changes has been acknowledged in the revised IMWG diagnostic criteria (Rajkumar et al, 2014). A multidisciplinary imaging and haematologist expert panel has supported the measurement of cell density using an apparent diffusion coefficient (ADC) for the early diagnosis of changes in bone marrow infiltration and myeloma focal lesions (Messiou 2019). Recommendations for myeloma diagnosis and response assessment has been published (MYRADS) recently. We used data from a prospective plasma cell dyscrasias imaging study (NCT03951220) to validate these recommendations.
Aims: This prospective imaging study used a DW-MRI protocol to quantify longitudinal changes in tumour burden and bone disease. To improve sensitivity of bone marrow lesion identification healthy volunteers (HV) were also recruited. One of the study aims is to validate MYRADS protocol recommendations.
Methods: To validate the recommendations in the MYRADS protocol we took an unselected population of 18 MM pts, 12 MGUS pts and 6 HVs recruited between April 2018 and January 2019. See Table 1 for participants' characteristics. After enrolment patients had a DW-WBMRI abbreviated protocol on the 3T Avanto MRI scanner (Siemens, Germany). In 18 participants with MM and MGUS the scan was repeated after 6 months using the same protocol. Qualitative assessment of bone marrow changes were made using the MYRADS recommendations. In each positive scan (Myeloma patients) we used the changes in ADC value (quantitative) of a single lytic lesion (MYRADS response assessment categories) and matched them with the serological parameters of disease.
Results: All 36 participants safely completed the protocol at baseline. Ten scans (28%) were positive for vertebral fractures (1 to 8 vertebral bodies involved); pathological fractures were associated with known active myeloma only (2 NDMM, 2 RRMM; new fractures in 3/4 cases). Focal lesions were identified in 7 (19%) baseline scans (3 NDMM, 3 RRMM, 1 MGUS), mostly affecting spine and pelvis. Other findings included extraskeletal involvement (2/36), cord compression (1/36) and previous vertebral interventions (3/36 vertebroplasty, 1/36 stabilisation, 1/36 radiotherapy). Bone marrow appearance was normal in all HV scans, focal in 1/12 MGUS scans and otherwise normal, whereas a focal infiltrative pattern and an indeterminate pattern were demonstrated in 2/9 SMM cases. 4/9 of active myeloma cases showed a focal infiltrative pattern. For response assessment, no change was noticed in the patients with normal bone marrow pattern at baseline. No change was noticed in a patient with focal infiltrative pattern who received anti-myeloma treatment with lack of serological response, whereas two patients achieving a complete serological response were in the "highly likely to respond" category based on the change in bone marrow pattern and ADC measurement.

Table 1. Study population

n= 36	
Age *(median)*	40-82 *(65)*
Gender *(%)*	21 M *(58)* 15 F *(42)*
Diagnosis *(%)*	12 MGUS *(33)* 9 SMM *(25)* 5 NDMM *(14)* 4 RRMM *(11)* 6 Healthy volunteers *(17)*
Diagnosis date	April 2014 – February 2019
ISS at diagnosis *(%)* – myeloma cases	10 ISS I *(56)* 8 ISS II *(44)*
Paraprotein/light chain type *(%)* – myeloma, MGUS cases	22 IgG *(74)* 5 IgA *(17)* 1 IgM *(3)* 1 kappa *(3)* 1 lambda *(3)*
Calcium levels at baseline *(%)* – myeloma, MGUS cases Normal range 2.2-2·6 mmol/L	25 normal *(83)* 3 high *(10)* 2 low *(7)*
Alkaline phosphatase levels at baseline *(%)* – myeloma, MGUS cases Normal range 30 – 130 IU/L	28 normal *(93)* 2 low *(7)*

Summary/Conclusion: Using MYRADS recommendations, WB DW MRI serves as a good qualitative discriminator between HV/MGUS and myeloma patient cohorts. In the myeloma cohort, we validated MYRADS recommendations to demonstrate patterns of disease infiltration and disease response categorisation. We aim to report results at the meeting from a larger cohort in the ongoing study.

PB1672 REDEFINING OUTCOMES IN MULTIPLE MYELOMA IN COVID-19 INFECTED PATIENTS. RECONSIDERING THE THROMBOSIS AND INFECTIVE RISK.

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Background: There role and factors about susceptibility to the outcome of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients with multiple myeloma (MM) with a thrombotic event presents numerous challenges. As MM is a disease of the elderly, characterised by immunosupresion, hence, patients with MM might be considered more susceptible to severe complications from COVID-19.
Aims: To evaluate the outcomes in the COVID myeloma hospitalised population.
Methods: We undertook this retrospective study to characterise the baseline and outcome data of COVID-19 infection in 50 patients with plasma cell disorders, collected by two different Trust institutional analysis to identify potential predictors of outcome. Apart from the specific MM-related symptoms, most patients display Infections and thrombosis as more common disease complications, and unfortunately remain a major cause of death.
Patients with MM and confirmed COVID-19 diagnosed between January 2020 to January 2021, Furthermore, corticosteroids, and especially dexamethasone, are used as for hospitalised MM patients.
Results: The 39% presented with severe COVID-19 (need of oxygen and/or intensive care support - admission). Severe COVID-19 was associated

with more advanced age (≥65 years) (odds ratio 3.72 [95% CI 1.79-7.71]). 39.7% with severe COVID-19 were receiving or had recent (≤ 12 months) treatment for MM at the time of COVID-19 versus (patients with mild stable disease. Hospitalisation rate for severe COVID-19 was lower ($p < 0.05$) for patients on oral regimen (IMIDs) and good control paraprotein versus those on other regimens or off treatment.
the median age was 71 years, and all patients received at least one line of previous treatment. Approximately 36% were recently diagnosed (2019-2020), and only 32% of patients were receiving first-line therapy. The mortality associated to admission were approximately 6 % of hospitalised patients. More of the half of the patient (54%) had at leat one previous cardiovascular positive past medical history. In addition, patients were long hospitalised or partially immobilised or 23% patients received previous ESAs (EPO) or severe renal impairment. The principal thrombotic event were segmental pulmonary embolism and in less proportion STEMI, renal infarct or stroke. In the mean time they received LMWH prophylaxis was 4.7 months. After reevaluation of thrombotic risk, most of the patients maintained LMWH with more strict control and in the group with good outcomes switched to DOAC. There were no cases of severe bleeding complications with the use of adequate thromboprophylaxis. Univariate analysis identified age, International Staging System stage III (ISS-III), renal disease, high-cytogenetics risk disease, delays (toxicities) or suboptimal myeloma control (active or progressive disease), and more than two co-morbidities as risk factors for higher rates of death. Neither history of transplant, including within a year of diagnosis, nor other anti-MM treatments were associated with outcomes.
Summary/Conclusion: Age and co-morbidities did impact on mortality, alluding to a relevant role of MM and immunodeficiency. Among hospitalised patients, We did not observe any significant correlation between active PI, IMiD, anti-CD38 monoclonal antibody, alkylating agents, steroids, or other treatments and the COVID-19 outcome.
The management of MM in the era of COVID-19 requires careful consideration of individual approach- and disease-related factors to decrease the risk of acquiring COVID-19 infection, while not compromising disease control through appropriate MM treatment.

PB1673 REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES IN PATIENTS WITH MULTIPLE MYELOMA IN DIFFERENT GEOGRAPHICAL REGIONS: FINDINGS FROM A SYSTEMATIC LITERATURE REVIEW

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Background: The introduction of new agents and classes of therapy has improved outcomes in patients with multiple myeloma (MM). However, there is limited understanding of the variations in use of new therapies across different geographical regions and the extent to which these variations translate into improved outcomes.
Aims: To perform a systematic literature review (SLR) to investigate trends in MM treatment patterns and clinical outcomes reported in published real-world studies.
Methods: Searches were performed in PubMed and EMBASE from January 2010 to November 2020 to identify English-language publications reporting the efficacy and safety of therapies for patients with newly diagnosed MM (NDMM) and relapsed or refractory MM (RRMM) in any geographical region. Relevant conferences in 2019 and 2020 were also searched. The citations were systematically screened in 3 stages following predefined eligibility criteria (PICOs). Data were analysed in MS excel and the relevant data extracted for further interpretation.
Results: A total of 472 publications were identified; 60% were published in 2016 or later. Most reported findings for studies conducted in Europe (n=180 [38%]), North America (n=98 [21%]), or Asia (n=171 [36%]). Almost half (n=222 [47%]) involved patients with RRMM, 41% (n=195) included patients with NDMM and 12% (n=55) had a mix of MM populations. A total of 149 publications described multicentre/claims database/registry studies involving >50 patients. Of these, 28 reported median OS and 23 reported median PFS data. Median OS was 5.2–60.0 months in patients with NDMM and 5.4–41.9 months in patients with RRMM. Median PFS was 10.3–33.6 months in patients with NDMM and 4.9–27.6 months in patients with RRMM. Differences in the most commonly cited regimens were noted between geographical regions (**Table**). In studies reporting outcomes in patients with NDMM, bortezomib-based regimens predominated in Europe and Asia, whereas in US studies, lenalidomide + dexamethasone (Rd)–based regimens and bortezomib-based regimens were equally described. The most commonly described bortezomib-based regimens in Europe and Asia were bortezomib + dexamethasone (Vd), VCd, VMP, and VTD. In studies reporting outcomes in patients receiving treatment for RRMM, Rd and Rd-based triplets (including RVd, KRd, and IRd) were the most commonly used regimens across the 3 regions. Bortezomib-based regimens described in >4 European studies included Vd, VCd, and VTD. Few US or Asian studies described bortezomib-based regimens. Differences in efficacy outcomes according to geographical regions will be presented.

Table. Number of studies [n=109] reporting outcomes with different regimens per geographical region

Regimen	NDMM				RRMM		
	North America	Europe	Australia + Asia	Latin America	North America	Europe	Australia + Asia
Lenalidomide-based							
Rd	5	3	1	0	0	16	6
RVd	6	0	2	0	2	3	0
KRd	0	0	1	0	3	5	0
IRd	0	0	1	0	1	4	1
Bortezomib-based							
Vd	5	7	9	0	1	10	2
CyBorD	1	0	2	2	0	0	0
VCd	3	6	5	1	1	4	1
VMP	0	6	7	0	0	2	0
VTD	2	6	6	2	0	6	1
PAD	0	3	6	0	0	3	0
Others							
KPd	0	0	0	0	1	0	1
Kd	0	0	1	0	2	2	1
DARA	0	0	0	0	2	3	0
CTD	0	5	3	0	0	2	2
MPT	0	4	3	0	0	1	2
VAD	1	6	11	0	0	2	2

CyBorD, cyclophosphamide-bortezomib-dexamethasone; CTD, cyclophosphamide-thalidomide-dexamethasone; DARA, daratumumab; IRd, isazomib-lenalidomide-dexamethasone; Kd, carfilzomib-dexamethasone; KPd, carfilzomib-pomalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; MPT, melphalan-prednisolone-thalidomide; PAD, bortezomib-doxorubicin-dexamethasone; Rd, lenalidomide-dexamethasone; RVd, lenalidomide-bortezomib-dexamethasone; VAD, vincristine-doxorubicin-dexamethasone; VCd, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.

Summary/Conclusion: The findings from the SLR indicate that, over the last 10–15 years, there have been differences in the reported use of the new therapies and regimens in different geographical regions, particularly between North America vs Europe and Asia. Reported survival outcomes differ widely between different studies, possibly reflecting differences in regimens used and patient management. Understanding these differences in real-world clinical practice and their outcomes will help inform clinicians of the optimal use of available treatments, identify unmet needs, and help further improve long-term outcomes for patients.

PB1674 PARATHYROID HORMONE LEVELS AND PROGNOSIS IN MULTIPLE MYELOMA?

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Background: Based on anecdotal reports of raised serum parathyroid hormone (PTH) levels in some patients with multiple myeloma, we set out to investigate if this is a common finding.
Aims: To establish if parathyroid hormone levels act as predictors of outcome in multiple myeloma.
Methods: Patients with newly diagnosed multiple myeloma at Cambridge University Hospitals between 2015 and 2021 were identified from electronic records (EPIC). Blood parameters including paraprotein, PTH, beta-2 microglobulin (β2M), albumin and others, recorded near the time of diagnosis were collected. We use the International Staging System (ISS), defined as, ISS stage I: β2M < 3.5 mg/L and albumin ≥ 35 g/dL, ISS stage II: neither I or III, ISS stage III: β2M ≥ 5.5 mg/L and our novel 'ISS+PTH' score, calculated from a sum of: β2M < 3.5 mg/L (0), ≥ 3.5 mg/L (1); PTH < 10 pmol/l (0), ≥ 10 pmol/l (1); albumin < 35 g/dL (1), ≥ 35 g/dL (0). We use Pearson correlation and Kaplan-Meier survival analyses to investigate factors that correlate with PTH levels and assess their impact on prognosis.
Results: We identified 1066 patients with multiple myeloma (640 men/426 women). Median age at diagnosis was 70 years and median survival was 832 days. Of these, 182 had PTH levels assayed at diagnosis. Median serum PTH level was 4.77 pmol/l (range 0-103.3 pmol/l) and 35 patients had PTH >10 pmol/l. Median survival for those with PTH >10 pmol/l was 859 days, compared to those with PTH <10 pmol/l, with a median survival of 1495 days ($p<0.229$). PTH level significantly correlated with creatinine and other parameters (Table 1A).

To understand if PTH levels can enhance the predictive power of the International Staging System (ISS), we compared the performance of the ISS score to a modified score including PTH as a variable, applied to participants for whom all relevant tests were available. We noted that β2M and albumin levels correlated significantly to each other (r=-0.37), raising the possibility that additional variables could be used to refine prognosis. Therefore, we tested if PTH could be added to ISS and re-stratified patients into 4 categories (Table 1B). Upon incorporation of PTH, we found that distribution across the classes was similar, but the worse prognostic group faired significantly worse (Table 1B). As noted by the mean survival differences between ISS and ISS+PTH, we observed better separation of the categories on survival curves by the latter. Of particular note, 17 patients with a very high PTH (>15 pmol/l) had a significantly poorer mean survival of 368 days and high median values for albumin (28.5 g/L), β2M (12.2 mg/L), creatinine (258 umol/L) and Corrected Calcium (2.35 mmol/L).

(A) Significant Correlations to PTH	R value	Unsignificant Correlations to PTH	R value
Creatinine	0.520**	Phosphate	0.110
Urea	0.439**	Age at diagnosis	0.079
Potassium	0.326**	ALP	0.043
β2M & Lambda free light chain	0.192*	Sodium	0.033
Vitamin D	-0.185*	Albumin	0.015
Adjusted calcium	-0.222*	Kappa/Lambda ratio	-0.023
Paraprotein	-0.226*	Survival	-0.128
(B)		Number of patients	Mean survival
Score (ISS)	I	67 (23.8%)	1651
	II	192 (68.3%)	1360
	III	22 (7.8%)	1152
Total score (ISS+PTH)	0	50 (27.6%)	1480
	1	65 (35.9%)	1712
	2	54 (29.8%)	1108
	3	12 (6.6%)	823

Table 1: Comparison of ISS and ISS-PTH prognostic scores
A. Correlations to PTH, * significant. **B.** Numbers per class and mean survival (days) for patients classified using the ISS and ISS+PTH scores.

Summary/Conclusion: Collectively, our findings show that PTH levels correlate with other parameters and do not significantly improve the prognostic ability of the ISS score overall, but do identify a group with particularly poor prognosis. PTH has a very short half-life of 5 minutes, as it is rapidly cleared by the liver and kidney, so the correlation with creatinine and urea may allude to renal failure being at least partially responsible for PTH accumulation. In addition, our findings show that PTH levels in multiple myeloma are often inappropriately elevated in relation to the prevailing calcium level, a factor that can contribute to the cytokine-driven myeloma bone disease. Therefore, will next investigate the impact of inappropriately raised PTH on myeloma bone disease per se and any clinical/therapeutic implications this may have on patient management.

PB1675 DEMOGRAPHIC, CLINICAL, AND PROGNOSTIC CHARACTERISTICS OF PRIMARY PLASMA CELL LEUKEMIA IN LATIN AMERICA, A STUDY OF GELAMM GROUP.

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Background: Primary plasma cell leukemia (pPCL) is an infrequent plasma cell disorder that accounts for 1.3%–3.4% of all plasma cell dyscrasias. Its prognosis is poor, with a median survival of 36 months, even after the use of novel drugs. The ideal treatment is not well established. There is scarce data on this disorder in Latin America (LA).

Aims: The aim of this study was to describe demographic, clinical and prognostic characteristics of newly diagnosed pPCL in LA.
Methods: This is a retrospective, multicentric observational study. Patients from 9 countries of LA with diagnosis of pPCL between 2012 and 2020 according to current definition were included. Demographic and clinical data were collected from clinical records. Survival curves were estimated using the Kaplan–Meier method. Uni- and multivariable Cox proportional hazards models were used to assess risk factors.
Results: Sixty patients from Chile, Argentina, Ecuador, Cuba, Perú, México, Paraguay, Colombia and Uruguay were included. Median age was 55 years (range 28 to 92), 53% were male. Anemia was present in 83% at diagnosis (mean 8.1 g/dL), hypercalcemia in 47% (mean 11 mg/dL), renal failure in 50% (mean 2,6 mg/dL of creatinine), thrombocytopenia in 53% (mean 105.000/mm^3) bone lytic lesions in 80%. High LDH was observed in 72%. Extramedullary disease was reported in 28% of patients, 3 of them with CNS involvement. Type of paraprotein was IgG in 33%, IgA in 13%, light chain in 45% (55% Kappa), and not reported in 9%. Flow cytometry was performed in 78% of patients, and FISH and conventional cytogenetics in 28%.
Five patients died before receiving any specific treatment. Most patients (83%) were classified as eligible for transplant and received at least 1 cycle of treatment. Thirty-two patients received a bortezomib-based induction, and 17 an intensive chemotherapy-based approach, like VTD-PACE. The most used regimens were CyBorD in 26%, VTD-PACE in 22%, VAD in 16%, and CTD in 14%. Only 1 patient received daratumumab-based therapy. Five patients died during induction, and 12 achieved a complete remission. Twelve patients (24%) received an autologous transplant as consolidation, in 7 cases with tandem modality, and 19% had maintenance therapy. Eleven patients relapsed.
With a median follow up of 16 months, 35 patients (58%) died, and 12 patients remained in complete remission. Median progression free survival (PFS) was 11 months (CI95% 4-18) for the whole cohort, while in patients that receive a bortezomib-based treatment median PFS was 22 months (CI95% 8-73). Median overall survival (OS) was 18 months (CI95% 9-59), and not reached for patients with bortezomib-based induction.
In the multivariate analysis (Table 1) only proteosome inhibitor (PI)-based induction was an independent factor of improved OS.

	Overall Survival – Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Age > 60 years	1.18	0.58 - 2.39	0.645	1.54	0.66 – 3.60	0.315
Female Sex	1.62	0.82 – 3.20	0.163			
PS ECOG > 2	1.28	0.59 - 2.79	0.525			
Extramedullary Disease	**2.27**	**1.05 – 4.93**	**0.036**	1.09	0.44 – 2.71	0.843
Renal Failure (Cr > 2 mg/dl)	1.11	0.56 – 2.23	0.750			
Anemia (Hb < 10 g/dl)	2.02	0.70 – 5.81	0.191			
PC in peripheral blood > 20.000/mm3	1.26	0.54 – 2.95	0.584			
Platelets < 100.000/ mm3	1.58	0.78 – 3.23	0.202			
Calcium > 11 mg/dl	0.85	0.42 – 1.71	0.654			
High LDH	1.61	0.71 – 3.60	0.247			
Albumin < 3.5 g/dl	**2.90**	**1.34 – 6.25**	**0.007**	2.18	0.84 – 5.68	0.109
PI-based treatment	**0.35**	**0.17 – 0.74**	**0.006**	**0.40**	**0.17 – 0.94**	**0.036**
Maintenance treatment	**0.25**	**0.09 – 0.68**	**0.007**	0.32	0.10 – 0.99	0.32
CR or better	**0.26**	**0.08 - 0.89**	**0.032**	0.28	0.07 – 1.10	0.07

Summary/Conclusion: As reported internationally, LA patients with pPCL were younger than myeloma patients, and clinical features at diagnosis show a more aggressive disease. Of notice, they show more bone lesions than classically described. Reasons for this finding have not been addressed in this analysis. Whether this can be attributed to the use of more sensible imaging techniques or to late diagnosis remain to be elucidated. Frontline therapies were heterogeneous, and autologous transplant were performed in only one quarter of patients. Reasons for 76% of potential candidates not being transplanted merit further analysis. OS is still very poor. Bortezomib-based therapies were associated to improved OS.

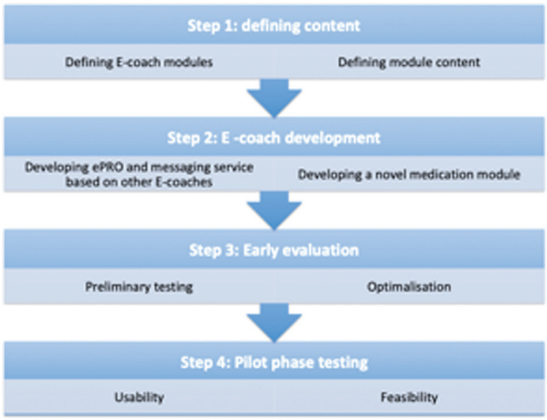
PB1676 DEVELOPING A MULTI-MODULE E-HEALTH APPLICATION FOR PATIENTS WITH MULTIPLE MYELOMA RECEIVING COMPLICATED TREATMENT REGIMENS.

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Background: Digital applications in healthcare (e-health) are increasingly used. In solid oncology, implementing electronic patient-reported symptom monitoring was associated with improved survival. Currently, medication support applications are not available. Patients with multiple myeloma are faced with complicated treatment regimens. They may receive various treatment lines containing several anti-myeloma and

supportive care medications. Treatment is based on tumor and patient characteristics, but also on patient preferences and side effects.
Aims: To explore the needs of patients with Multiple Myeloma and their health care providers, with regard to supportive care using eHealth. Additionally, to design an eHealth application to address these needs and evaluate its usability and feasibility.
Methods: This study was performed in a large non-academic hospital, collaborating with an experienced E-Coach developer. First, to define the current standard of care the Multiple Myeloma treatment pathway was identified within a value based healthcare (VBHC) trajectory. Second, health care providers' (physicians, nurses, pharmacists and supportive staff) needs were explored during five focus group sessions. Patients and their spouses participated in the third session. The focus group topic agenda was based on the VBHC trajectory outcome and on two surveys amongst 18 patients with Multiple Myeloma. The first survey explored the current experience with care delivery and the needs for the eHealth application. The second evaluated potential patient reported outcomes (PROs), based on the EORTC QLQ-C30, MARS-5 and patient reported experience measures (PREMs). Finally, the application, called the 'E-Coach', was developed in a multi step process (figure 1): step 1, defining content; step 2, e-coach development; step 3, early evaluation; and step 4, pilot phase testing.
Results: Two sets of PROs were defined. First, a large set of PROMs and PREMs to perform periodic evaluations at large intervals (e.g.: 3 or 6 months). Second, a short list of PROs and one blank space for personal suggestions to prepare outpatient clinic visits. The participants expressed a need for medication support and overview and for a messaging service. The application was developed, using several modules. The messaging and PRO questionnaire modules were integrated in already existing application modules. Additionally, the medication module was developed during an iterative process with the health care providers. Then, a first version of the Multiple Myeloma E-coach was tested in a pilot study. During eight weeks, the application was used by twenty patients and a clinical multidisciplinary team (clinicians, nurses and pharmacists). Eighty-three percent of participants were satisfied using the E-coach. Fifteen recommendations were done for improvements, such as individualizing the built-in tool to check when medicines had been taken. Some patients preferred to check every medicine they took; others preferred to check several at the same time. The health care providers recommended creating a dashboard, for overview of all PROs and medication adherence. Based on all recommendations, the E-coach was adapted.



Summary/Conclusion: Using an approach that involved all relevant stakeholders, we developed a multi-module E-coach for patients with Multiple Myeloma receiving complicated treatment regimens. Most notable, we developed a medication module for support and overview of medication. To further evaluate the E-coach, a randomized controlled trial is planned to compare implementation of the E-coach with regular care (EudraCT 2020-005267-31).

PB1677 IMMUNOPHENOTYPIC PROFILE AND CLINICAL CHARACTERISTICS OF PRIMARY AND SECONDARY PLASMA CELL LEUKEMIA

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Background: Plasma cell leukemia (PCL) is rare, aggressive plasma cell (PC) disorder, characterized by presence of circulating PC (cPC) in peripheral blood (PB). PCL can be divided in 2 groups - primary PCL (pPCL) which originates *de novo* and secondary PCL (sPCL), a leukemic transformation of MM. Detection of cPC by flow cytometry (FC) is important for early diagnostics and for distinguishing PCL from reactive plasmacytosis as well, but less about PCs phenotype profile is known.
Aims: Analyses of differences in number and phenotypic profile PCs between pPCL and sPCL aiming at their association with clinical outcomes and evaluation of the prognostic value of PCs immunophenotype.
Methods: Investigation of PB and/or bone marrow (BM) of 18 pPCL and 15 sPCL patients was done by FC. Expression of surface antigens (CD19, CD20, CD27, CD28, CD44, CD56, CD81, CD117 and CD200) with intracellular nestin was studied. Medians of relative expression and positivity (cut-off 20%) were used.
Results: There were found no significant differences in clinical characteristics of pPCL and sPCL patients except increased level of platelets in pPCL compared to sPCL (median 129.5 vs 49.1x10^9L, p=0.004, respectively). Median OS was 17.6 months in pPCL, 0.9 months in sPCL; (p<0.001). Significantly higher number of cPCs was identified by FC when compared to morphology (26.7 vs 13.5%, p=0.02). The number of cPCs was lower in pPCL than in sPCL (25.1% vs. 30.2%), the number of PCs in BM was significantly lower in pPCL than in sPCL (39.2% vs. 64.9%; p=0.02).
Phenotypic profile of pPCL was very close to sPCL in PB and/or BM, although there were some alterations. Unlike pPCL, no CD19 and CD20 positive patients were detected in sPCL. Interestingly, co-expression of CD28 and CD56 with no expression of CD117 was observed in 75% (3/4) $CD20^+$ pPCL cases. Low level of expression and similar positivity of CD27, CD28, CD81, and CD117 were found in PB and/or BM of both PCLs. On the other hand, missing CD56 was not a dominating event in both PCLs, although its decreased expression was found in PB when compared to BM. Lower CD200 expression was found in sPCL when compared to pPCL in PB (51.5% vs 99.7%) and similarly in BM. Positivity of nestin was similar for both PCL, but lower expression was found in PB of pPCL (9.3% vs. 32.0%). Total lack of CD20 and higher difference in number of $CD81^+$ PC in BM compared to PB was associated with higher risk of death. Patients with platelets below 70x10^9/l had 3.9 times higher risk of death, patients with ECOG 2–3 had three times higher risk of death compared to patients with ECOG 0–1.
Summary/Conclusion: Even when limited number of PCL patients was analyzed, it was proved that polychromatic FC analysis of cPCs is more accurate than morphology assessment and should be used diagnostics of all patients suspected with PCL. Phenotype differences were mostly not significant in both PCLs, but lack of CD20 and decreased CD81 in PB seems to be risk factors of shorter survival.
Supported by grant AZV NV18-03-00203.

PB1678 CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA

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Background: Carfilzomib is an epoxyketone proteasome inhibitor of second generation, proved to be effective and safe in relapsed and refractory Multiple Myeloma (rrMM), in combination with dexamethasone or lenalidomide and dexamethasone.
Aims: In this retrospective observational trial, it has been evaluated efficacy and safety of carfilzomib, in combination with lenalidomide-dexamethasone (KRD) as salvage regimen in patients with rrMM, refractory to lenalidomide, where lenalidomide-based regimens have no proven efficacy.
Methods: 41 patients (23 M/18 F), with rrMM, median age at diagnosis 63.7 years (r. 43-82), median age at start of treatment 67 years (r. 48-84) previously treated with several lines of treatments (median 3, r. 2-11), underwent to KRD regimen (ASPIRE trial schedule) for a median treatment cycles of 8 (r 2-18). ISS was equally distributed, and all patients had previously

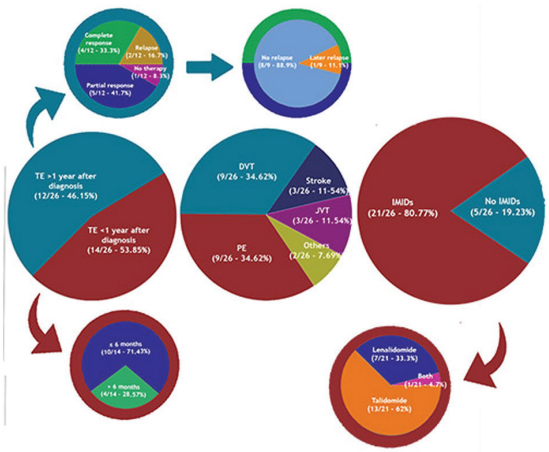
been treated with bortezomib and IMIDs, and were refractory to this agents. 61% (19/31) of them had undergone at least to a single ASCT.
Results: According to IMWG criteria, after a median follow-up of 9 months (r. 2-18), ORR was 68,2% (28/41: 9 CR, 12 VGPR, 7 PR) with 5 progressive diseases (PD) and 8 patients in stable disease (SD): this can be considered as an impressive result in this subset of rrMM patients, refractory to lenalidomide. In particular, for 11 patients, KRD was, after having achieved at least a PR, a bridge to second/third autologous SCT. Median time to response was 1.3 months (r.1-4), median OS from diagnosis was 62 months (r. 9-170), median OS from start of Carfilzomib was 11 months (r. 2-18). Carfilzomib was well tolerated, with grade 2 anemia in 39%(16/41) of patients, successfully managed by ESAs, without necessity of blood transfusions; 29% (12/41) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedalization was required, no septic shocks were observed); 34% (14/41) grade 2, 21% (9/41) grade 3 and 12% (5/41) grade 4 thrombocytopenia, without hemorrhagic events and transfusion-dependency. Moreover, it was observed pneumonia in 39% (16/41) of patients, treated by common antibiotic drugs and always solved. A cardiac monitoring was performed for all patients: hypertension (grade 2-3) in 34% (14/41) of patients; fatigue in 39% (16/31) of patients.
Summary/Conclusion: Carfilzomib-Lenalidomide-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, also lenalidomide, and it could be considered as a bridge to a second autologous or allogenic SCT.

PB1679 PREVALENCE OF THROMBOTIC EVENTS IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH IMIDS.

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Background: Multiple myeloma (MM) induces a hypercoagulability state which increases the occurrence of thrombotic events (TE). The common usage of immunmodulatory imide drugs (IMIDs) has had a relevant prognostic impact in patients with multiple myeloma, although a major risk of TE has been detected throughout the years. Besides, therapeutic strategies including high-dose corticosteroids, central venous catheters and comorbidities already present at the usual age of debut of the disease (such as diabetes, high blood pressure, obesity, dyslipidemia or coexistence of previous neoplasms) also cast an increased risk of TE.
Aims: Describe the incidence of thrombotic events in MM patients treated with IMIDs in our hospital.
Methods: 287 patients diagnosed from 2014 to 2021 were reviewed. Further risk factors, lines of therapy and antithrombotic prophylactic measures were also included.
Results: Of all the patients reviewed (287), 26 developed TE (9.06%). Out of these events, 14 occurred in the first year after the diagnosis (53.85%). Of all these cases, 19 (73.08%) featured more than one additional risk factor. Furthermore, 21 (80.77%) had received IMID-based therapies. Most common events were pulmonary embolism (9 - 34.62%), deep vein thrombosis (9 - 34.62%), strokes (3- 11.54%) and jugular venous thrombosis (3 - 11.54%) followed by other events (2 - 7.69%).



Summary/Conclusion: Prevalence of TE in MM patients in our institution is 9.06%, with a high proportion of them (80.77%) receiving IMID-based therapies and occurring in the first year after the diagnosis (53.85%).
Most of the events developed despite the usage of prophylactic antithrombotic measures, hence early high-risk prophylactic measures should be mandatory in MM patients treated with IMID-based therapies.

PB1680 RENAL IMPAIRMENT IN MULTIPLE MYELOMA: CHARACTERISTICS AND OUTCOMES OF 55 MOROCCAN PATIENTS

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Background: Renal impairment occurs in 20 to 50% of newly diagnosed multiple myeloma (NDMM) patients. It is associated with worse outcome of the disease. The recent use of new agents and the development of novel techniques of light chain removal have been associated with improved renal and patient outcomes in MM patients. Nevertheless, dialysis-dependent patients with MM have higher mortality than other dialysis patients.
Aims: The aim of this study was to describe renal impairment in patients with MM at time of diagnosis and to investigate renal response factors and overall survival.
Methods: This retrospective study analyzed the medical records of all patients newly diagnosed with MM between January 2008 to November 2020 at the Nephrology department of the military Hospital in Morocco. Diagnosis of MM was based on the IMWG 2014 criteria. We collected patients' data as age, sex, presenting symptoms, hematological and laboratory features. Renal impairment was defined as serum creatinine >2 mg/dl or eGFR<60 ml/min/1,73 m^2 and/ or elevated proteinuria/ creatinuria (>0,5 g/g). We reported renal biopsy results, anti-myeloma treatment. We evaluated the hematological and renal response and overall survival. Descriptive statistics of continuous variables were presented as medians. Survival curves were constructed according to the Kaplan-Meier method, and the curves were compared using log-rank test. Cox proportional hazard analysis was used to identify factors influencing the overall survival.
Results: Fifty-five NDMM patients with initial RI were included. The median age was 60 years. Sex ratio was 2,6. Sixteen patients (29.1%) had light chain Lambda myeloma, 15 (27.3%) had monoclonal IgG kappa MM. Thirty patients had stage 5 CKD and 44 (80%) had serum creatinine 2>mg/dl. Seventeen (35.5%) patients required dialysis at the diagnosis. Twenty seven (49%) patients had a kidney biopsy. Cast nephropathy was reported in 15 cases, Randall-type monoclonal immunoglobulin deposition disease in 7 patients and renal amyloidosis was found in 5 patients. The treatment regimens included a CTD in 19 patients (35.8%), VTD in 13 patients (24.5%) and VAD in 12 patients. Seven patients were referred for stem cell transplantation. Hematologic and renal responses were observed in 31 patients (76.5%) and 34 patients (60.7%) respectively. Dialysis was withdrawn in one patient only. Patient sub-groups with and without renal response were similar in age, gender distribution, LDH levels, thrombocytopenia and histological type. Serum creatinine was >2 mg/dl in 60% of patients who did not achieve renal response versus 40% in patients achieving renal response (p=0.02). The renal response rate in the group treated with bortezomib based regimens was slightly superior compared with the group not treated with bortezomib (p=0,07). Only multivariate analysis only female sex and Bortezomib use appear to be associated with renal response. In a mean follow-up of 17 months 25 patients died (51.9%). The median overall survival from diagnosis was estimated at 35 months. In a univariate analysis, age, gender, thrombocytopenia, LDH, renal response and treatment with bortezomib were not found to influence OS. In multivariate analysis a serum creatinine > 2 mg/dl was significantly associated with decreased OS (p=0.03).
Summary/Conclusion: Our study showed a dismal outcome and a short survival in of NDMM with RI in our center. Mainly because a large proportion of our patients did not receive new agents in front line therapy and only a few were transplanted. This study emphasise also the importance of bortezomib based regimens in this setting.

PB1681 FIRST-LINE TREATMENT OF OLDER PATIENTS WITH MULTIPLE MYELOMA (MM) WITH BORTEZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (VCD)

K. Liapis [1,*], F. Panitsas [2], S. Hatzileontiadou [3], S. Papadakis [4], I. Liapis [4], G. Vrachiolias [1], A. Bouchla [5], E. Hatzimichael [6], N. Gianakoulas [7], E. Hatziharisi [3], A. Bilalis [8], C. Misidou [1], A. Sherif Damadoglou [1], G. Melissinidis [1], E. Mpogatsa [1], C. Roubakis [1], I. Xilouri [4], V. Pappa [5], E. Papadaki [4], M. Papaioannou [3], I. Kotsianidis [1], E. Spanoudakis [1]

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Background: First-line treatment with VCD is well-studied in transplantation-eligible younger patients with MM (overall response rate [ORR] 83%, with 56% achieving ≥VGPR). Although VCD has not been approved by the European Medicines Agency for untreated older patients with MM, its use is recognized in the current ESMO guidelines. There have been few systematic studies of VCD in older patients with MM and data on its efficacy and safety is limited.
Aims: We did a retrospective, multicenter, cohort study of newly-diagnosed older patients with MM treated with VCD.
Methods: We identified all newly-diagnosed patients with MM aged ≥70 who were treated with VCD in six Greek hospitals between 2007-2020. We used Kaplan-Meier curves and Cox regression for the primary outcomes (overall survival [OS] and progression-free survival [PFS]).
Results: A total of 99 patients (52 men; 47 women) were included in our study. Median age was 76 years (range, 70-92). 16 patients (16.2%) aged ≥80 years. Performance status (PS) was ≥2 in 44 patients (50%). The median Charlson Comorbidity Index (CCI) was 4 (range, 2–9); 51.6% had multimorbidity (CCI≥4). 46 patients (54.8%) had ISS 3 and 37 (37.8%) had high LDH. Renal impairment was seen in 27 patients (27.3%). Median follow-up was 25.3 months (IQR 8.9–49.4), during which 25 (25.2%) patients died. The median number of VCD cycles received was 6 (IQR 4–7). Most patients received weekly VCD (61.2%). Bi-weekly VCD was given in 38.8%, mainly as initial treatment (cycles 1-2). 22 patients (23.1%) received ≥8 cycles. Maintenance therapy was given in 24.7%. ORR was 83.6%, including CR 25.3% (23/91), VGPR 28.6% (26/91), and PR 29.7% (27/91). Stable disease occurred in 11% (10/91) and progressive disease in 5.5% (5/91). VCD produced rapid responses (median time to ≥PR: 2 cycles [range, 1-6]). We saw no difference in ORR in patients aged ≤75 vs. >75 years (P=0.845). Median OS was 62.7 months (IQR 28.9–98.4); 2-year OS was 80.4%. Median PFS was 26.6 months (IQR 9.7–46.6) and 18-month PFS 58.8%. We noted no difference in PFS between patients ≤75 years vs. > 75 years (P=0.999), ISS 3 vs. 1-2 (P=0.99), LDH (P=0.57), and CCI (P=0.70). Significant baseline risk-factors associated with OS in the multivariate analysis included ISS (HR 4.46, 95% CI 1.35–14.7; P=0.014), PS (3.19, 1.02–10; P=0.047), LDH (5.3, 1.16–24.2; P=0.031), plasmacytomas (7.4, 1.8–30.6; P=0.006), and amyloidosis (8.5, 1.37–53; P=0.021). Subjectively VCD was well tolerated (7 patients discontinued VCD). Bortezomib dose was reduced in 23.9% (22/92). Grade ≥2 peripheral neuropathy occurred in 19.3% (19/98), grade 3/4 myelosuppression in 4.4% (4/91). Systematic G-CSF was used in 2 patients (2.2%). 42.4% of patients relapsed after VCD. Lenalidomide-dexamethasone was the most common second-line regimen (ORR 58.3%).
Summary/Conclusion: Our results show that VCD is a safe, feasible triplet for older patients with MM. It enables a high proportion of patients to achieve ≥VGPR (53%) and can be continued for >8 cycles for enhanced disease control. It is associated with long remissions (PFS 26.6 months) and may be given by nonintravenous route, which is particularly important for older patients.

PB1682 SKELETAL RELATED EVENTS IN MULTIPLE MYELOMA: A RETROSPECTIVE SINGLE CENTRE ANALYSIS

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Background: A risk-adapted algorithm for mitigation of skeletal-related events (SREs) in myeloma can help guide intensity and duration of bisphosphonate (BP) therapy.
Aims: The aim of study was to investigate characteristics of SREs and associate clinical with any laboratory factors which might predict a higher SRE risk in plasma cell dyscrasias.
Methods: Patients receiving treatment for plasma cell disorders between January 2016 and December 2020 were retrospectively identified. SREs were identified and defined as: humeral, femoral, vertebral, rib and other fractures, skeletal and pain-related procedures. Skeletal events were divided into 5 periods: A: occurring between presentation and induction; B: occurring from initiation to end of induction; C: from end of induction till biochemical relapse, D: from biochemical relapse/progression to second-line therapy; E: second-line therapy onwards.
Results: Included were 113 patients, with a median age of 66 years (range 28–83 years) of whom 44 were female and 69 were male. The diagnoses were: 108 active myeloma, 3 solitary plasmacytomas, 2 plasma cell leukaemia and 1 POEMS. Ninety (79.6%) patients received zoledronic acid, 6 (5.3%) received pamidronate, 5 (4.4%) received both drugs. Twelve (10.6%) patients did not receive BP.
There were 128 SREs identified during follow-up, with a median of 1 SRE per patient. Sixty-four (56.6%) patients experienced SREs: 23 (20.4%) had 1 SRE, 26 (23.0%) had 2 SREs, nine (8.0%) had three SREs, four (3.5%) had four SREs and two (1.8%) patients had five SREs. These occurred as follows: Period A: 53 (41.4%) SREs; Period B: 45 (35.2%), Period C: 22 (17.2%), Period D: 2 (1.6%) and Period E: 6 (4.7%) events. SREs included: 60 (46.9%) vertebral fractures, 21 (16.4%) radiotherapy treatments, 13 (10.2%) hospitalisations with bone pain, 8 (6.25%) rib fractures, and 11 (8.6%) orthopaedic and pain procedures. Three (2.7%) had cord compression, comprising 2.3% of SREs.There was no significant difference in the interval between diagnosis and administration of first dose of BP between the patients with SREs and those without.
Patients with SREs likely to be younger (median age 63.5 years vs 69 years, ***P*=0.002**), have light chain myeloma (***P*=0.025**) and more than 4 lytic lesions on baseline imaging (**P<0.001**). There was no significant difference with respect to gender, immunoglobulin isotype, light chain type, ISS stage, cytogenetics, presence of hypercalcaemia, anaemia or renal impairment at diagnosis, and baseline alkaline phosphatase level. There was no difference in OS between those experiencing SREs and those who did not (***P*=0.555**).
Summary/Conclusion: Our study found an SRE rate comparable to other European countries. Most occurred early following diagnosis. Baseline characteristics associated with increased risk of SREs include younger age, light chain myeloma and more than four lytic lesions on imaging. Identification of baseline risk factors for SREs may help us move towards a risk-adapted strategy.

PB1683 FREQUENCY AND PROGNOSTIC SIGNIFICANCE OF MEDITERRANEAN FEVER GENE MUTATIONS IN MULTIPLE MYELOMA AND OTHER PLASMA CELL NEOPLASMS

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Background: Mediterranean FeVer (MEFV) gene, a member of a highly conserved gene family that regulates embryonic development, hematopoiesis, oncogenesis, and inflammation, encodes pyrin protein, an important regulator of apoptosis, inflammation and communication between cytokines. The relationship of MEFV gene mutations with malignancies is an intriguing issue. It is suggested that MEFV gene mutations may cause a decrease in apoptosis, increase in inflammation and nuclear factor-kappa B (NF-kB) activity by disrupting the structure of normal pyrin protein and its interaction with other proteins. The role of increased NF-kB activity in the pathogenesis of multiple myeloma (MM) is well defined. However, there is no information that MEFV mutations may play a role in the pathogenesis of MM through a decrease in apoptosis and an increase in NF-kB activity.
Aims: In our study, we aimed to investigate the frequency of MEFV gene mutations in MM and the effect of these mutations on the disease prognosis.
Methods: Sixty-five patients diagnosed with plasma cell neoplasia followed in our hematology department were included in the study. MEFV

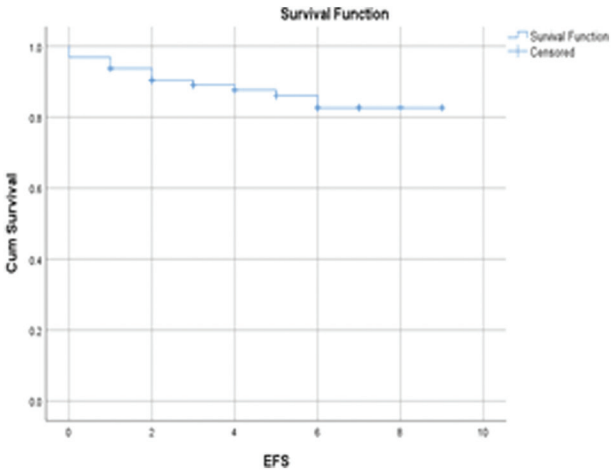
gene mutation analyzes were performed from the blood samples of all patients. The gene mutation frequency was compared with the results of 186 healthy individuals. The clinical characteristics and survival rates of patients with and without mutations were compared by evaluating the data obtained from the patient files.
Results: Fifty five patients diagnosed with multiple myeloma, and ten patients diagnosed with monoclonal gamopathy of undetermined significance, solitary plasmacytoma, smoldering myeloma and amyloidosis were included in our study. MEFV gene mutation was observed in 11 (16.92%) patients in all patient group and it was found that the frequency did not increase compared to the control group. Nine MEFV gene mutations were found in eight patients (14.54%) in the MM group and it was observed that the frequency did not increase compared to the control group. However, it was found that the frequency of E148Q mutations decreased significantly compared to the control group (1.88 % versus 10.71 %), but the difference remained within the statistical significance limit (p=0.0524). When the clinical data of patients with and without mutations in the MM patient group were compared, it was observed that there was no significant difference between the two groups in terms of International Staging System (ISS) stages, anemia and the frequency of renal involvement. In the survival analysis, there was no statistically significant difference between the 2 groups in terms of 3-year progression-free survival and overall survival rates.
Summary/Conclusion: In our study we found that there is no increase in the frequency of MEFV gene mutations in MM patients compared to the control group. However, the frequency of the E148Q mutation was significantly reduced in the patient group compared to the healthy control. We also observe that carrying the MEFV gene mutation does not have a significant effect on the clinical course and survival of the disease. However, due to the low number of patients with mutations, it seems necessary to conduct studies involving more patients for a more accurate evaluation. The fact that the frequency of E148Q mutations is significantly lower in MM patients compared to the healthy control group seems to be an area that needs to be investigated and confirmed by studies involving more patients, especially in order to understand the role of this gene mutation in the malignant transformation process.

PB1684 DARATUMUMAB IN TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA – EXPERIENCES OF THE CROATIAN COOPERATIVE GROUP FOR HEMATOLOGIC DISEASES (KROHEM)

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Background: Multiple myeloma (MM) remains uncurable disease, with multiple relapses and clone evolution leading to refractoriness. However, recently significant therapeutical advancements were achieved leading to improvement of patient's survival.
Aims: The aim of this analysis was to show real world data on treating multiple myeloma patients with relapsed/refractory (RR) disease with daratumumab.
Methods: We performed a retrospective analysis of outcomes of MM patients treated with daratumumab, in combination with bortezomib and dexamethasone (DVd) or lenalidomide and dexamethasone (DRd) in 13 Croatian hematology centers in the period between June 2019 and February 2020 (daratumumab available and reimbursed since June 2019).
Results: A total of 96 patients with RR myeloma were included. Median age at the start of daratumumab treatment was 66.5 years (range 41 – 86). There were 41 male and 57 female subjects. Median number of previous lines of therapies was 3 (range 2 – 8). 49 patients (51%) previously underwent autologous stem cell transplantation (ASCT) in the first line of treatment (12 patients received tandem ASCT) and 16 patients (17%) as salvage ASCT (6 patients had tandem ASCT). 57 patients (59%) were bortezomib exposed and 31 (32%) lenalidomide exposed. DVd was administered to 36 patients (38%) and DRd to 60 patients (62%). In the DVd group response rate (better or equal to partial response; PR) was 72%, while in the DRd group response rate was 76%. After a median follow up of 6 months, median progression free survival (PFS) was not reached in both groups. During the study, hematologic toxicities were reported for the entire group: anemia, thrombocytopenia and neutropenia in 30, 27 and 26 patients, respectively. Infective complications were reported in 21 patients in total. During the study 12 patients died.



Summary/Conclusion: This real-world data analysis confirms that in the setting of RR MM daratumumab has significant efficacy with acceptable and manageable toxicities. Our data support previously reported clinical trials data.

PB1685 LENALIDOMIDE VERSUS THALIDOMIDE OR BORTEZOMIB AS MAINTENANCE REGIMEN FOR NON-TRANSPLANT PATIENTS WITH MULTIPLE MYELOMA: MULTI-CENTER REAL WORLD EXPERIENCES IN CHINA

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Background: The current situation of maintenance (MT) after front-line therapy in non-transplant patients with multiple myeloma (MM) is not adequate in China.
Aims: We conducted this multi-centered retrospective real-world study on efficacy and safety of the mainstream maintenance regimens, thalidomide (T-MT), lenalidomide (L-MT) and bortezomib (B-MT).
Methods: Clinical data of newly diagnosed MM patients were collected from 6 centers of North China MM Registry from January 2010 to May 2020. The progression-free (PFS) and overall survival (OS) from maintenance, and drug toxicities were compared in T-MT, L-MT and B-MT groups.
Results: A total of 291 patients were enrolled, including 153 in T-MT, 101 in L-MT and 37 in B-MT. At baseline, the gender ratio, paraprotein isotype, ISS and R-ISS, as well as response evaluation before MT were comparable (Figure 1). Patients on L-MT were older than the other groups. Meanwhile, greater proportions of patients on L-MT and B-MT had high-risk cytogenetic abnormalities (HRCA), defined as amplification 1q21 (1q21+), deletion 17p (17p-), t(4,14), t(14,16), or dual HRCAs (double hit).
The median follow-up duration since maintenance was 35.6, 19.4 and 17.3 months (m) in T-MT, L-MT and B-MT groups, respectively. Disease progression was recorded in 95 patients (62.1%) with T-MT, 49 (48.5%) with L-MT and 13 (35.1%) with B-MT. While mortality was 43(28.1%),

20(19.8%) and 2(5.4%), respectively. The median PFS was 22.5m in T-MT, as compared with 20.0m in L-MT and 37.0m in B-MT (p=0.61). Median OS was 79.5m in T-MT, whereas not reached (NR) in the others (p=0.21). Patients reaching complete response (CR) or stringent CR (sCR) before MT had significantly prolonged PFS compared to those with very good partial response (VGPR) or less in T-MT (28.0m vs 16.1m, p=0.02) and L-MT groups (27.0M vs 13.2M, p=0.01), while comparable in B-MT (NR vs 16.5m, p=0.36). Meanwhile, patients in each cohort had similar OS despite of different response before MT.

Patients with 1q21+ on T-MT had shorter median PFS compared to those without (16.1m vs 22.5m, p=0.14), so did impaired median OS (52.3m vs 96.5m, p= 0.003). While PFS was similar in patients with 1q21+ or without in L-MT group (33.5m vs 17.9m, p=0.29), and 4-year estimated OS was 52% and 51%(p=0.99). 1q21+ or not did not affect PFS in B-MT (15.2m vs 16.5m, p=0.89), and OS was not reached.Only a few patients with 17p- in T-MT and B-MT, yet presented remarkably inferior PFS (6.7m vs 22.5m, p=0.007) and OS (39.6m vs 79.5m, p=0.02) with T-MT. As for L-MT, PFS (15.4m vs 27.0 m, p=0.33) and OS (37.6m vs NR, p=0.99) were not of discrepancy between 17p- or without.In patients with any adverse CA, T-MT resulted in impaired PFS (11.9m vs 20.9m, p=0.06) and OS (52.3m vs NR, p < 0.01). In contrast, PFS and OS were both comparable in L-MT or B-MT, no matter with HRCA or not.

The main reason of maintenance withdrawal was disease progression. Adverse event related discontinuation was seen in 5.3%, 6.1% and 0 patients in T-MT, L-MT and B-MT.

		Thalidomide N= 153	Lenalidomide N= 101	Bortezomib N= 37	p-value
Gender (male%)		89 (58.2%)	55 (54.5%)	16 (43.2%)	0.26
Age (ave±sd/yr)		58.0±12.3	64.4±6.8	56.6±12.9	*0.001
Paraprotein isotype (%)	IgG	71 (46.4%)	44 (43.6%)	15 (34.1%)	0.64
	IgA	34 (22.0%)	23 (22.8%)	6 (13.6%)	
	IgD	5 (3.3%)	4 (4.0%)	4 (9.1%)	
	Light Chain	38 (24.8%)	24 (23.8%)	10 (22.7%)	
	Other or NA	5 (3.3%)	6 (5.9%)	2 (4.5%)	
ISS	I	35 (19.0%)	19 (10.3%)	7 (18.9%)	0.94
	II	34 (18.5%)	32 (17.4%)	10 (27.0%)	
	III	68 (37.0%)	41 (22.3%)	13 (35.1%)	
	Missing	16 (8.7%)	9 (4.9%)	7 (18.9%)	
RISS	I	12/77 (15.6%)	6/45 (13.3%)	3/20 (15%)	0.49
	II	54/77 (70.1%)	28/45 (62.2%)	14/20 (70%)	
	III	11/77 (14.3%)	11/45 (24.4%)	3/20 (15%)	
HRCAs		39/94 (37.2%)	43/65 (66.2%)	15/26(57.7%)	*0.01
Cytogenetic abnormalities	Gain(1q21)	30/106 (28.3%)	33/70 (47.1%)	10/26 (38.5%)	*0.04
	Del(17p)	7/106 (6.6%)	14/63 (22.2%)	3/25 (12%)	*0.01
	t(4,14)	0/89 (0)	7/56 (12.5%)	3/22 (13.6%)	*0.002
	t(14,16)	1/89 (1.1%)	8/56 (14.3%)	3/22 (13.6%)	*0.005
	Double HIT	3/94 (3.2%)	13/65 (20.0%)	5/26 (19.2%)	*0.002
Response prior to maintenance	sCR+CR	33.6%	36.8%	43.2%	0.10
	VGPR	45.5%	33.3%	13.5%	
	PR	14.9%	24.1%	24.3%	
	MR	2.2%	1.1%	2.7%	
	SD	3.7%	4.6%	13.5%	

ISS: international staging system; R-ISS: revised-ISS; HRCAs: high risk cytogenetic abnormalities.

Summary/Conclusion: In this multi-centered real-world study, thalidomide, lenalidomide or bortezomib as maintenance after front-line therapy in non-transplant NDMM patients suggest that a response of CR or better predicts superior PFS. HRCAs drag down survival in T-MT, while L-MT and B-MT mostly reverse the negative effects. Although patients on L-MT and B-MT have greater proportion of HRCAs, PFS in three groups are comparable. Clinicians in real practice prefer to select lenalidomide or bortezomib as maintenance in high-risk patients.

PB1686 CONVENTIONAL CYTOGENETIC ANALYSIS IN PATIENTS WITH MULTIPLE MYELOMA – SINGLE CENTER STUDY

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Background: Multiple myeloma (MM) is a clonal malignant hematological disease characterized by a broad range of genetic abnormalities that contribute to the disease course, treatment outcome and overall survival. Metaphase cytogenetics requires proliferating cells and is not sensitive for the detection of primary or secondary cytogenetic abnormalities. Nevertheless, any finding of a metaphase-detected abnormality is probably associated with more proliferative and aggressive form of MM.

Aims: The aim of the study is to define the role of conventional cytogenetics in the disease phenotype, time to next treatment (TNT) and overall survival (OS).

Methods: We analyzed 103 patients with newly diagnosed MM between February 2012 – December 2020. Mean age of the group is 62,3; male:female ratio - 1,06:1. According to ISS: 25,2% (n=26) are stage I; 18,4% (n=19) - stage II and 56,3% (n=58) - stage III. 36,5% are IgG kappa, 15,5% gG lambda, 10,7% IgA kappa, 6,8% IgA lambda, 22,3% FLC myeloma, 2,9% non secretory myeloma and 1,9% biclonal myeloma, 2,9% plasma cell leukemia. Regarding lines of therapy, 54,4% received 1, 23,3% - 2, 13,6% - 3, 3,9% - 4 lines of therapy and 4,9% did not receive any treatment. G-banding was performed on bone marrow samples. The cytogenetic risk was determined according to the Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy (mSMART) classification v.3.0. Patients with high risk are 8,7%, standard risk-82,5%. In 8,7% metaphases for cytogenetics are not obtained. Patients are distributed in 8 groups based on karyotype: normal karyotype-74,8%, hypodiploids-6,8%, hyperdiploids-2,9%, diploid-1,9%, high risk deletions-2,9%. One patient is with pseudodiploid karyotype and one is with complex karyotype. Statistical analysis is performed with SPSS v.19.

Results: By crosstab descriptive analysis approximately half of the patients with standard cytogenetic risk are stratified in ISS 3-54,1% (n=46). In the high risk group 81,8% are categorized in ISS 3. Regarding the karyotype classification, in ISS 1, 20 of the patients are with normal karyotype and only 2 have pathological karyotype: one is hypodiploid and one is with del(21)(q22). In the ISS 2, from 19 patients 17 are with normal karyotype and 1 is hyperdiploid. In ISS 3 the distribution is heterogeneous with normal karyotype in 40; hypodiploids in 6; hylerdiploid in 2, pseiudodiploid in 1, diploid in 2, high risk deletions in 2 and complex karyotype in one patient. The mean OS of the whole group is 39,7±4,2 months. We found significant difference in the mean OS based on the cytogenetic risk - 40,8±4,4 months in standard risk and 19,6±6,9 in high risk group (p<0,05). We found a significant difference in the time to third treatment (TTT) within the cytogenetic risk groups (p<0,001). The mean TTT in patients with standard risk is 2,1±5,2 months compared to 0 months in high risk group. We found a tendency showing that patients with standard risk have longer time to second treatment (TST) compared to those with high risk (12,9±18,8 months; 4,5±9 months; p=0,6). There is no difference between number of therapies, cytogenetic profile and myeloma type according to the karyotype.

Summary/Conclusion: The cytogenetic profile in MM is of utmost importance for risk stratification. Deviations from the normal karyotype detected by G-banding are found in approximately 20% of patients. Despite the importance of FISH-based risk stratification of MM, the role of conventional cytogenetics should not be underestimated, giving the opportunity of detecting a vast majority of cytogenetic abnormalities.

PB1687 COMPARISON OF 140MG/M2 VS 200MG/M2 DOSE OF MELPHALAN IN MYELOMA AUTOGRAFT – A SINGLE CENTER EXPERIENCE FROM CHENNAI, INDIA.

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Background: Melphalan at a dose of 200mg/m^2 is considered the standard autograft dose in patients with multiple myeloma without major co-morbidity. This was formulated in early years before the era of novel agent induction and maintenance. Considering the deeper remission achieved by novel agents and prevailing refractory gram negative sepsis in most Indian setups.

Aims: We compared 140mg/m^2 (MEL140) vs 200mg/m^2(MEL200) of Melphalan in Indian myeloma patients who achieved a complete remission before transplant without having any major co-morbidity.

Methods: We analyzed myeloma autograft patients from September 2014 to February 2018. 49 patients received MEL200 and 51 patients received MEL140. These patients were clinically randomized. Diabetes on oral medications was randomized equally on both sides. The median age of patients in MEL200 was 52 years and MEL140 was 53.6 years. There were 60% and 55% males in MEL200 vs MEL140 respectively. ISS-III patients were 48% and 49% in MEL200 vs MEL140 respectively. The standard induction regimen was three to four cycles of RvD chemotherapy. Around 16% patients in MEL140 group had a creatinine clearance between 30-50ml/min. The mobilization regimen followed was

5 days of GCSF based mobilization. The stem cell cut-off was kept to a minimum of 2 x 10^6/CD34+ve cells/kg bodyweight.
Results: In outcome analysis, there was no transplant related mortality in both groups. The mean day of engraftment was around Day +9 in MEL140 vs Day +11 in MEL200. The rate of Gram Negative Bacilli sepsis was around 14% in MEL140 vs 27% in Mel200 (p 0.02). This reflected in use of high end antibiotics like Colistin and Fosfomycin in such patients and there was a delay in engraftment which may have been confounded by sepsis. The median progression free survival was 26.1 months in MEL200and 27.2 months in MEL140 group. The cumulative incidence of relapse at 3 years was not significantly different between the Mel200 (36.3%) and Mel140 (37.9%) groups. The adjusted HR for relapse was 0.98. Subgroup analysis suggests that in overall survival, progression-free survival, and cumulative incidence of relapse there was no significant advantage associated with melphalan 200 mg/m^2.
We formulated to compare a lower dose melphalan to prevent a stormy post-transplant course and prevent patients succumbing to sepsis. This may not be an issue in western countries where gram negative sepsis rates are lower. The biggest worry for us is not to compromise the myeloma outcome due to lower doses of Melphalan in fit patients who achieve complete remission. This study concluded that there is not much of a difference in overall survival, Progression free survival and cumulative incidence of relapse at three years among MEL200 vs MEL140.
Summary/Conclusion: We conclude that Melphalan autograft at a dose 140mg/m^2 can achieve comparable responses to 200mg/m^2 in Indian myeloma patients who are taken to transplant post complete remission. We need a bigger multicentric study and a longer follow up to recommend MEL140 as standard of care in Indian setting.

PB1688 CLINICAL OUTCOMES OF IXAZOMIB-BASED REGIMENS IN CHINESE PATIENTS WITH MULTIPLE MYELOMA PREVIOUSLY RECEIVING BORTEZOMIB-BASED INDUCTION REGIMEN: PROTOCOL FOR MODIFY STUDY

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Background: Bortezomib-based triple drug regimen is the standard of care in Chinese multiple myeloma (MM) patient in front line setting, but there is huge economic and disease burden, and toxicity to bortezomib-based regimen. Oral regimen offers convenience to the patients, especially in China, because of the scarcity of top tier MM center and the community healthcare service system is not well established. Hence frequent communication between home and hospital is a burden for patients and their family. The feasibility of the in-class transition from a bortezomib-based treatment to an all oral ixazomib treatment has previously been demonstrated. Relatively good safety profiles of ixazomib make it possible for switching from a bortezomib-based induction regimen to an ixazomib-based regimen.
Aims: To assess the effectiveness of all oral ixazomib-based regimen in Chinese patients with MM, who had at the least a partial response (PR), after receiving bortezomib-based regimens as initial treatment.
Methods: This study will be an open-label, single-arm, multicenter, observational study among Chinese patients with MM in real world clinical setting. Patients (aged ≥18 years) who have been newly diagnosed with MM (NDMM) using International Myeloma Working Group criteria and have received a bortezomib-based triple-drug regimens for more than 2 cycles as initial therapy including bortezomib, cyclophosphamide and dexamethasone (VCD) or lenalidomide, bortezomib, and dexamethasone (VRD) or bortezomib, doxorubicin and dexamethasone (PAD) or bortezomib, thalidomide, and dexamethasone (VTD) will be enrolled in this study. At the time of enrollment, patient must achieve at least PR as defined by IMWG criteria. Approximately 320 eligible patients at 15 top MM hospitals in China will be treated with ixazomib-based regimens. All patients will be followed for 24 months once every 3 months unless withdraw of informed consent form, death or lost to follow-up, termination of the study by the sponsor, whichever comes first.
Results: This study will assess the progression free survival (PFS) at 2 years for Chinese NDMM patients switched from a bortezomib-based induction regimen to ixazomib-based regimens as primary endpoint. The clinical effectiveness, safety and tolerability, patient-reported outcomes and heath economic/resource utilization will be evaluated as secondary endpoint. Meanwhile, we propose to get more available data to exploratorily evaluate minimal residual disease, influence on medication adherence and impact factors for clinical outcome.
Summary/Conclusion: The available clinical data has been confirmed that long-term therapies are necessary for MM
patients to improve disease control compared with fixed-duration treatment. The results of this
study may provide evidences to verify the benefits of switching from bortezomib-based induction regimen to ixazomib-based regimens in Chinese NDMM patients in real world clinical setting. Meanwhile, we hope the study could provide treatment ideas in clinical practice to ensure clinical efficacy while reducing burden of disease and toxicity which will help to achieve the goals of maximal benefit with long term treatment in MM patients.

PB1689 CLINICAL CHARACTERISTICS AND OUTCOMES, OF REFRACTORY OR RELAPSED MULTIPLE MYELOMA PATIENTS TREATED WITH ANTI-CD38 MONOCLONAL ANTIBODIES

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Background: Anti-CD38 monoclonal antibodies (Mab) used in treatment of multiple myeloma (MM) patients have high response rates both in combination with other drugs and in monotherapy. However, a proportion of patients will eventually be resistant or relapsed (R/R). Patients R/R to anti-CD38 Mab present dismal prognosis and constitute a group for which therapeutic needs are still not defined.
Aims: In this study we aimed to describe the clinical and biological features as well as outcome of daratumumab R/R MM patients.
Methods: This is a retrospective analysis of 54 MM patients R/R to Daratumumab. Refractoriness was defined as progression within the first two months of treatment. Clinical and analytic data were collected from medical history. We used chi-square test to compare categorical variables and the Kaplan-Meier method and log rank test for the survival analysis. We performed multivariable analysis using logistic regression. IBM SPSS (v25.0) was used for the statistical analysis.
Results: The median age was 66 years; R(36-85), 57.4% were female. The cohort received a median of 4 lines of treatment; R(1-12). 70.4% had been previously treated with lenalidomide, 81.1% with bortezomib and 64.8% with both. Daratumumab was used as a first line therapy in 7 patients (14.8%), and as third or later line in 32 (59.3%). The median time to daratumumab progression was 6 months; R(1-53). 18 patients (33.3%) were primary refractory to daratumumab and 21 patients (38%) achieved very good partial response (VGPR) or better response. The median overall survival (OS) was 20 months; R(0-73). The most frequent combinations were with lenalidomide (DRd; 11%), bortezomib (DVd; 16%), bortezomib and melphalan (D-VMP; 13%) and with carfilzomib (KDd; 27%). 26% received daratumumab in monotherapy or with corticosteroids.
Only high cytogenetic risk (p=0,001) and treatment outside a clinical trial (p=0.003) were predictors of primary refractoriness to daratumumab. High cytogenetic risk remained statistically significant in the multivariable analysis (p=0.007). Patients with primary refractoriness to daratumumab had significantly shorter OS, with a median of 3 months vs 47 months in patients with eventual progression to Daratumumab (p=0,0001), as well as patients not treated within a clinical trial (p=0.0001) and patients treated in monotherapy (p=0.006). Interestingly, Daratumumab-resistant patients had longer OS when treated with regimens containing pomalidomide (median survival of 13 vs 46 months; p=0.021).
Resistance to daratumumab as a first line treatment was observed in 7 patients. The median OS in this group was 52 months and the median time of response to daratumumab was 12 months with 1 patient presenting refractoriness. All of them were treated within a clinical trial and none had high risk cytogenetics.

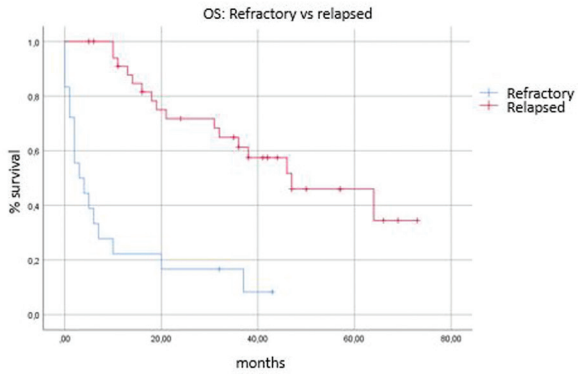


Figure 1. Survival in anti-CD38 monoclonal antibody refractory vs relapsed patients.

Summary/Conclusion: Patients R/R to CD-38 targeted monoclonal antibodies present dismal prognosis, with a median OS of 20 months. Only high cytogenetic risk was predictive of primary refractoriness according to the literature. Patients who received anti-CD38 Mab as a first line treatment had longer responses and OS, although the differences did not reach statistical significance, suggesting that even in this poor prognosis setting, patients benefit from using potent treatments as a first line. Particularly, the cohort treated with pomalidomide after daratumumab progression reached a longer OS, indicating that new drugs may represent an interesting approach for this subgroup of patients. Studies describing mechanisms of resistance to anti-cD38 Mab are essential to select the best option for each patient.

PB1690 THERAPEUTIC RESULTS OF BORTEZOMIB MULTIPLE MYELOMA TREATMENT: A MONOCENTRIC STUDY

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Background: Multiple myeloma (MM) is an incurable pathology whose treatment has progressed over time. Bortezomib is now considered as a treatment that improves the prognosis of the disease in all stages. Given that Tunisia is a country with limited resources, the use of Bortezomib as a treatment for MM has only begun in 2016 as a part of a prospective protocol and could be administered only for high-risk patients (pts).
Aims: Our study aims to report the therapeutic results of pts with MM from southern Tunisia treated with Bortezomib.
Methods: It is a retrospective study over 4 years (2016-2019) which included young patients (<65 years old) with high-risk myeloma (ISS at 3, renal failure, and cytogenetic abnormalities with poor prognosis) and treated at the hematology department of Hedi Chaker Hospital Sfax, Tunisia with Bortezomib according to the 2016 national MM treatment guidelines. The treatment consists of 4 VTD courses every 21-day followed by an autograft. If autograft is not possible, consolidation at the base of 4 other CT courses should be received. Point-date is January 2021. We are interested in the response to treatment, overall survival (OS), and progression-free survival (PFS).
Results: Thirty-eight patients were treated with VTD. The reason for treatment was an ISS score at 3, a renal failure, and a high-risk cytogenetic abnormality were recorded in respectively 28, 21, and 9 pts (2pts with 17p del and 7pts with t (4,14)). Evaluation after 3 courses showed a complete remission (CR) in 8 pts(21%), a very good partial response(VGPR) in 11 pts(28.9%), a partial response (PR) in 9 pts(23.6%), a minor response (MR) in 2 pts(5.26%), a stable disease (SD) in 2 pts(5.26%), and progression in 6 pts(15.7%). Autograft of hematopoietic stem cells was performed in 10 pts. After autograft, CR, VGPR, PR rates were respectively 20%, 70%, and 10%. Twenty-eight patients did not benefit from autograft either for early death, severe comorbidities or because of the limitation of hospitalization at the national bone marrow transplant center in Tunis because of Covid 19 pandemic. Among un-grafted patients, 17 have received a consolidation treatment, the rest either progressed (10.7%) or died (28.5%) before consolidation. The median survival was 26 months and two-year OS was 84.5%. OS was 100% for autografted pts and 84% for those who received consolidation with significant difference (p=0.003). PFS was 61.6% at 24 months with PFS equal to 76% for autografted patients and 51.8% for those who received consolidation (p=0.021). Response after 3 courses influenced significantly the OS (p=0.027) in a multivariate analysis.
Summary/Conclusion: Despite its high cost, Bortezomib has been a major breakthrough in the treatment of severe forms of MM. Although in our review we obtained an OS equal to 84.5% and an OR equal to 73.6% which remains lower than the results found in the literature (OS at 24 months better than 90% and OR varies between 85 and 100%) which is explained by the use of Bortezomib only for high-risk patients and by the unavailability of autograft for all patients by its non-feasibility in our center, it is still better than results obtained by the old therapeutic protocol used in Tunisia based on DT, this prompts us to use this product for all patients and not only for high-risk ones and to generalize autograft.

PB1691 VCD VERSUS VRD-BASED REGIMENS AS INDUCTION THERAPIES IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA (MM): UPDATED UKRAINIAN RETROSPECTIVE MULTICENTER ANALYSIS

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Background: Recently more effective induction chemotherapy regimens have been developed and patients treated with these new regimens are able to achieve higher and deeper responses than those previously treated on older regimens. But there are still discussions about which regimen in the first line of therapy is the priority.
We studied the difference between the median of VCd regimen progression-free survival (PFS) and the PFS of VRd treatment used as initial therapy for MM.
Aims: The primary endpoint was to study the best response to VCd/VRd treatment at the time of early response, as well as PFS of newly diagnosed patients with MM.
Methods: Between 2011 and 2021, we analyzed 98 newly diagnosed patients with MM (males:51, females:47) at 6 Ukrainian centers. 70.4% and 29.5% of patients received VCd and VRd regimens, respectively (p<0.05). The response was evaluated at the end of 3-4 cycles and the end of treatment, as per IMWG criteria. The patients' characteristics were similar in both groups according to ISS stage (ISS III –VRd: 29%, VCd: 24.4%), and median age (VRd -51.5 y.o; VCd-54.5 y.o).
Results: Both VRd and VCd groups ORR was high, (79.3% and 81.1%, respectively). Patients in both groups achieved similar rates ≥VGPR (44.9% VCd vs 51.7% VRd). CR/sCR rates were superior in the VRd arm; 37.9 % vs 28.9%, p< 0.05.
We compared the median of rapid early response with VCd regimen, taking in consideration a larger percentage of CR achievement in the patient group with Lenalidomide-containing regimen. However, we could not obtain an accurate result as the median of rapid response was similar in both groups: 3.1 months for VRd vs 3.2 months for VCd.
The mean of PFS median was 31.93 months, and the OS median was not reached. The PFS was correlated with therapy response. Patients who achieved ≥VGPR vs MR/progression, (84% vs 20%, p<0.0001), had a significantly longer 5-year PFS.
It is interesting to note that during our patient cohort analysis, we discovered a significant risk mitigation of disease relapse in the near 5 years when using a VRd regimen compared to the VCd one, (5-year PFS 50% vs 35%, log-rank test, p<0.0001). The OS level remains nevertheless the same and does not constitute a statistically important result.
Summary/Conclusion: Our data suggest that the response to therapy affects the prediction of clinical outcome in patients with MM. Other than OS or PFS, alternative primary endpoints need to be developed for an adequate future assessment of treatment efficiency using VRd and VCd regimens in order to determine the therapy "leader" in newly diagnosed patients with multiple myeloma.

PB1692 THE HIGH-RISK CYTOGENETIC (HRC) INFLUENCES IN THE OUTCOME OF THE NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM).

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Background: MM is the 2nd most common hematologic malignancy. It has different overall survival (OS) and progression-free survival (PFS) depending on cytogenetic abnormalities. A 15% of NDMM has an HRC, which supposes an aggressive behaviour, with frequent relapses, until it becomes refractory. There are drugs that partly overcome the adverse effect of HRC on PFS and OS.
Aims: 1. Evaluate efficacy and number of relapses until achieving a good treatment response or death. 2. Prognostic impact of clinical-biochemical diagnosis data in a heterogeneous NDMM HRC`s cohort.
Methods: Unicentric, descriptive and retrospective analysis, using clinical and analytical NDMM HRC patient's data from 2009 to 2020 at Guadalajara University Hospital. HRC is defined by fluorescence in situ hybridization (FISH): mutations on chromosome 1, del17p, t(4;14), t(14;16), t(14;20) or plasmablastic leukemia. Survival data or Cox regression were used. Risk measures; Hazard Ratio (HR) with 95% CI. Negative binomial regression to analyze count variables. P value <0.05 was considered significant.
Results: We identified 53 patients (pts) with HRC NDMM, whose clinical characteristics and treatment (tt) data are listed in Table 1. NDMM HRC first-line tt was chosen, regardless of the FISH results: 90,6% of the pts received bortezomib (V) - based induction, of them 35% (n=17) were treated with alkylating agents, 48% (n=23) received immunomodulatory drugs and 17% (n=8) V with dexamethasone (d). Whereas 24,5% (n=13) received a nonintensive tt as Vd, melphalan-d or lenalidomide-d, because they were older than 70 years and the tt was chosen before 2017. Twenty-one pts (39,6%) underwent autologous stem-cell transplantation (ASCT) as part of first-line tt, the vast majority under 65 years. Overall response rate (ORR) after induction was 37%; and declined in subsequent treatment lines, 49% achieved ≥ very good partial response (VGPR).
Median follow-up for surviving patients was 47,25 months (IQ 23,8 – 97, 58). The PFS was 50.26 months (IQ 16.37 - 68.70). 18 pts deceased during the time of the follow-up.
In multivariate analysis to predict OS rate: being a woman (HR: 1.036; p = 0.948) and age >65 years (HR: 1.053; p = 0.087) was associated with a risk factor, but no data showed a statistically significant association.
Equal characteristics such as age, sex, ISS, D&S and analytical data, the only variable that was independently associated with the relapse rate during the follow-up time was ISS-2 versus ISS-1, multiplying by 1,86 the number of times the event appears. Relapse rate: 1.86; p = 0.037) (figure 1).
Summary/Conclusion: Our case series presents a longer survival compared to those commented in other studies. It describes similar % cytogenetic abnormalities as in the literature, except for del(17p), which has an incidence of 28.3%. Most frequent combination was the one between 1q gain among pts with del(17p). Our study validates the ISS as the factor with the greatest impact on its prognosis. A longer follow-up and higher HRC NDMM pts`s recruitment will be necessary to better define the response to tt regimens based on individual cytogenetic groups.

Datum		All cohort (n=53)	
Demographics			
Age (median, Q1-Q3)—years		70,35 (59,27 - 79,35)	
Gender (Female, %)		29 (54,7)	
Baseline disease characteristics			
Previous MGUS (n ,%)		22 (41,5)	
Myeloma Type (n, %)			
IgG		24 (45,3)	
IgA		21 (39,6)	
IgD		1 (1,8)	
Bence-Jones		2 (3,8)	
CL		3 (5,7)	
Non-secretory		2 (3,8)	
M spike (median, Q1-Q3) gr/dL		3 (2 - 4)	
PC% in BM (median, Q1-Q3)		40 (24 - 67)	
Immunoparesis (n, %)		46 (86,8)	
CRAB at diagnosis (n, %)			
Ca>11 gr/dL		15 (28,3)	
Cr>2 mg/dL		15 (28,3)	
Hb<10 mg/dL		47 (88,7)	
Lytic lesions		32 (60,4)	
ISS (n, %)	R-ISS (n, %)		
1	1	6 (11,3)	3 (5,7)
2	2	29 (54,7)	13 (24,5)
3	3	18 (34)	37 (69,8)
FISH/cytogenetics (n, %)			
Del (17p)		15 (28,3)	
t (4;14)		4 (7,5)	
t (14;16)		1 (1,9)	
t (14;20)		1 (1,9)	
Gain 1q		15 (28,3)	
Plasmablastic leukemia		3 (5,7)	
Del 17p + gain 1q		10 (18,9)	
t (4;14) + gain 1q		1 (1,9)	
t (14;16) + gain 1q		1 (1,9)	
Del17p + t (14;16) + gain 1q		1 (1,9)	
t (4;14) + t (14;16) + t (14;20)		1 (1,9)	
Treatment characteristics (n, %)			
Bortezomib-based tt (1st line)		48 (90,6)	
VCD/ VMP (1st line)		12 (22,6) / 5 (9,4)	
VRd/ VTd (1st line)		19 (35,8) / 4 (7,5)	
Vd / MP / Rd (1st line)		8 (15) / 1 (1,8) / 4 (7,5)	
Autologous HCT (1st line)		21 (39,6)	
Allogeneic HCT (at any time)		2 (3,8)	
Lines of therapy			
2		24 (45,3)	
3		13 (24,5)	
4		5 (9,4)	
5		3 (5,7)	

Table 1. Characteristics of HR multiple myeloma patients. Q interquartile range; CL light chain; PC plasma cells; BM bone marrow; Ca calcium; Cr creatinine; Hb hemoglobine; R-ISS revised international staging system; tt treatment; V Bortezomib; C cyclophosphamide; d dexamethasone; R lenalidomide; M melphalan; T thalidomide; P prednisone.

PB1693 REAL-LIFE OUTCOMES OF DARATUMUMAB TREATMENT IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA: EXPERIENCE FROM A SMALL PERIPHERAL HOSPITAL

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Background: Multiple myeloma (MM) is the second most common hematological cancer worldwide. Although it is still considered an incurable disease, MM might be controlled for long periods of time. Notwithstanding the therapeutic approach to MM is guided by eligibility to autologous stem cell transplantation (ASCT), treatment was markedly improved with the availability of agents approved in the last 15 years, leading patients with MM to improvements in 5 to 10 year survival rates. Daratumumab (Dara) is a CD38 monoclonal antibody approved in Portugal in monotherapy or in combination with bortezomib (DVd), Lenalidomide (DRd) with dexamethasone, for the treatment of relapsed or refractory myeloma (RRMM).
Aims: The aim of this study was to characterize a portuguese RRMM population of a small center treated with Daratumumab in different regimens.
Methods: We performed a retrospective observational cohort study of 55 adult MM patients diagnosed between 2010 and 2019 and analyzed a subpopulation of 11 RRMM patients treated with Daratumumab regimens. We assessed response according to IMWG criteria and progression free survival (PFS) was determined using Kaplan-Meier analysis.
Results: Of 55 MM patients, 20% received regimens with Daratumumab (N=11/55). In this subgroup of patients 36% (n=4/11) had relapsed MM and 64% (n=7/11) presented MM refractory to one or more previous treatment lines. Amongst Dara associations, 63,6% patients (n=7/11) received DRd, 18% (n=2/11) received DKd, one patient received Daratumumab in monotherapy and one patient received DVd (Daratumumab, Bortezomib, Dexamethasone). The median age at diagnosis was 59 years (range 41-69). The median time to initiation of Dara from diagnosis was 4 years (range 1-8). Patients had received a median 2 prior lines of therapy (range 1-3). Seven patients (64%, n=7/11) had previously undergone single or tandem ASCT. In the Rd-and Kd-groups all patients were previously exposed to bortezomib. In the Kd-group and Vd-group patients were exposed to Lenalidomide. The median number of administered cycles was 15 (range 2-27) in the Rd-group, 5 (range 1-9) in the Kd-group and 45 cycles in the Vd-group. The regimens were well tolerated with few grade adverse events (AE). Grade 3/4 neutropenia and thrombocytopenia (18%) were the most common AE. One patient developed toxidermia to Lenalidomide. When treated with Dara regimens, clinical relapse was observed in two patients (18%) and death in 6%. One patient was on hemodialysis as renal failure related to MM, and during DRd treatment there was vital improvement in renal functional with hemodialysis independency. Regarding to response,

in the Rd-group CR was achieved in 71% and VGPR in 14%, in the Kd-group CR was achieved in 100% and in Vd-group VGPR was achieved in 100%. Stable disease after Daratumumab was achieved by 7 patients (64%). OS was 65,8 months (range 17-120). Median PFS on Dara was 18 months (range 2-40, 95%>IC) in Rd-group, 13 months (range 1-25) in the Kd-group and in the Vd-group 39 months. Patients with extra medullary disease had poorer median PFS than those without.

Summary/Conclusion: Current MM prevalence is expected to increase since incidence is higher than mortality and new pharmacological treatments have been reshaping the market and the treatment landscape. These small real-life results are lined up with the results of POLLUX trial and demonstrate that in daily practice, Daratumumab regimens are safe, well-tolerated with benefits on PFS and OS in RRMM.

PB1694 REAL WORLD TWO-CENTER EXPERIENCE OF DARATUMUMAB MONOTHERAPY IN HEAVILY PRETREATED RELAPSED/ REFRACTORY MULTIPLE MYELOMA

I. Sanchez [1,2,*], J. Aspa [2], H. P. J. Lam [1], G. Milner [1], I. El-Najjar [1], S. Sachchithanantham [1], M. Gleeson [1], M. Kazmi [1], K. Bailey [3], R. Benjamin [3], K. Cuthill [3], L. Yuen [4], J. Garcia [2], M. Streetly [1]

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Background: Daratumumab, an anti-CD38 monoclonal antibody, was approved in May 2016 by the European Medicines Agency (EMA) for relapsed/refractory multiple myeloma (RRMM) patients whose previous therapies included a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD). In June 2020, subcutaneous (SC) daratumumab gained EMA approval.

Aims: To assess clinical characteristics, response rates and toxicity profile of RRMM patients treated with daratumumab monotherapy in 2 European centers.

Methods: This two-center retrospective study included 25 RRMM patients who started daratumumab monotherapy between 05/2018 and 09/2020 at Guy's Hospital (London) or Hospital Príncipe de Asturias (Madrid). Patients' data were reviewed from electronic records. Patients who completed ≥1 cycles were included in response analysis. Kaplan-Meier was used for survival outcomes.

Results: Median age at the start of daratumumab was 65 (range 47-91); 11 (44%) patients were male. Clinical characteristics are summarised in Table 1. All patients had previous exposure to a PI (bortezomib 100%, ixazomib 48%, carfilzomib 8%) and an IMiD (lenalidomide 100%, thalidomide 76%, pomalidomide 16%). Two (8%) were bortezomib-refractory, 1 (4%) was lenalidomide-refractory; another (4%) patient was refractory to both VTd (bortezomib, thalidomide, dexamethasone) and IRd (ixazomib, lenalidomide, dexamethasone) therapies. Twelve (50%) patients had undergone autologous stem cell transplant. Six (25%) had been included in a clinical trial (with no anti-CD38).

All patients had progression before starting daratumumab, with extramedullary disease in 4 (16%) patients. Median treatment duration was 4.3 months (m) (0.7-22.7) and median number of doses given was 28 (3-35). Seventeen (68%) patients discontinued therapy: 12 (70.6%) due to progressive disease and 5 (29.4%) died. Two deaths were due to refractory myeloma, 2 as a result of bleeding complications with thrombocytopenia grade≥3 and 1 sepsis-related.

At median follow-up of 8.7 months (0.7-23), 23 patients completed ≥1 cycles. Overall response rate (ORR) was 39.1% (9/23), with very good partial response (VGPR) in 17.4% (4/23). Median time to partial response (PR) was 2.3 m (2-3.6). Median progression-free survival (PFS) is 5.5 m, with longer PFS associated with completion of ≥1 cycle (median 6.5 months) and with deeper response (VGPR vs. PR or less, 15.3 vs. 3.9 m (p 0.012)). Median overall survival (OS) is 15.5 m.

Administration was SC in 4 (16%) patients and was converted from intravenous (IV) to SC in 4 (16%) others. First-dose infusion related reactions (IRR) occurred in 9 (36%) patients; 8/9 (88.9%) were associated with IV daratumumab and 3 were classified as grade ≥3 (including hypertension, fevers, desaturation and vomiting).

Common (≥15%) AEs were anaemia (92%), lymphopenia (80%), thrombocytopenia (72%), neutropenia (32%) and infections in 11 (44%), the majority being non-severe respiratory infections (45.4%).

Grade ≥3 AEs were found in 13 (52%) patients. Grade ≥3 thrombocytopenia was seen in 5 (20%), anaemia in 7 (28%), lymphopenia in 7 (28%) and neutropenia in 1 (4%). Grade ≥3 new proven infections after daratumumab start happened in 4/13 (30.8%) patients: sepsis related to Gram negative bacteriaemia leading to death, sepsis of unknown origin, pneumonia and urinary tract infection.

Table 1. Clinical characteristics of the population.

Characteristics (n=25)	Overall data (%)
Multiple myeloma type	
- IgG	15/25 (60%)
- IgA	5/25 (20%)
- Bence-Jones	5/25 (20%)
ISS stage at diagnosis	
- I	8/25 (32%)
- II	4/25 (16%)
- III	10/25 (40%)
- Unknown	3/25 (12%)
ISS-R stage at diagnosis	
- I	6/25 (24%)
- II	6/25 (24%)
- III	3/25 (12%)
- Unknown	10/25 (40%)
Cytogenetics at diagnosis*	
- Non-high risk	10/25 (40%)
- High risk	5/25 (20%)
- Unknown	10/25 (40%)
ECOG performance scale ≤2	20/25 (80%)

*Abbreviations: ISS: International Staging System. ISS-R: Revised International Staging System. ECOG: Eastern Cooperative Oncology Group. *High risk cytogenetics at diagnosis: t(4;14), del(17/17p), t(14;16).*

Summary/Conclusion: In summary, our experience with daratumumab monotherapy demonstrates encouraging response rates in heavily pretreated patients, similar to those reported in a pooled analysis of GEN501 and SIRIUS phase 1-2 trials. It shows an acceptable safety profile.

PB1695 POMALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background: Pomalidomide is a new generation IMID, with a very good compliance, thanks to oral administration, which can be used also in heavily pretreated patients, in a domestic setting.

Aims: In this retrospective observational trial, It has been evaluated efficacy and tolerance of pomalidomide plus dexamethasone (PD) as salvage regimen in heavily pretreated patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe.

Methods: 57 patients (31 M/26 F), with rrMM, median age at diagnosis 69 years (r. 52-86), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-11), every refractory to all the drugs previously received (also Bortezomib, Thalidomide and Lenalidomide), received Pomalidomide-Dexamethasone (Pomalidomide 4 mg for 21 days, Dexamethasone 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. ISS was equally distributed, and cytogenetic at relapse was evaluable in 14 patients. All the patients had previously been treated with schedule containing bortezomib and IMIDs. 63% (36/57) had undergone at least to a single ASCT. All patients were relapsed and refractory to last therapies received before PD.

Results: Pomalidomide was well tolerated, with grade 3-4 transfusion-dependent anemia in 58% (33/57) of patients, 44% (23/57) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no hospitalization was required, no septic shocks were observed), 40% (23/57) grade 3-4 thrombocytopenia without hemorrhagic events and transfusion-dependence. No severe extra-hematologic toxicity was observed. According to IMWG, ORR1 (≥PR) was 47.3% (27/57: 5 CR, 11 VGPR,

7 PR, 4 MR), but, considering that we are evaluating a cohort of heavily pretreated patients, with poor prognosis, another parameter should be considered, ORR2 (≥SD), considering stable disease as a successful result in progressive MM. ORR2 was 77.1% (17 SD). These can be considered as impressive result in this subset of patients. Oral treatment gives a really good compliance, in frail and unfit patients, and response, when present, is always really fast (median time to response: 2 months (r.1-6)), median OS from diagnosis was 94 months (range 21-234), median OS from start of pomalidomide was 9 months (range 1-25). Nine patients have surprisingly achieved a notable response (3 VGPR, 4 PR, 2 MR) after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide).

Summary/Conclusion: Pomalidomide-dexamethasone has shown significant efficacy and a very good compliance, thanks to oral administration, in a particularly severe setting of heavily pretreated patients, relapsed and refractory to all available therapeutic resources, also after failure of novel agents.

PB1696 FOUR PATIENTS DIAGNOSED OF AL AMYLOIDOSIS WITH SEVERE ORGAN DAMAGE WHO UNDERWENT AN AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOLLOWING AN INDUCTION TREATMENT: EXPERIENCE IN A THIRD LEVEL HOSPITAL

N. Alba [1,*], C. Encinas [1,2], I. Regalado-Artamendi [1], M. Argüello-Tomás [1], G. Oarbeascoa [1,2], E. Zataraín [2,3], I. A. Gómez-Centurión [1,2], J. Badiola [1,2], S. Monsalvo [1,2], L. Solán [1], M. Kwon [1,2], J. L. Díez-Martín [1,2]

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Background: The organ damage at the time of AL amyloidosis diagnosis infers a high morbi-mortality and a poor prognosis. Most patients have some degree of cardiac involvement and the stringent selection criteria for ASCT exclude many of them despite an appropriate age, making upfront ASCT not a suitable option. The novel agent-based schemes (Palladini et al. Ash publications Blood 2020) with an excellent toxicity profile and efficacy may allow to undergo ASCT due to a better hematologic and organic response.

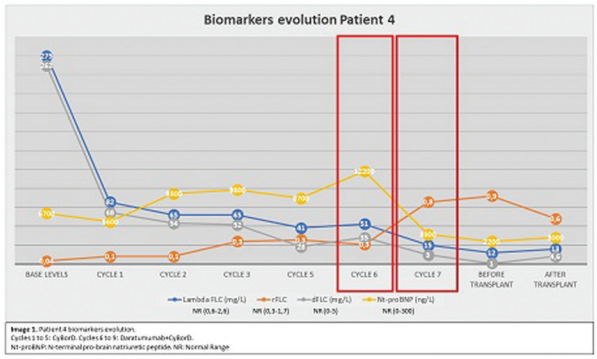
Aims: To describe our experience in patients treated in our center who are not eligible for ASCT (Kumar et al. J. Clin. Oncol. 2012) with an in induction treatment based on immunomodulator (IMID) and proteasome inhibitor (PI), with Daratumumab in one, allowing them to undergo ASCT later.

Methods: Descriptive and retrospective analysis of four cases of AL Amyloidosis, diagnosed and treated in our center between 2010 and 2020.

Results: Baseline characteristics are described in Table 1A. The induction treatment, hematologic and organ response and the patient´s evolution are presented in table 1B. Patients 1, 2 and 4 presented severe cardiac damage and patient 3 has subacute liver failure (bilirubin 30 mg/dL). All the patients had a Mayo Clinic 2012 stage II or superior, so their survival prognosis was less than 1 year. After the induction treatment, we could perform an ASCT in all patients. Image 1 shows the evolution of the free light chains (FLC) of patient 4 with severe cardiac damage, and we present how the improvement of the hematologic response (to get dFLC less than 10 mg/L), allowed the organ response, and she could undergo a transplant. With a median follow-up of 23,5 months, all patients are currently alive and maintain a hematologic and organ response.

Tabla 1A. Patient

	1	2	3	4
Age (years)/Gender	61/Female	47/Female	54/Male	49/Female
rFLC/dFLC (mg/L)	0.1/81.8	0.092/-	40/480	0.04/262.5
Creatinine (mg/dL)/24h urine protein (mg/dL)	0.61/126	-/70	2.5/570	0.65/3054
Nt-proBNP (ng/L)/TnT (ng/L)	2236/60	10055/normal	8231/50	6700/47.2
ECOG/NYHA	3/III	3/III	3/I	3/III
LVEF (%)/thickness ventricular wall (mm)	55/16	45/14	65/17	45/17
Bilirrubine (mg/dL)	0.4	-	29.5	0.9
Mayo Stage 2012	III	II	III	IIIB



Summary/Conclusion: In our experience, patients with the diagnosis of AL amyloidosis and severe organ damage who underwent a ASCT after an induction therapy using new agents outlived their initial poor prognosis.

PB1697 REAL WORLD EVIDENCE OF CARFILZOMIB IN RELAPSED REFRACTORY MULTIPLE MYELOMA (RRMM)

V. Douka [1,*], M. Iskas [1], A. Giannakopoulou [1], S. Tagara [1], S. Dimou-Besikli [1], C. Lalayanni [1], M. Papathanasiou [1], C. Vadikoliou [1], G. Papaioannou [1], A. Papalexandri [1], A. Anagnostopoulos [1]

Table 1B. Patient

	1	2	3	4
Induction treatment (nº cycles)/months to best response	*CyBorD (3)/7*	*Lenalidomide-Melphalan-Dexamethasone (9)/9*	*CyBorD (8)/1*	*CyBorD (5)* *Daratumumab-CyBorD (4)/3*
Hem./Organ response pre-ASCT	*PR/stable heart disease*[*2]*	*CR/response heart disease **	*CR/response liver disease*[*1]*	*Stringent CR/response heart disease**
ECOG/NYHA pre-ASCT	*1/I*	*1/I*	*1/I*	*1/I*
Timing of ASCT from diagnosis (months)	*5*	*13*	*9*	*13*
Conditioning regimen/Post-ASCT complications	*Mel-140/Engrafment Syndrome (ES), mild Congestive Heart Failure (CHF)*	*Mel-140/Mild CHF*	*Mel-200/ES*	*Mel-200/-*
Hem./ organ response nowadays	*Stringent CR/CR*	*Stringent CR/CR*	*CR/CR*	*Stringent CR/-*
Follow-up time (months)	*24*	*132*	*23*	*18*

*Response heart disease: decrease>30% of Nt-proBNP from the value at diagnosis; *[1] Liver response: decrease>50% of the initial FA level; *[2] Stable heart disease: Nt-proBNP and Tn without significative changes

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Background: Duration of response in multiple myeloma patients has significantly ameliorated due to introduction of new drugs, such as proteasome inhibitors, immunomolulatory agents and monoclonal antibodies. Carfilzomib is an approved treatment option beyond first line.
Aims: The aim of our study is the efficacy and safety of carfilzomib in daily practice.
Methods: In a cohort of 30 patients since 2017, 21 received carfilzomib in combination with lenalidomide and dexamethasone (KRd), 9 with dexamethasone only (Kd). The study cohort consists of 11 male and 19 female patients with median age 68 (41-80) years old, 17 IgG, 10 IgA, 3 free light chain disease. Carfilzomib was administered as 2nd line treatment in 12 patients, as 3rd in 5, as 4th in 8, as 5th in 3 and as 6th in 2 patients. Patients received a median of 8 (1-51) treatment cycles. Left ventricular ejection fraction (LVEF%) was determined by heart ultrasound prior to treatment initiation in all patients. Median LVEF% value was 65% (55%>80%).
Results: Serum creatinine and markers of hemolysis (reticulocyte count, LDH, bilirubin) remained constantly within normal ranges. Platelet count did not deviate from baseline throughout treatment. No schistocytosis or microangiopathy occurred. One female patient developed new onset hypertension during the 6th KRd cycle and one Kd patient was in need of antihypertensive regimen modifications upon treatment initiation. All patients underwent LVEF reevaluation by echocardiogram beyond 6-mo treatment and q6mo thereafter. Reduction in LVEF more than 10% comparing to baseline was noted in 3/20 (15%) evaluated patients. Two sudden deaths occurred in two patients without cardiac history, one 72 y-o male patient during cycle 7 and one 75 y-o female upon treatment initiation. Death was attributed to physical causes and no autopsy was performed. Disease assessment was performed in 29 patients. At least partial response (PR) was achieved in 22 (76%) patients, 7 (32%) in VGPR. Median progression free survival (PFS) and overall survival (OS) was 15 (1-31) and 34 (18-50) months respectively. Median PFS and 3-year PFS was significantly higher in patients with 1-3 vs >3 prior treatment lines 37 (19-54) vs 9 (8-10) months and 40% vs 0% respectively, p<0.001. A trend for improved OS and 3-year OS was evident in patients with 1-2 vs >2 prior treatment lines, not reached vs 22 months and 61% vs 19% respectively, p=0.06. For lenalidomide refractory patients receiving Kd vs lenalidomide naïve KRd patients, median PFS was 9 (4-14) mo vs 28 (21-35) mo (p<0.001). Twelve-month PFS and 36-mo PFS was, 27% vs 69% and 39% vs 0% respectively.
Summary/Conclusion: In conclusion, carfilzomib administration in relapsed/refractory multiple myeloma exhibits adequate efficacy. Cardiovascular assessment is mandatory prior to treatment initiation and during treatment cycles. Quality and duration of response was augmented when integrated in 1st or 2nd relapse treatment plan.

PB1698 DREAMM-5 PLATFORM TRIAL: BELANTAMAB MAFODOTIN (BELAMAF) IN COMBINATION WITH FIVE DIFFERENT NOVEL AGENTS IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

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Background: Single-agent belamaf (GSK2857916, BLENREP), a B-cell maturation antigen–targeting antibody-drug conjugate, induced durable responses in patients with RRMM, with a manageable safety profile with 13 months of follow-up (DREAMM-2; NCT03525678). The unique multimodal mechanisms of action (MoAs) of belamaf in combination with MoAs of selected agents, have the potential to achieve synergistic effects in RRMM to further enhance the benefit-risk profile. The DREAMM-5 study (NCT04126200), a platform trial, allows for efficient evaluation of belamaf in combination with other anti-tumor agents, including a humanized wild-type immunoglobulin (Ig)G1 anti-OX40 agonist, an IgG4-inducible T-cell co-stimulator (ICOS) agonist (feladilimab), a gamma-secretase inhibitor (nirogacestat), a humanized programmed cell death (PD)-1 antagonist (dostarlimab), and a humanized wild-type IgG1 CD38 antagonist (isatuximab).
Aims:.
Methods: DREAMM-5 is a Phase I/II study that utilizes a master protocol with separate sub-studies comprised of sequential dose-exploration (DE) and cohort-expansion (CE) phases, to identify promising, effective belamaf combinations when compared with a shared single-agent belamaf control arm (CE phase only). The DE phase consists of multiple dosing cohorts with belamaf combinations in which patients are assigned to treatment slots by a predetermined algorithmic approach (N≤10 per cohort). A recommended Phase II dose (RP2D) for each combination treatment will be identified based on the safety and preliminary efficacy in the DE phase. At the end of the DE phase, an interim analysis of safety, pharmacokinetic, biomarker, and efficacy data will also be performed for each sub-study treatment combination to determine whether the combination should move forward at the RP2D to the CE phase. Patients in the CE phase (N≥35 per cohort) will be randomized to a sub-study, and within a sub-study to either combination treatment or the belamaf monotherapy control arm shared across sub-studies; patients will also be stratified by number of prior therapies. Eligible patients will have RRMM and will have received ≥3 prior therapy lines, which includes a prior immunomodulatory agent, proteasome inhibitor, and anti-CD38 antibody; all patients will provide informed consent for participation. The primary objectives of the study are to identify the RP2D (DE phase) and the overall response rate (≥partial response, CE phase), along with safety and tolerability, for each combination treatment.
Sub-study 1 (combination with GSK3174998, OX40 agonist antibody) is no longer open to enrollment. Sub-studies 2 (combination with GSK3359609, feladilimab, anti-ICOS agonist), 3 (combination with nirogacestat [PF-03084014; SpringWorks Therapeutics], gamma-secretase inhibitor), and 4 (combination with dostarlimab, PD-1 antagonist antibody) are currently open to enrollment. Sub-study 5 (combination with isatuximab [Sanofi], CD38 antagonist antibody) will be open to enrollment soon. Additional sub-studies will be explored based on scientific rationale and/or preclinical combination data available.
Results:.
Summary/Conclusion:.
Funding: GSK (Study 208887, NCT04126200); belamaf drug linker technology licensed from Seagen Inc; belamaf monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa; nirogacestat gamma-secretase inhibitor produced by and used in collaboration with SpringWorks Therapeutics and isatuximab produced by and used in collaboration with Sanofi.

PB1699 A RAPID RESPONSE WITH DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE COMBINATION IN A PATIENT WITH CASTLEMAN VARIANT OF POEMS SYNDROME

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Background: POEMS syndrome (POEMS) is a rare paraneoplastic syndrome of an underlying plasma cell disorder (PCD). Castleman disease (CD),itself,can also cause symptoms or signs of polyneuropathy,volume overload,cytokine release,but only those with peripheral neuropathy and a plasma cell clone can be classified as classical POEMS.
Aims: Both classical POEMS syndrome with CD and castleman disease variant of POEMS syndrome(CD-POEMS),literature lacks a standardized treatment approach.
Methods: Here we present a case who is diagnosed with CD-POEMS and successfully treated with a combination of Daratumumab, Lenalidomide and Dexamethasone (DRd).
Results: A 54-yr-old man had admitted to our department of neurology with weakness of both arms and legs. Three years ago,patient developed tingling on legs and ataxia. He needed assistance for walking. The

neurological examination showed bilateral upper and lower limb muscle weakness especially dominant on distal parts of the extremities on admission. There was an evident atrophy on distal part of the extremities. Stocking-glove pattern for loss of vibration and pinprick sensation was found. Romberg sign was present. The rest of the neurological examination was normal. Electrodiagnostic study showed that sensory nerve action potential,compound muscle action potential is diminished on bilateral upper and lower extremities. To exclude a possible accompanying plasma cell disorder,serum protein electrophoresis,serum immunofixation electrophoresis, serum free kappa and lambda light chains were odered and revealed no monoclonal protein. But further urine immunofixation electrophoresis revealed a lambda monoclonal protein in urine. Then serum VEGF and IL6 levels were ordered. At the same time because of a previous CT scan showing multiple mediastinal masses, a PET scan was ordered to document any FDG avid masses. Serum VEGF level was 531 pg/ml (<96 pg/ml) and serum IL-6 level was measured as 24.75 pg/ml (<7 pg/ml) PET scan revealed axillary, paraaortic and aorta-caval masses with a biggest dimension of 5x4 cm and a maximum SUVmax of 3.5. Excisional biopsy of the most FDG avid mass was reported as hyalin vascular type Castleman Disease. He also suffered from coronary artery disease and a chronic subdural hematoma, which are now regarded as the vascular complications of PCD. The patient was diagnosed as CD-POEMS and a combination of Daratumumab – Lenalidomide – Dexamethasone was initiated with a protocol of weekly Daratumumab 16 mg/m2 for first 2 cycles, then once in every two weeks for 4 cycles and then once in a month with the same dose, Lenalidomide 25 mg po 21/28 and dexamethasone 20 mgs per day D1,2 D8,9 D15,16 /28. The aforementioned triple combination was well tolerated. After the 1st cycle of the treatment a VEGF response was achieved, and serum VEGF level was declined to 27.2 pg/ml. Also the serum IL-6 level was decreased and measured as 6.31 pg/ml. The patient was able to stand up and walk with the help of two walking sticks. The PET scan revealed a complete response regarding the Castleman component of the disease. At the third cycle of DRd combination he also underwent a successful revascularization of coronary arteries for the treatment of coronary artery disease. He is now on the 6th Cycle of the treatment with an ongoing and even deepening hematological and neurological response and able to walk without any support.

Summary/Conclusion: This case should serve as a proof of consept among the efficacy and safety of Daratumumab-Lenalidomide-Dexamethasone combination in the treatment of castleman variant of POEMS syndrome.

Myeloproliferative neoplasms - Clinical

PB1700 SCREENING OF SOMATIC MUTATIONS IN THE CALR GENE BY HIGH-RESOLUTION MELTING CURVE ANALYSIS

D. Kurochkin [1,*], T. Subbotina [1], A. Khazieva [2], E. Dunaeva [3], K. Mironov [3]

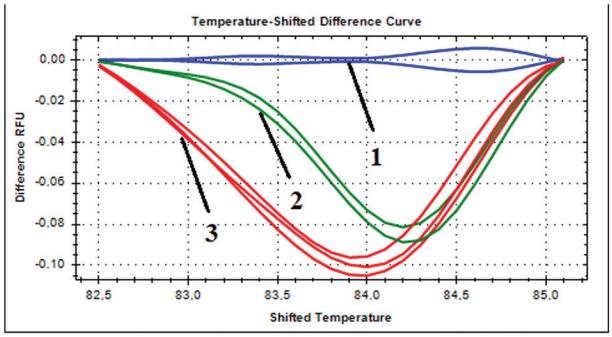
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Background: In accordance with the WHO clinical guidelines, the analysis of somatic mutations in the CALR gene, as well as mutations in the JAK2 and MPL genes, are included in the list of criteria for the Ph-myeloproliferative neoplasms (Ph-MPN) diagnosis. More than 50 different mutation variants have been found in the CALR gene, among which the most frequent are a 52 bp deletion (p.L367fs*46), also called type 1, and a 5 bp insertion (p.K385fs*47), also called type 2 (88%). The remaining 12% are other type less frequent indels or combinations. Therefore, it is important to develop an inexpensive screening test that can detect any mutations in the analyzed DNA fragment of the CALR gene.

Aims: The aim of this study was to screen CALR mutation by HRM analysis using the CFX96 thermocycler and the Precision Melt Analysis software (Bio-Rad, USA) for patients with Ph-MPN.

Methods: 5 CALR«+» DNA samples from MPN patients were included in this study. HRM analysis was performed using a Precision Melt Supermix reagent kit in the presence of Eva Green dye (Bio-Rad, USA). PCR with an additional high-resolution melting step was carried out on a CFX96 device (Bio-Rad, USA) according to the following program: denaturation at 95 ° C for 2 minutes, then 40 cycles at 95 ° C for 10 seconds, 57 ° C in for 30 seconds and 72 ° C for 30 seconds. The high resolution melting program consisted of denaturation at 95 ° C for 30 seconds, renaturation at 60 ° C for 1 minute, and melting at 65 ° C to 95 ° C with a 0.2 ° C gradient in 10 seconds. For the most common CALR mutations (c.1092_1143del and c.1154_1155insTTGTC), a threshold determination of the mutant allele presence was analyzed. To analyze the threshold for determining the proportion of the mutant allele, dilution of cloned wild-type and mutated samples was performed to obtain samples with different levels of allelic loads 100%, 50%, 25%, 12.5%, 6.25%, 3.13%

Results: The results of CALR«+» samples analysis after processing in the "Precision Melt Analysis" program are shown in Figure 1. According to the figure, all melting curves of amplification products from CALR«+» DNA samples are clearly divided into two clusters relative to samples without mutations (cluster No 1). So, two out of five CALR«+» samples (the sample with a classical mutation of type 2 (c.1154_1155insTTGTC) and the sample with a combined mutation (c.1128_1129insCTTTGCT; c.1131_1133delAGA)) were assigned to one cluster (cluster No 2). The three other samples with type 1 mutation (c.1092_1143del) were assigned also to one cluster (cluster No 3). The detection thresholds in case of the c.1092_1143del and c.1154_1155insTTGTC mutation analysis are 12.5% of the presence of the mutant allele in the samples.



Summary/Conclusion: Therefore, the HRM analysis that was conducted on the CFX96 allows screening of highly specific mutation for the diagnosis of Ph-MPN in the exon 9 of the CALR gene. The inclusion of this screening research in the laboratory testing algorithm improves the efficiency and accessibility of molecular genetic technologies in the diagnosis of Ph-MPN.

PB1701 SYSTEMIC MASTOCYTOSIS: A RETROSPECTIVE STUDY OF A SINGLE-CENTER'S EXPERIENCE ON A RARE DISEASE

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Background: Systemic Mastocytosis (SM) is a rare and heterogeneous disease characterized by the proliferation and accumulation of neoplastic mast cells in one or more organ systems. Its manifestations range from an indolent disease, to a highly aggressive neoplasm with associated multiorgan failure. Due to its rarity and wide range of symptoms, SM can be challenging to diagnose so a high index of suspicion should be maintained throughout the course of investigation of these patients.

Aims: To describe a single-center's experience on the diagnosis and management of SM with special emphasis on its presenting manifestations and symptoms.

Methods: A retrospective revision of adult patients referred to our department and diagnosed with SM was performed. The diagnosis of SM followed the 2016 WHO classification criteria. Laboratory/diagnostic

findings and patient management was carried out in collaboration with a specialized center.

Results: Eleven patients were diagnosed with SM at our institution, 5 females (45%) and 6 males (55%), with a median age at diagnosis of 52 years (range 38-68). Most patients (n=9, 82%) were referred to our clinic from other departments at our institution, while 2 patients (18%) were referred directly from their General Practitioner. Four patients (36%) presented with cutaneous manifestations, had a previous skin biopsy which confirmed mastocytosis in the skin, and were referred to exclude SM; 3 patients (27%) had previous severe anaphylaxis requiring hospitalization, 1 with cardiac arrest and admission to an Intensive Care Unit; 1 patient (9%) was referred for suspicion of an acute leukemia; the remainder 3 patients (27%) were referred for investigation of splenomegaly, polycythemia and eosinophilia. Regarding the diagnostic approach, all patients performed a complete blood count and basic biochemical evaluation, serum tryptase level measurement, bone marrow biopsy with morphologic and immunophenotypic study of mast cells. Nine patients (82%) had a *KIT D816V* mutation analysis. The presence of B and C findings was also evaluated. Hence 7 patients (64%) were diagnosed with Indolent SM (ISM) and 4 patients were diagnosed with other forms of SM, 1 case (9%) each: Smoldering SM (SSM); Aggressive SM (ASM); Mast Cell Leukemia (MCL); and SM with an associated hematological neoplasm (SM-AHN). The median time from first symptoms to diagnosis was 4 years, ranging from 3 months to 38 years. The main symptoms of our cohort are presented on Table 1. All patients received symptomatic treatment according to their needs, with H1 and H2 anti-histamines, sodium cromoglycate, biphosphonates, bee/wasp immunotherapy, omalizumab, among others. The patient with ASM received several cytoreductive therapies (pegylated interferon-α, cladribine, dasatinib), but only after initiation of midostaurin was the disease stabilized. The MCL patient was treated with cladribine with poor response, dying from refractory disease 1 month after diagnosis. All the remaining patients are still alive and under clinical surveillance.

Table 1: Clinical Manifestations

	Total	ISM	SSM	ASM	MCL	SM-AHN
Number	11 (100%)	7 (63,6%)	1 (9,1%)	1 (9,1%)	1 (9,1%)	1 (9,1%)
Clinical Manifestations						
Cutaneous	9 (81,8%)	6 (85,7%)	1 (100%)	1 (100%)	0	1 (100%)
Anaphylaxis	4 (36,3%)	3 (42,9%)	0	1 (100%)	0	0
Hymenoptera venom	3 (27,3%)	3 (42,9%)		0		
Food/Drugs	1 (9,1%)	0		1 (100%)		
Gastrointestinal	6 (54,5%)	4 (57,1%)	1 (100%)	1 (100%)	0	0
Nausea/Vomiting	2 (18,2%)	1 (14,3%)	0	1 (100%)		
Gastritis	4 (36,4%)	3 (42,9%)	1 (100%)	0		
Diarrhea	2 (18,2%)	1 (14,3%)	0	1 (100%)		
Cardiovascular	2 (18,2%)	1 (14,3%)	0	1 (100%)	0	0
Syncope	1 (9,1%)	0		1 (100%)		
Flushing	1 (9,1%)	1 (14,3%)		0		
Neurological	4 (36,3%)	4 (57,1%)	0	0	0	0
Brain fog	2 (18,2%)	2 (28,6%)				
Depression	2 (18,2%)	2 (28,6%)				
Headache	1 (9,1%)	1 (14,3%)				
Musculoskeletal	3 (27,3%)	1 (14,3%)	1 (100%)	1 (100%)	0	0
Osteopenia/porosis	3 (27,3%)	1 (14,3%)	1 (100%)	1 (100%)		
Osteolysis	1 (9,1%)	0	0	1 (100%)		
Bone pain	3 (27,3%)	1 (14,3%)	1 (100%)	1 (100%)		
Constitutional	3 (27,3%)	0	0	1 (100%)	1 (100%)	1 (100%)
Organopathy	3 (27,3%)	0	1 (100%)	1 (100%)	1 (100%)	0
Hepatomegaly	2 (18,2%)		0	1 (100%)	1 (100%)	
Splenomegaly	3 (27,3%)		1 (100%)	1 (100%)	1 (100%)	
Cytopenias	2 (18,2%)		0	1 (100%)	1 (100%)	

ISM: Indolent Systemic Mastocytosis; SSM: Smoldering Systemic Mastocytosis; ASM: Aggressive Systemic Mastocytosis; MCL: Mast Cell Leukemia; SM-AHN: Systemic Mastocytosis with an Associated Hematological Neoplasm

Summary/Conclusion: Our data illustrates the heterogenicity of the clinical manifestations of SM. Patients range from nearly asymptomatic to severely ill, with a wide array of symptoms that can mimic other diseases. A multidisciplinary approach is of utmost importance for an earlier diagnosis of this rare condition and for a correct approach on the treatment options for these patients. Furthermore, an international collaborative work would certainly help further understand the clinical course of this disease and would be beneficial for the development of novel treatment strategies.

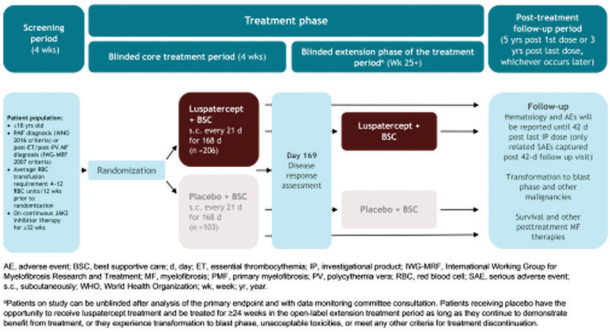
PB1702 EFFICACY AND SAFETY OF LUSPATERCEPT VERSUS PLACEBO IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASM-ASSOCIATED MYELOFIBROSIS ON JAK2 INHIBITOR THERAPY AND REQUIRING RBC TRANSFUSIONS (INDEPENDENCE TRIAL)

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Background: Myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) is a clonal myeloid neoplasm characterized by defective bone marrow (BM) function, BM fibrosis, ineffective erythropoiesis, and increased risk of progression to acute myeloid leukemia (AML). Up to 60% of patients (pts) with MF present with anemia at diagnosis, and eventually all pts go on to develop anemia. Anemia associated with transfusion-dependent MF is associated with poor survival and there are limited treatment options. Luspatercept is a first and only erythroid maturation agent approved in both the EU and the USA for treatment of anemia in pts with β-thalassemia who require red blood cell (RBC) transfusions and in pts with lower-risk myelodysplastic syndromes with ring sideroblasts who failed erythropoiesis-stimulating agent (ESA) treatment and require RBC transfusions. In a preliminary analysis of a phase 2 trial evaluating luspatercept in pts with MF-associated anemia (NCT03194542), 27% of pts achieved at least one ≥12-week (wk) episode of RBC transfusion independence (TI) with luspatercept within the first 24 wks of treatment (Gerds et al. *Blood* 2020;136(suppl 1):47–48).
Aims: This trials-in-progress abstract details eligibility criteria and trial design of the currently enrolling phase 3 INDEPENDENCE trial.
Methods: INDEPENDENCE is a phase 3, double-blind, randomized trial to evaluate the efficacy and safety of luspatercept versus placebo in pts with MPN-associated MF receiving concomitant JAK2 inhibitor therapy who require RBC transfusions. Eligible pts must be ≥18 years old, have a documented diagnosis of primary MF, post-essential thrombocythemia MF or post-polycythemia MF, require regular RBC transfusions (defined as 4–12 RBC units/12 wks prior to randomization), and receiving JAK2 inhibitor therapy for ≥32 wks (on stable daily dose for ≥16 wks) prior to randomization. Exclusion criteria include presence of anemia due to causes other than MPN-associated MF or JAK2 inhibitor therapy, and prior use of hydroxyurea, immunomodulatory compounds (pomalidomide, thalidomide), ESAs, androgenic steroids, or other drugs with potential effects on hematopoiesis ≤8 weeks before randomization. Following screening, ~309 pts will be randomized 2:1 to either luspatercept (starting at 1.33 mg/kg with titration up to 1.75 mg/kg) subcutaneously every 3 wks, or placebo (Figure). Best supportive care, including RBC transfusions, iron chelation therapy, antibiotic, antiviral, and/or antifungal therapy, is permitted in both treatment arms. Stratification factors include RBC transfusion burden and Dynamic International Prognostic Scoring System (DIPSS) score at baseline.
Results: Clinical benefit (CB) will be assessed after 24 wks of treatment, and is defined as RBC-TI for any consecutive ≥12-wk period during Wks 1–24 of study, a reduction in RBC transfusion burden by ≥50% and by ≥4 units for ≥12 wks during Wks 1–24, or an incomplete duration of response, defined as being free from RBC transfusions for ≥4 wks immediately up to the end of 24 wks. Pts achieving CB can continue luspatercept treatment as long as they continue to benefit, or until progression to AML, unacceptable toxicities, withdrawal of consent, or until meeting any other criteria for treatment discontinuation. Primary endpoint of the study is the proportion of pts who become RBC-transfusion free over any consecutive 12-wk period starting from randomization up to and including Wk 24.

Figure. The INDEPENDENCE trial design



AE, adverse event; BSC, best supportive care; d, day; ET, essential thrombocythemia; IP, investigational product; IWG-MRF, International Working Group for Myelofibrosis Research and Treatment; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera; RBC, red blood cell; SAE, serious adverse event; s.c., subcutaneously; WHO, World Health Organization; wk, week; yr, year.

*Patients on study can be unblinded after analysis of the primary endpoint and with data monitoring committee consultation. Patients receiving placebo have the opportunity to receive luspatercept treatment and be treated for ≥24 weeks in the open-label extension treatment period as long as they continue to demonstrate benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

Summary/Conclusion: The INDEPENDENCE trial is registered at EudraCT (2020-000607-36) and ClinicalTrials.gov (NCT04717414).

PB1703 THE FREQUENCY OF CD34+ CELLS PER CD45+ CELLS IN PERIPHERAL BLOOD ENUMERATED BY AUTOMATED METHOD IS EFFECTIVE AS A NON-INVASIVE MARKER OF MYELOFIBROSIS IN THE PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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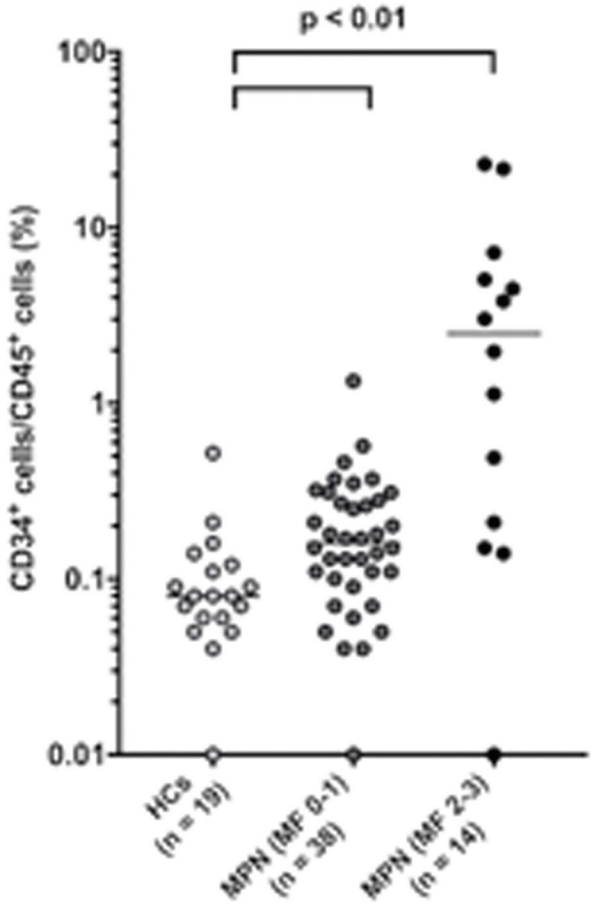
Background: The CD34+ cells in peripheral blood (PB) increased in myeloproliferative neoplasm (MPN) patients with myelofibrosis (MF) compared with MPN patients without MF, and were significantly correlated with disease duration, spleen volume, liver volume and risk classification. Further, the CD34+ cells in PB could be useful as a biomarker for prognosis and follow-up in the allo-SCT setting in MPN patients with MF.

Flow cytometric applications for CD34+ cell enumeration provide a rapid, quantitative, and reproducible method. However, significant site-to-site variation has been reported. Moreover, the variability associated with hematology-derived absolute counts is quite considerable. Single-platform flow cytometric absolute cell counting protocols have been shown to provide increased robustness of CD34+ enumeration. Enumeration of the cell populations in this study is obtained using an automated method for gating and analysis.

Aims: This study aimed to investigate the correlation between the frequency of CD34+ cells per CD45+ cells in PB (CD34+ cells/CD45+ cells) and MF progression, splenomegaly or cytokine levels.

Methods: We measured CD34+ cells/CD45+ cells of 19 healthy controls (HCs) and 52 MPN patients without ruxolitinib (Rux) treatment using BD™ Stem Cell Enumeration Kit®. The MPN patients with Rux treatment were excluded from this study because these patients had already been diagnosed MF before Rux treatment and Rux could affect the cytokine profiles and splenomegaly. The bone marrow biopsy was also performed at the same time as the PB sample collection. We also examined the concentration of 24 cytokines in the serum of 52 MPN patients using Human Luminex® Assays. Thereafter, we assessed the correlations between CD34+ cells/CD45+ cells and MF onset, splenomegaly or cytokine levels.

Results: The median percentage of CD34+ cells/CD45+ cells of HCs (n = 19), MPN patients with MF grade 0-1 (n = 38) and MPN patients with MF grade 2-3 (n = 14) were 0.08%, 0.16%, and 2.49%, respectively. Compared with HCs and MPN patients with MF grade 0-1, CD34+ cells/CD45+ cells of MPN patients with MF grade 2-3 significantly increased ($p < 0.01$). Further, MPN patients with MF grade 2-3 had significantly higher CD34+ cells/CD45+ cells than MPN patients with MF grade 0-1 ($p < 0.01$). For the ROC curve, the sensitivity and specificity for classifying MF grade 2-3 were 71.4% and 94.7% with the cutoff set to > 0.5%. Moreover, the sensitivity for detecting MF progression of CD34+ cells/CD45+ cells (71.4%) was approximately two times higher than that of the blast emergence in hemogram (35.7%). On the other hand, the median percentage of CD34+ cells/CD45+ cells of MPN patients without splenomegaly (n = 41) and MPN patients with splenomegaly (n = 11) were 0.17% and 3.81%. MPN patients with splenomegaly had significantly higher CD34+ cells/CD45+ cells than those without splenomegaly ($p < 0.01$). For the ROC curve, the sensitivity and specificity for classifying splenomegaly onset were 72.7% and 95.1% with the cutoff set to > 1.0%. In addition, TNF-a, IL-8 and CXCL1 showed significant correlations with CD34+ cells/CD45+ cells ($R^2 = 0.538$, 0.435 and 0.260, respectively).



Summary/Conclusion: In our study, CD34+ cells/CD45+ cells in PB elevated in MPN patients with MF grade 2-3, and was significantly correlated with MF grade, splenomegaly, TNF-a, IL-8 and CXCL1. It would be worth evaluating the efficacy of CD34+ cells/CD45+ cells as non-invasive markers of MF progression in a prospective study.

PB1704 CLINICAL BENEFIT IN REAL LIVE OF ALTERNATIVE RUXOLITINIB DOSING REGIME IN MYELOFIBROSIS PATIENTS

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Background: Despite ruxolitinib is considered the standard of care for patients with myelofibrosis (PMF and post-ET/post-PV MF) in not allogeneic stem-cell transplant candidates with Intermediate or High-risk IPSS, is necessary to confirm in real live the clinical benefit, in spleen, symptomatic responses and overall survival (OS) outcomes, achieved in COMFORT-I and -II trials. In the other hand, nearly half of the patients develop grade 3/4 anemia or thrombocytopenia, that usually lead to a dose reduction, that can have a negative impact on its efficacy.

Aims: We conducted this study to evaluate the differences on clinical benefit of alternative rusolitinib dosing regime in real live.

Methods: 6-year observational retrospective study of 53 patients with myelofibrosis (years 2013 -2019), 41 of them, not allogeneic stem-cell transplant candidates on ruxolitinib therapy, stratified by IPSS, DIPSS-PLUS and MIPSS 70+ v.2.0, and divided into 2 arms according to the maximum dose reached of ruxolitinib (A ≥ 15 mg BID and B <15 mg BID). We evaluated the rate of response according to IWG-MRT-2013 criteria, and we perform a survival analysis.

Results: 41 not candidates for transplantation on Ruxolitinib therapy (median age 62 year; 11 PMF and 30 Post-ET and Post-PV). Group A ≥

15 mg BID (N=19) and B <15 mg BID (N=22). With a median follow-up of 19 months (9,5-45), we observe a similar duration of treatment, IPSS and DIPSS-Plus score in both arms, although the MIPSS70+ high score was more frequent in B arm (66,7% vs. 15,4%; p=0.026). We did not observe statistically significant differences in spleen response (A 52,9% vs. B 25,0%; p=0.081), symptomatic responses (A 84,2% vs. B 63,6%; p=0.138) or 5-years OS (A 89.5% vs. B 75.1%; P=0.300), although the hematological improvement is more frequent in arm A (63.5% vs. 22.7%; p=0.009).
Summary/Conclusion: Despite the observed trend of lower spleen and symptomatic responses in arm B (ruxolitinib <15 mg BID), these are not statistically significant, and these do not translate into differences in OS in real live. High-risk MIPSS 70+ more frequently need dose reduction of Ruxolitinib, due to their baseline cytopenias, and probably this factor is the most important for evaluation of clinical benefit of Ruxolitinib in real live.

PB1705 REAL-LIFE RUXOLITINIB EXPERIENCE IN AN INTERMEDIATE-1 RISK PREDOMINANT COHORT

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Background: Data regarding ruxolitinib safety and efficacy in intermediate-1 risk patients are scarce.
Aims: In this retrospective study, we aimed to document a real-life clinical experience with ruxolitinib in predominantly intermediate risk primary and secondary MF patients.
Methods: Fifty six patients who received ruxolitinib were included into the analyses. All patients were at least 18 years of age and they had INT-1/2 or high risk disease according to DIPSS-plus risk classification.
Results: Patients
The median age of patients was 58 (23-80) years. Overall, 50.9% of patients were male and 49.2 % had PMF. Patient assignment according to DIPSS-plus risk categories goes as follows: 33 patients (57.9 %) in INT-1, 23 patients (40.4 %) in INT-2, 1 patients (1.8%) in high-risk. Hydroxyurea was used previously by 91.2% of the patients before ruxolitinib. JAK2 was obtained positive in 71.9% of the patients.
Efficacy
Overall, a spleen size reduction of at least 35% (spleen response) was achieved in 56.6% of patients (30/53) at any time. A spleen response at 6 months was observed in 41.5 % of patients. Only 36.6 % (11/30) of the patients in INT-1 myelofibrosis group achieved a spleen response at 6 months.
Twenty three patients had MPN-SAF TSS during the course of the treatment. Five patients (21.7%) had at least 50% reductions in myelofibrosis associated symptoms. In 10 patients (43.5%), a 20-50% reduction in symptom score was observed. Four patients (17.4%) had only mild (5-10%) symptom responses.
Safety
Median duration of exposure to ruxolitinib was 22 months (range: 1-80 months). Forty-two patients (%73.7) were still receiving ruxolitinib. Initial dose of ruxolitinib was 20 mg bid in 67% of the patients.
Fifty two out of 57 (91%) experienced any kind of hematologic side effect. Most common hematologic adverse events were anemia (all grades, 84.2%; grade 3-4, 42.1%) and thrombocytopenia (all grades, 38.6%; grade 3-4, 17.5%). Cytopenias were more prominent within the first three months.
A total of 27 out of 57 patients experienced non-hematologic side effects, which were generally grade 1-2. Most common non-hematologic adverse events were fatigue, pneumonia, and elevated liver enzymes. Pulmonary embolism was observed in two patients who had pneumonia. Herpes zoster infection, hepatitis B virus (HBV) reactivation, and urinary tract infection were noted. Overall, three patients diagnosed with cancer including pancreas adenocarcinoma, squamous cell carcinoma of the skin and metastatic neuroendocrine tumor. Patients with INT-1 risk had the similar safety profile.
Survival
A total of 17 (29.8%) deaths occurred during a median follow-up of 22 months. Causes of death were as follows: transformation to acute myeloid leukemia (n=5), disease progression (n=11), and pancreas adenocarcinoma (n=1). In all cohort, overall survival probability at 24 months was 75.1% (95% CI: 59.8% to 85.3%). Median overall survival was not reached.
Since previous studies claim that basal hemoglobin levels lower than 10 g / dL was associated with worse survival outcomes, we stratified survival probabilities according to basal hemoglobin levels as well. Median survival was not reached in both group with Hb< 10 g / dL and Hb ≥ 10 g / dL during the first 2 years, patients with a Hb ≥ 10 g / dL seem to have a better survival. Two year survival probabilities were 58.5 % (95% CI: 34.5 to 76.4%) versus 87.5 % (95% CI: 65.5% to 95.9%), respectively. However, survival curves merged at month 33 and beyond (p=0.15).
Summary/Conclusion: Ruxolitinib is safe and effective in all risk groups of patients with myelofibrosis.

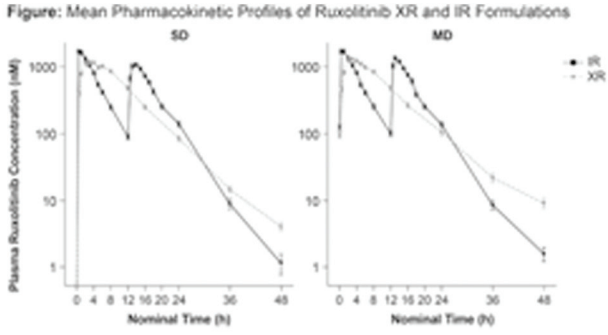
PB1706 BIOEQUIVALENCE OF 50 MG ONCE-DAILY RUXOLITINIB EXTENDED RELEASE (XR) TABLETS COMPARED TO 25 MG TWICE-DAILY RUXOLITINIB IMMEDIATE RELEASE (IR) TABLETS

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Background: Ruxolitinib is currently dosed twice-daily (BID) using an immediate release (IR) formulation for the treatment of myelofibrosis, polycythemia vera, and acute graft-versus-host disease. An extended release (XR) formulation of ruxolitinib was developed to allow once-daily (QD) dosing. Five XR tablet strengths were developed, containing 10, 20, 30, 40, and 50 mg of ruxolitinib, free base equivalent.
Aims: To establish the bioequivalence of the highest strength of ruxolitinib XR tablets (50 mg) dosed QD to the highest strength of ruxolitinib IR tablets (25 mg) dosed BID, following a single dose and at steady-state.
Methods: This phase 1, open-label, randomized, 2-period, 2-way crossover study in 60 healthy adult participants evaluated single-dose and steady-state bioequivalence of ruxolitinib 50 mg XR tablets compared to ruxolitinib 25 mg IR tablets. In treatment period 1, participants were randomly assigned to receive ruxolitinib XR or ruxolitinib IR; following a 9-day washout period, participants entered treatment period 2 and crossed over to receive the other formulation (IR or XR, respectively). Each treatment period consisted of single-dose and multiple-dose parts. In the single-dose part of the study, participants received either ruxolitinib XR 50 mg as a single dose or ruxolitinib IR as 2 doses of 25 mg each administered 12 hours apart; in the multiple-dose part of the study, participants received ruxolitinib XR 50 mg QD or ruxolitinib IR 25 mg BID for 4 days (4 doses and 8 doses, respectively). Standard non-compartmental pharmacokinetic (PK) analysis methods were used to calculate PK parameters. Average bioequivalence analysis was performed for the determination of geometric mean ratio (GMR) and 90% confidence interval (CI) for the comparison of PK parameters between the test formulation (XR) and the reference formulation (IR). Bioequivalence criteria required the point estimate and 90% CI limits to lie within the range of 0.8-1.25. The measures used for bioequivalence evaluation included C_{max}, C_{24h}, AUC_{0-t}, and $AUC_{0-\infty}$ from the single-dose part, and $C_{max,ss}$, C_{24h}, and AUC_{0-24h} from the multiple-dose part. Safety and tolerability were assessed by monitoring the frequency and severity of adverse events; performing physical examinations; and collecting vital signs, 12-lead electrocardiograms, and clinical laboratory data.
Results: The PK profiles of ruxolitinib XR and IR for single dose and multiple-dose parts are shown in Figure 1. The 50 mg ruxolitinib XR tablet formulation met the bioequivalence criteria for AUC parameters both following a single dose and at steady-state; bioequivalence was not achieved for C_{max} or C_{24h}. All treatments were well tolerated and no new safety findings were observed with administration of ruxolitinib XR.

Figure: Mean Pharmacokinetic Profiles of Ruxolitinib XR and IR Formulations



IR, immediate release; MD, multiple-dose; SD, single dose; XR, extended release.
Error bars represent ±1 × standard error.

Summary/Conclusion: Ruxolitinib XR 50 mg tablets dosed QD is bioequivalent to 25 mg IR tablets dosed BID, based on AUC parameters. No new safety concerns were observed with ruxolitinib XR.

PB1707 ESSENTIAL THROMBOCYTHEMIA AND THE RISK OF POLYPHARMACY: ASSESSMENT OF POTENTIAL DRUG-DRUG AND FOOD-DRUG INTERACTIONS

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Background: Polypharmacy is defined as the concurrent use of 5 or more medications/day by a single subject. As the lifespan increases worldwide, patients diagnosed with essential thrombocythemia (ET) are often exposed to polypharmacy due to age-related comorbidities and lifelong ET management.
Aims: Identify polypharmacy use and the risk of potential drug-drug (DDI)/food-drug interactions (FDI) in ET patients on risk-adapted therapy.
Methods: The electronic medical records of the Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest, Romania, were searched from inception (available since August 2014) to February 2021. We included all ET patients who received risk-adapted therapy, had signed the written informed consent for participation in medical research and for whom information regarding prescribed medications was available. The study was approved by the hospital's ethics council (35552/22.10.2020). DDI/FDI were evaluated using an online drugs interaction checker.
Results: We identified 15 ET patients, median age 65 years, range 41-80 years, 60.0% females. Cytoreductive therapy was based predominantly on hydroxycarbamide (73.3%), anagrelide (13.3%) or their combination (13.4%). Due to thrombotic risk and associated comorbidities, most patients received antiplatelet drugs (acetylsalicylic acid 13.3%, clopidogrel 13.3%) or systemic anticoagulation alone (acenocoumarol 20.0%, dalteparin 13.3%) or their combination (acetylsalicylic acid + acenocoumarol 6.67%, clopidogrel + rivaroxaban 6.67%). Polypharmacy was detected in 66.67% of ET cases, all patients receiving at least 3 drugs/day. The mean number of prescribed drugs, DDI and FDI were 6.67±2.91 (range 3-12), 4.40±5.83 (range 0-24) and 1.87±1.82 (range 0-8). We recorded 66 DDI (20 major, 1.33±1.81/patient; 36 moderate, 2.40±3.44/patient; 10 minor, 0.67±0.87/patient) and 28 FDI (6 major, 0.40±0.61/patient; 20 moderate, 1.33±1.49/patient; 2 minor, 0.13±0.34/patient). Hydroxycarbamide led to 2 major DDI with infliximab and 1 moderate DDI with *Saccharomyces boulardii*. Anagrelide led to 5 major DDI with amiodarone, ciprofloxacin, dalteparin, ivabradine and rivaroxaban, and 2 moderate DDI with carvedilol and omeprazole. The main DDI and the drugs which led to FDI are reported in the attached tabel. The mean number of drugs prescribed correlated with the number of DDI (r=+0.887, P<0.001), major DDI (r=+0.743, P=0.002), moderate DDI (r=+0.834, P<0.001), minor DDI (r=+0.706, P=0.003), FDI (r=+0.735, P=0.002), moderate FDI (r=+0.731, P=0.002), but not with the number of major/minor FDI (P=0.207 and P=0.242, respectively). The number of DDI-per-patient also correlated with the number of FDI-per-patient (r=+0.879, P<0.001), major (r=+0.548, P=0.035) and moderate (r=+0.785, P=0.001) FDI, but not minor FDI (P=0.179). Surprisingly, there was no correlation between the age of ET patients and the number of drugs prescribed/DDI/FDI or major/moderate/minor FDI/DDI.
Summary/Conclusion: Risk-adapted therapy remains safe in ET, yet due to age-related comorbidities and increased risk of polypharmacy, these patients should be closely monitored to avoid DDI and FDI and reduce medication burden. To our knowledge, this is the first assessment of polypharmacy and DDI/FDI in ET. However, since there was no correlation of the number of drugs prescribed or of the DDI/FDI with the age of the participants, this might signal that polypharmacy is emerging as a public health issue irrespective of age and points out that the multidisciplinary team involved in the management of ET patients could also include clinical pharmacists/pharmacologists.

Major DDI	N	%
hydroxycarbamide - infliximab	2	10.00%
anagrelide - amiodarone	1	5.00%
anagrelide - ciprofloxacin	1	5.00%
anagrelide - dalteparin	1	5.00%
anagrelide - ivabradine	1	5.00%
anagrelide - rivaroxaban	1	5.00%
acenocoumarol - amiodarone	1	5.00%
acenocoumarol - aspirin	1	5.00%
acenocoumarol - ciprofloxacin	1	5.00%
acenocoumarol - metronidazole	1	5.00%
amiodarone - ciprofloxacin	1	5.00%
amiodarone - furosemide	1	5.00%
ciprofloxacin - glimepiride	1	5.00%
clopidogrel - esomeprazole	1	5.00%
clopidogrel - omeprazole	1	5.00%
clopidogrel - rivaroxaban	1	5.00%
dalteparin - naproxen	1	5.00%
infliximab - budesonide	1	5.00%
infliximab - methylprednisolone	1	5.00%
TOTAL	20	100%

Minor DDI	N	%
acenocoumarol - propranolol	2	20.00%
aspirin - carvedilol	1	10.00%
aspirin - pantoprazole	1	10.00%
calcium carbonate - methylprednisolone	1	10.00%
ciprofloxacin - furosemide	1	10.00%
ciprofloxacin - metoprolol	1	10.00%
esomeprazole - glimepiride	1	10.00%
insulin - potassium chloride	1	10.00%
nitroglycerin - omeprazole	1	10.00%
TOTAL	10	100%

Moderate DDI	N	%
anagrelide - carvedilol	1	2.77%
anagrelide - omeprazole	1	2.77%
hydroxycarbamide - saccharomyces boulardii	1	2.77%
acenocoumarol - allopurinol	1	2.77%
acenocoumarol - amoxicillin	1	2.77%
acenocoumarol - esomeprazole	1	2.77%
acenocoumarol - glimepiride	1	2.77%
acenocoumarol - metformin	1	2.77%
acenocoumarol - omeprazole	1	2.77%
acenocoumarol - pantoprazole	1	2.77%
acenocoumarol - ranitidine	1	2.77%
amiodarone - metoprolol	1	2.77%
amlodipine - aspirin	1	2.77%
aspirin - calcium carbonate	1	2.77%
aspirin - methylprednisolone	1	2.77%
budesonide - saccharomyces boulardii	1	2.77%
candesartan - lorazepam	1	2.77%
carvedilol - insulin	1	2.77%
carvedilol - lorazepam	1	2.77%
celecoxib - diclofenac	1	2.77%
ciprofloxacin - metformin	1	2.77%
ciprofloxacin - pioglitazone	1	2.77%
esomeprazole - furosemide	1	2.77%
esomeprazole - naproxen	1	2.77%
ferrous sulfate - omeprazole	1	2.77%
furosemide - glimepiride	1	2.77%
furosemide - metformin	1	2.77%
furosemide - metoprolol	1	2.77%
furosemide - pioglitazone	1	2.77%
glimepiride - metformin	1	2.77%
glimepiride - metoprolol	1	2.77%
infliximab - metronidazole	1	2.77%
infliximab - saccharomyces boulardii	1	2.77%
lorazepam - nitroglycerin	1	2.77%
mesalamine - vancomycin	1	2.77%
methenin - naproxen	1	2.77%
TOTAL	36	100%

FDI
Major
metformin
metronidazole
ivabradine
amiodarone
metformin
metronidazole
6 (100.00%)
Moderate
esomeprazole
esomeprazole
insulin
budesonide
methylprednisolone
calcium carbonate
lorazepam
candesartan
atorvastatin
acenocoumarol
propranolol
ciprofloxacin
metoprolol
glimepiride
pioglitazone
esomeprazole
acenocoumarol
acenocoumarol
propranolol
20 (100.00%)
Minor
amlodipine
ferrous sulfate
2 (100.00%)

PB1708 LYMPHOPENIA IS HIGHLY PREVALENT IN OVERT MYELOFIBROSIS AT DIAGNOSIS AND ASSOCIATED WITH THE DEGREE OF ANEMIA AND THROMBOCYTOPENIA.

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Background: Lymphopenia is common in a variety of malignancies, including lymphoma and myelodysplastic syndromes. Little is known about its prevalence in BCR-ABL1-negative myeloproliferative neoplasms (MPN) and its association to prognostic factors or systemic inflammation.
Aims: To evaluate the prevalence of lymphopenia in BCR-ABL-negative MPN at diagnosis and its possible association with disease-related or prognostic factors.
Methods: Patients diagnosed with a BCR-ABL1-negative MPN between 2010-2020 and having given informed consent were evaluated for the absolute lymphocyte count (ALC) at diagnosis. In addition, parameters of the DIPSS-(plus)-Score and markers of systemic inflammation (albumin, CRP) were retrospectively collected from hospital records. The study was approved by the local ethics committee.
Results: 116 patients were included into this preliminary analysis. The median ALC was significantly lower in overt Myelofibrosis (MF) compared to Essential Thrombocythemia (ET), Polycythemia Vera (PV) and prefibrotic PMF (1.3x10^9/L versus 1.8x10^9/L, 2.05x10^9/L and 1.9 x10^9/L, respectively; p=0.005).
An absolute lymphopenia (defined as ALC <1.0x10^9/L) was observed in 10/35 patients with overt MF (29%; primary MF n=24, post-ET MF n=3, post-PV MF n=8), 2/35 with ET (6%) and not seen in PV (0/30) and prefibrotic PMF (0/16).
Regarding the single factors of the DIPSS-(plus), the ALC was significantly lower in patients with a hemoglobin < 10 g/l and with platelets < 100x10^9/L (1.1 vs. 1.6x10^9/L; p=0.019; and 0.75 vs. 1.5 x10^9/L; p=0.036, respectively). Patients with leukocytes > 25x10^9/L (n=3) had higher lymphocyte counts (median 2.5 vs. 1.3 x10^9/L; p=0.02). For transfusion-dependency, a trend towards a lower ALC was observed (median 0.9 vs. 1.5x10^9/L, p=0.134). No significant differences of the median ALC were observed for absence/presence of constitutional symptoms, age ≤/> 65 years and peripheral blasts 9/L, intermediate-1 [n=12] 1.4x10^9/L, intermediate-2 [n=14] 1.2x10^9/L and high-risk [n=5] 1.9 x10^9/L; p=0.876). Since metaphase cytogenetics were available in a minority of patients only, the DIPSS-plus could not be evaluated.
Patients with a CRP > ULN (5 mg/l) or an albumin-concentration <35 g/l did not differ in regard to their median ALC (1.5 vs. 1.2x10^9/L, p=0.32 and 1.4 vs. 1.3x10^9/L, p=0.886). In addition, there was no difference of the median ALC between the different risk groups of the Glasgow Prognostic Score (GPS), which combines CRP >10mg/l and albumin < 35 g/l (GPS 0 [n=19]: 1.5 x10^9/L; GPS 1 [n=8]: 1.4 x10^9/L, GPS 2 [n=3] 1.1x10^9/L; p=0.927).
Summary/Conclusion: Within our MPN cohort, lymphopenia at diagnosis was largely restricted to patients with overt myelofibrosis with considerable prevalence in this entity. Its association with a lower hemoglobin concentration and lower platelet counts points towards a causal relationship of lymphopenia and the pathobiology of the MF-associated bone marrow failure. We were not able to show any influence of systemic inflammation on the ALC or any association of lymphopenia with disease-risk according to DIPSS. However, interpretation of our data is considerably hampered by

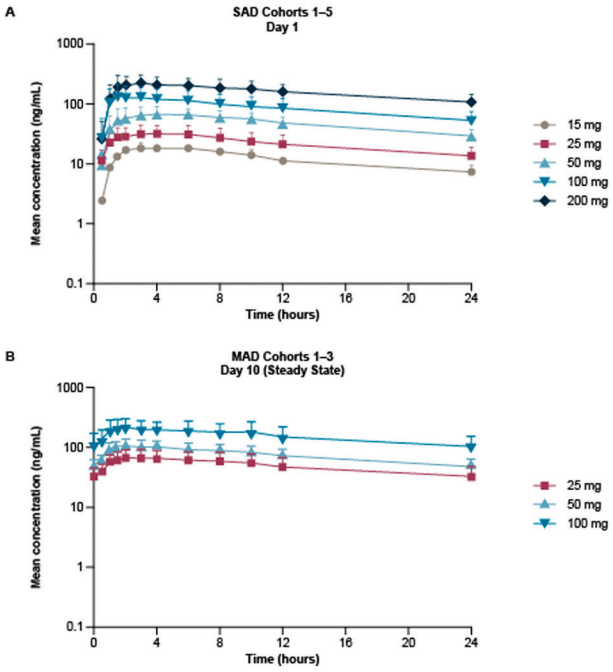
the low patient numbers and the retrospective nature of the analysis. Given the rarity of the disease, evaluation of larger (prospective) multicentric patient cohorts would be desirable in order to identify factors related to lymphopenia and to further elucidate its prognostic impact.

PB1709 SAFETY AND PHARMACOKINETICS OF BLU-263, A NEXT GENERATION KIT INHIBITOR, IN NORMAL HEALTHY VOLUNTEERS

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Background: BLU-263 is an investigational, potent, and selective oral small molecule inhibitor of KIT with sub-nanomolar potency against D816V-mutant KIT. Systemic mastocytosis is driven by the *KIT* D816V mutation in approximately 95% of cases and is vulnerable to KIT D816V inhibition. BLU-263 was highly active in a murine model of mastocytosis and was well tolerated with minimal central nervous system penetration in preclinical species.
Aims: Here we report the safety, tolerability, and pharmacokinetics (PK) of BLU-263 in an ongoing Phase 1, randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study.
Methods: In the SAD portion of the study, cohorts of eight normal healthy volunteers aged ≥19 years received either oral placebo (n=2/cohort) or single oral doses of BLU-263 (n=6/cohort) of 15, 25, 50, 100, or 200 mg. In the MAD portion of the study, normal healthy volunteer cohorts received either oral placebo or BLU-263 at 25, 50, or 100 mg once daily (QD) on each of 10 consecutive days. Blood plasma samples were collected for PK analyses at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-dose in SAD cohorts, and the same post-dose time points after dosing on days 1 and 10 in the MAD cohorts. Safety was assessed according to incidence and severity of adverse events (AEs) in recipients of BLU-263 as compared with placebo.
Results: BLU-263 was well tolerated across the five BLU-263 SAD cohorts and three MAD cohorts. Only Grade 1 AEs were reported, and most were assessed as not related to the study drug by the investigator. These AEs included pain at the blood-sampling site, headache, dry/itchy skin, nausea, and stomachache. No serious AEs were reported, and there were no clinically relevant findings in laboratory, electrocardiogram, or vital signs parameters. After administration of BLU-263 at single doses, the median time to maximum concentration ranged from 1.5 to 6 hours post-dose. The mean half-life of BLU-263 ranged from 20 hours to 28 hours, indicating that steady-state would be reached by Day 7, supporting QD dosing. After 10 days of repeated oral administration of 25 to 100 mg BLU-263, the geometric mean accumulation ratio for area under the curve ranged from 1.6 to 1.8. The geometric mean apparent volume of distribution ranged from 753 to 973 L, indicating wide tissue distribution. Overall, a dose-proportional increase in systemic exposure to BLU-263 was observed across the SAD and MAD cohorts (Figure).
Summary/Conclusion: BLU-263, a next-generation investigational KIT inhibitor, was well tolerated across all SAD and MAD cohorts in normal healthy volunteers. The PK of BLU-263 were linear across the dose ranges in SAD and MAD cohorts and support QD dosing. These data support the continued development of BLU-263 in patients with systemic mastocytosis and other mast cell disorders.



PB1710 GENERAL CHARACTERISTICS AND OUTCOME OF RENAL EXTRAMEDULLARY HEMATOPOIESIS IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS-A LITERATURE REVIEW

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Background: Extramedullary hematopoiesis (EMH) is hematopoiesis in organs outside the bone marrow.It occurs with several hematological conditions such as hereditary anemias,leukemias and myeloproliferative neoplasms (MPNs) such as myelofibrosis (MF), polycythemia vera (PV), essential thrombocytosis (ET) and chronic myeloid leukemias (CML). The sites of EMH include: Lymph nodes, thyroid, spinal, lung pericardium, pancreas.kidneys are a rare site to be involved. There are several theories with cytokines and growth factor production playing a central role in most. The spleen filter theory is an interesting one, where it is observed that in splenectomized patients, the kidneys will compensate as an EMH organ. Another theory speculates that haematopoietic cells are derived from resident kidney mesenchymal pluripotent cells that could proliferate as a response to a disease-related simulating factor.EMH can originate in the renal interstitium or could be perirenal, this leads to different clinical presentation such as proteinuria, nephrotic syndrome, and renal failure.
Aims: The objective is to review cases of EMH affecting the kidneys, focusing on demographics, clinical manifestations, treatment, follow up and outcomes.
Methods: We reviewed the literature using PubMed, Scopus, and Google scholar databases. Our search included all English language cited studies including case series and case reports that reported on renal EMH with a primary or background diagnosis of MPNs from 1990-2020
Results: forty-three patients (79 % males) were retrieved. The mean age of the cohort was 65 years (range 49-87years). Most of the cohort was white Caucasian 91 %. The type of MPNs was mostly MF, seen in 35 patients (81.4%), while PV was seen in 5 patients (11.6%), ET and CML were seen in 2(4.7%) and 1 (2.3%) patient, respectively.The most common renal manifestation was renal failure and nephrotic syndrome in 39.5 % of the cases, followed by renal failure alone 37.2 % and nephrotic syndrome only in 9.3 % and interestingly a renal mass was found 9% of the patient on imaging. Splenomegaly was found in 58 % of the patient while 14 % have already underwent Splenectomy. The average duration to developing EMH from time of diagnosis was 7.8 years (0- 20 years).Four patients developed EMH post-transplant, 3 of them allogenic while one autologous.The JAK mutation was reported in 7 patients and CALR mutation in one patient.Patient were treated with different medication including diuretics, anti-hypertensive (mainly ACE inhibitors) and steroids. However, for MPNs 25 % received HU, 14 % received Thalidomide or Thalidomide analogue while 16 % received JAK inhibitors; Ruxolitinib. The CML case was treated with Imatinib.The average duration of Follow up was 19 months with 42.5% death rate by the end of follow up.Kidney function improved in 31 % of patients, with Ruxolitinib administration correlating with improved kidney function and survival (6 out of 7 patients)
Summary/Conclusion: Kidneys are a rare but serious site for EMH. Unexplained Increase in renal function or proteinuria or kidney mass should raise the suspicion of this diagnosis among hematologist and nephrologist. We suspect there is underreporting in the hematology literature as there is lack of information on cytogenetics, types of mutations and risk stratifications.There is currently no consensus or guidelines on management of such cases. Ruxolitinib with the limitations of the small numbers treated may offer some benefit, however further studies and exploration of this drug and others in well-constructed prospective studies is needed

PB1711 PACIFICA: A RANDOMIZED, CONTROLLED PHASE 3 STUDY OF PACRITINIB VERSUS PHYSICIAN'S CHOICE IN PATIENTS WITH PRIMARY OR SECONDARY MYELOFIBROSIS AND SEVERE THROMBOCYTOPENIA

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Background: Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm (MPN) due to clonal proliferation of myeloid cells. Patients with MF and severe thrombocytopenia (platelet counts <50 x 10^9/L) are generally older and have more advanced disease with increased risk of bleeding, higher rates of anemia, higher rates of complex or unfavorable cytogenetics and shortened overall survival (~15 months) compared to those with higher platelet counts. Currently approved JAK inhibitors, ruxolitinib (RUX) and fedratinib (FED), were not studied in this high-risk population and neither drug has a recommended starting dose for the treatment of patients with severe thrombocytopenia. RUX often requires dose reductions for patients with platelet counts <100,000/mL, due to thrombocytopenia. Such dose reductions impair efficacy compared to higher doses. NCCN guidelines and ELN recommendations suggest enrollment in clinical trials for such patients due to limited therapeutic options. Pacritinib (PAC) is an oral JAK2/IRAK1 inhibitor that has demonstrated clinical activity in MF patients in prior phase 3 studies (PERSIST-1, PERSIST-2) and a phase 2 dose-finding study (PAC203), including in patients with severe thrombocytopenia.
Aims: The PACIFICA trial (NCT03165734) was designed to evaluate the efficacy and safety of PAC 200 mg twice daily (BID) vs physician's choice (P/C) therapy in patients with MF and severe thrombocytopenia.
Methods: PACIFICA is a multinational, multicenter, randomized, controlled phase 3 trial of PAC vs P/C in adult patients with primary or secondary MF who are not candidates for stem cell transplant, with DIPSS intermediate- or high-risk disease, ECOG PS 0-2, and platelet counts <50 x 10^9/L, who have had limited prior JAK2 inhibitor treatment or are JAK2 inhibitor-naïve. Additional exclusion criteria include recent cardiac or hemorrhagic events, ejection fraction <50%, QTc >450 msec, or use of medications that increase the risk of hemorrhage or QT prolongation. Patients in the PAC arm receive continuous PAC 200 mg BID. Patients in the P/C arm receive one of the following agents as selected prior to randomization: low-dose ruxolitinib, danazol, corticosteroids, or hydroxyurea. The primary objective is to compare the efficacy of PAC vs P/C as assessed by the proportion of patients achieving a ≥35% spleen volume reduction (SVR) from baseline to week 24. Secondary objectives include comparisons of the proportion of patients achieving a ≥50% reduction in total symptom score (TSS) at week 24, overall survival, safety, and proportion of patients who self-assess as "very much improved" or "much improved" as measured by the Patient Global Impression of Change (PGIC). Tertiary endpoints include leukemia-free survival, alternative SVR analyses, hematologic improvement (transfusion independence and improvement in hemoglobin and platelet levels), fatigue improvement as measured by the PROMIS v.1.0 - Fatigue - Short form 7a, and changes in biomarkers and gene expression. The study will enroll approximately 348 patients in a 2:1 ratio (PAC to P/C). The primary analysis (for SVR) will be based on approximately 168 patients, while the secondary analyses (for TSS) will be based on the full sample size. PACIFICA is currently enrolling, with approximately 140 sites worldwide (US, Australia, Europe, Canada, Middle East, Asia, Russia).
Results: N/A
Summary/Conclusion: N/A

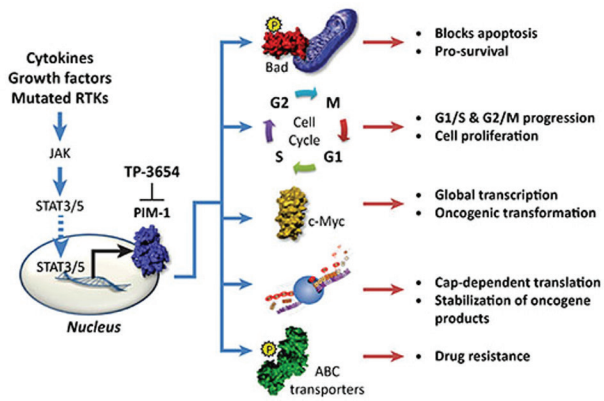
PB1712 A PHASE 1 STUDY OF TP-3654, AN ORAL PIM KINASE INHIBITOR, IN PATIENTS WITH INTERMEDIATE-2 OR HIGH-RISK PRIMARY OR SECONDARY MYELOFIBROSIS

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Background: Myelofibrosis (MF) is characterized by bone marrow fibrosis (BMF), ineffective hematopoiesis, splenomegaly, and debilitating symptoms. An activating Janus kinase 2 (JAK2) mutation (JAK2 V617F) has been frequently observed in MF. Ruxolitinib and fedratinib, approved JAK inhibitors, have been shown to reduce splenomegaly and improve constitutional symptoms in MF patients, but with a modest reduction of BMF. Patients (pts) with MF who progressed on, are intolerant to, or are ineligible for JAK inhibitors have limited treatment options. Proviral integration site of Moloney murine leukemia virus (PIM) serine/threonine kinases are downstream targets of the JAK/STAT signaling pathway (**Figure**). Expression of PIM1 is significantly elevated in MF primary hematopoietic cells. Therefore, PIM kinase is a potential therapeutic target for MF. TP-3654, an oral, small molecule, investigational PIM kinase inhibitor, has been shown to inhibit proliferation and increase apoptosis in murine and human hematopoietic cells expressing JAK2 V617F mutation. TP-3654, alone and in combination with ruxolitinib, improves leukocyte counts, reduces spleen size, and reduces BMF in a JAK2 V617F murine MF model (Nath D, et al. *Blood.* 2018;132(suppl 1):54).
Aims: To evaluate TP-3654 monotherapy in pts with MF.
Methods: This phase I, multicenter, open-label, dose-escalation study is evaluating TP-3654 monotherapy in pts with MF who previously failed or are ineligible to receive a JAK inhibitor (ruxolitinib or fedratinib) (NCT04176198). Primary objectives are to determine the maximum tolerated dose (MTD) and/or to identify the recommended phase II dose (RP2D) of TP-3654 monotherapy. Secondary objectives are to assess preliminary activity (spleen volume reduction, symptom improvement, and BMF reduction), determine QT interval changes, and establish the pharmacokinetic profile. Exploratory objectives are to study pharmacodynamic markers in peripheral blood and bone marrow (BM) biopsy samples. Eligible pts have primary or secondary MF (post-polycythemia vera-MF/post-essential thrombocythemia-MF); intermediate-2/high-risk MF by the Dynamic International Prognostic Scoring System (DIPSS); previously failed or are ineligible to receive treatment with a JAK inhibitor; grade ≥2 MF, as confirmed by BM biopsy ≤12 weeks prior to screening; have a platelet count ≥50x10^9/L, absolute neutrophil count ≥1x10^9/L, hemoglobin level ≥8 g/L, peripheral blood blast counts <10%, ECOG performance status ≤2, life expectancy ≥3 months, and adequate renal and hepatic function; have spleen length ≥5 cm by palpation or spleen volume ≥450 cm^3 by CT/MRI, and show ≥2 measurable symptoms per the MF Symptom Assessment Form, version 4.0. Pts must not have had splenic irradiation ≤6 months prior to screening; have acute myeloid leukemia or myelodysplastic syndrome; or had prior stem cell transplantation (SCT) or be eligible for allogeneic BM or SCT. Enrollment of approximately 50 pts with MF is planned. Pts will receive oral TP-3654. Dose escalation will be performed using a Bayesian Logistic Regression Model (BLRM) with Escalation with Overdose Control (EWOC). Adverse events occurring during the first cycle will be considered in the determination of the MTD. Dose escalation will continue until identification of the MTD and/or a suitable RP2D. This study is currently recruiting pts. Informed consent is being obtained for each participant/potential participant in this trial, in accordance with the International Conference on Harmonization-Good Clinical Practice.
Results: -

Figure. PIM kinases are major effectors of JAK/STAT proliferative signaling downstream of multiple growth factors and cytokines, driving tumor cell survival and progression.



Adapted with permission from Garrido-Laguna I, et al. ASCO 2020. Poster 3586.

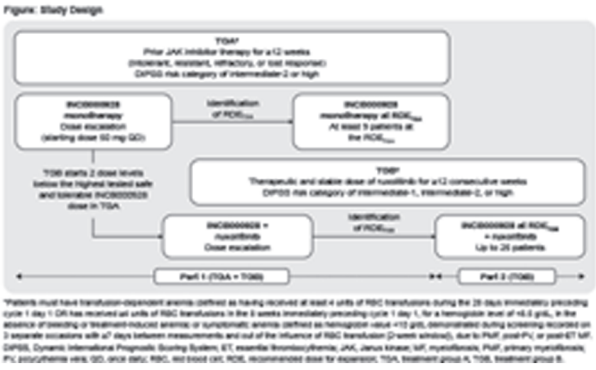
Summary/Conclusion: -

PB1713 A PHASE 1/2 STUDY OF INCB000928 AS MONOTHERAPY OR IN COMBINATION WITH RUXOLITINIB IN PATIENTS WITH ANEMIA DUE TO MYELOFIBROSIS (INCB 00928-104)

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Background: Anemia represents a therapeutic challenge in patients with myelofibrosis (MF). Activin receptor-like kinase-2 (ALK2) activation is associated with elevated hepcidin, which may contribute to anemia of chronic disease and anemia due to hematologic malignancies, and is associated with increased transfusion rate and reduced overall survival.
Aims: This phase 1/2, open-label, multicenter, dose-escalation/dose-expansion study will evaluate the safety and tolerability of INCB000928, a potent, highly selective, ALK2 inhibitor, as monotherapy or combined with ruxolitinib in patients with anemia due to MF (INCB 00928-104; NCT04455841).
Methods: Patients with histologically confirmed primary or secondary MF presenting with symptomatic anemia or transfusion dependence will receive oral INCB000928 either alone (treatment group [TG] A) or combined with ruxolitinib (TGB; Figure). In TGA, patients must have intermediate (INT)-2 or high-risk (per Dynamic International Prognostic Scoring System [DIPSS]) disease that is intolerant, resistant, refractory, or has lost response to prior JAK inhibitor therapy (≥12 weeks). In TGB, patients must have received stable ruxolitinib therapy for ≥12 consecutive weeks before first dose and have INT-1/INT-2, or high-risk disease. Eligibility also requires age ≥18 years, platelet count ≥75 × 10^9/L, ECOG PS 0–1 (dose-escalation) or 0–2 (dose-expansion), life expectancy >6 months, no other hematologic malignancy, no prior stem cell transplantation, no major surgery within 28 days, and no prior disease-directed therapy within 5 half-lives or 28 days of first dose. In part 1 (dose escalation), TGA will receive INCB000928 monotherapy starting at 50 mg/day (28-day cycles) (Figure). Dose-escalation will follow a Bayesian optimal-interval design to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE). Dose increases not exceeding 2-fold will continue until grade ≥2 treatment-related toxicity occurs. TGB will receive INCB000928 plus ruxolitinib; INCB000928 dose escalation will start 2 dose levels below the highest dose determined to be safe and tolerable in TGA. In part 2 (dose expansion), the RDE in TGB will be evaluated in combination with ruxolitinib in ~25 patients; treatment will continue for ≤12 months, and may continue if clinically beneficial and no progression occurs. Primary objective is to determine the safety and tolerability of INCB000928 as monotherapy or combined with ruxolitinib. Secondary objectives are to determine the efficacy of INCB000928 as monotherapy or combined with ruxolitinib (anemia response, duration of anemia response, mean change from baseline in hemoglobin, and RBC transfusion rate through weeks 24 and 48); evaluate INCB000928 pharmacokinetics; and evaluate effects of INCB000928 as monotherapy or combined with ruxolitinib on hepcidin levels and other measures of iron homeostasis and erythropoiesis. Sites are opening in the United States and Europe.
Results: Not applicable



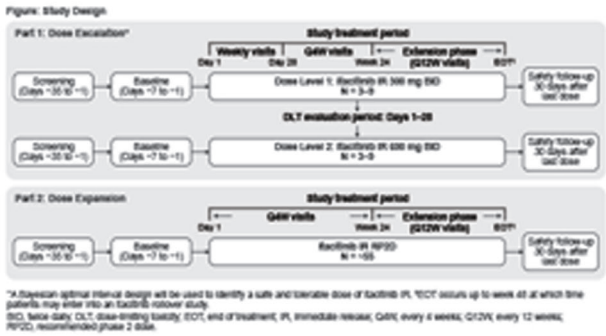
Summary/Conclusion: Not applicable

PB1714 A TWO-PART PHASE 2 STUDY OF ITACITINIB IMMEDIATE RELEASE IN PATIENTS WITH PRIMARY OR SECONDARY MYELOFIBROSIS WHO HAVE RECEIVED PRIOR RUXOLITINIB AND/OR FEDRATINIB MONOTHERAPY

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Background: Ruxolitinib (JAK1/JAK2 inhibitor) and fedratinib (JAK2/FLT3 inhibitor) are indicated in the United States for myelofibrosis (MF); however, some patients fail to achieve adequate/sustained response to initial JAK-inhibitor therapy. Itacitinib is a potent JAK inhibitor selective for JAK1 over JAK2 when administered as a once-daily sustained-release (SR) formulation. In a prior clinical trial, the SR formulation improved MF-related symptoms but had less effect with respect to spleen volume reduction (Mascarenhas JO, et al. Haematologica. 2017;102(2):327–335). When dosed as a twice-daily (BID) immediate release (IR) formulation, itacitinib, a selective JAK1 inhibitor, may attain sufficient JAK2 inhibition to better address the JAK2-mediated myeloproliferative features of the disease.
Aims: This open-label phase 2 study is designed to determine a tolerable and safe dose of itacitinib IR and whether that dose results in clinically significant reductions in symptoms and spleen volume in patients with MF who have previously received ruxolitinib and/or fedratinib monotherapy (INCB 39110-213; NCT04629508).
Methods: Eligible patients are aged ≥18 years, diagnosed with at least INT-1–risk (Dynamic International Prognostic Scoring System [Passamonti F, et al. Blood. 2010;115(9):1703–1708]) primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF and have received ruxolitinib and/or fedratinib monotherapy. Patients must also have palpable splenomegaly and platelets ≥50×10^9/L at screening. Exclusion criteria include receipt of a JAK inhibitor other than ruxolitinib or fedratinib, ≥10% myeloid blasts in peripheral blood or bone marrow, or inability to taper ruxolitinib/fedratinib over 14 days without use of other agents.
Two itacitinib IR dose levels (DLs) will be evaluated in part 1 following a Bayesian optimal interval design algorithm: 3–9 patients will be enrolled at DL1 (300 mg BID) and observed for 28 days for dose-limiting toxicity before enrollment at DL2 (600 mg BID) (Figure). Part 2 will enroll ~55 patients at the recommended phase 2 dose (RP2D) determined in part 1. Patients may remain on treatment until week 48 if they are receiving clinical benefit and have not met study withdrawal criteria. A safety follow-up will occur 30 days after treatment completion.
Primary objectives: part 1 - evaluate safety and tolerability of itacitinib IR and select the RP2D; part 2 - evaluate efficacy of itacitinib IR at the RP2D based on spleen volume reduction at week 24. Secondary objectives (part 2 only): evaluate safety and tolerability of itacitinib IR at the RP2D; evaluate efficacy of itacitinib IR at the RP2D with respect to MF symptom improvement at week 24 in patients with baseline total symptom score ≥10, quality-of-life improvement, and patient global impression of change. Sites are opening in the United States and Europe.
Results: Not applicable



Summary/Conclusion: Not applicable

PB1715 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF ADD-ON PARSACLISIB IN PATIENTS WITH MYELOFIBROSIS WHO HAVE SUBOPTIMAL RESPONSE TO RUXOLITINIB

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Background: Ruxolitinib (JAK1/JAK2 inhibitor) is indicated for the treatment of adults with intermediate (INT) or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF, and post-essential thrombocythemia MF, but a subset of patients may exhibit a suboptimal response due to possible persistent PI3K/AKT activation. Targeting PI3K/AKT signaling may therefore have clinically relevant effects on MF disease burden.
Aims: This phase 3, randomized, double-blind, placebo-controlled study will determine the effect of add-on parsaclisib, a highly selective PI3Kδ inhibitor, on signs and symptoms of MF in patients with suboptimal or declining response to stable ruxolitinib treatment (INCB 50465-304; NCT04551053).
Methods: Eligible patients are aged ≥18 years with a diagnosis of at least INT-1–risk (according to the Dynamic International Prognostic Scoring System [DIPSS]; Passamonti F, et al. Blood. 2010;115(9):1703–1708) primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF, have received ruxolitinib for ≥3 months with a stable dose (5–25 mg twice daily) for ≥8 weeks prior to receiving the first dose of study drug (day 1), have evidence of suboptimal response to ruxolitinib (palpable spleen ≥5 cm below left subcostal margin, and total symptom score ≥10), and ECOG PS ≤2. Patients are excluded if they received prior therapy with any PI3K inhibitor, experimental or standard drug therapy for MF (except ruxolitinib) within 3 months of starting study drug, or have platelet count <50×10^9/L, recent history of inadequate bone marrow reserve, or inadequate liver or renal function at screening. Approximately 212 patients on a stable dose of ruxolitinib will be randomized (1:1) to receive add-on parsaclisib 5 mg daily or matching placebo beginning on day 1, with stratification by platelet count (≥100×10^9/L or 50 to <100×10^9/L) and DIPSS risk category (high, INT-2, or INT-1) at randomization. Treatment will continue as long as tolerated and discontinuation criteria are not met. When a patient has completed 24 weeks of treatment, he/she will be unblinded and if found to be randomized to ruxolitinib plus placebo with adequate hematology parameters, the patient will be able to crossover to receive ruxolitinib plus add-on parsaclisib. The primary objective is to evaluate and compare the efficacy of add-on parsaclisib versus placebo on spleen volume at Week 24. Secondary objectives are to evaluate and compare the effect of add-on parsaclisib versus placebo on: patient-reported MF symptoms, overall survival, time to onset and duration of spleen volume response, and safety and tolerability. Sites are opening throughout North America, Europe, Asia, and Oceania.
Results: Not applicable
Summary/Conclusion: Not applicable

PB1716 A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF RUXOLITINIB PLUS PARSACLISIB IN PATIENTS WITH JAK- AND PI3K-INHIBITOR TREATMENT–NAÏVE MYELOFIBROSIS

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Background: Ruxolitinib (JAK1/JAK2 inhibitor) significantly improves outcomes in patients with myelofibrosis (MF); however, a subset of patients may experience a suboptimal response. Recent phase 2 data showed that addition of the PI3Kδ inhibitor parsaclisib to ruxolitinib monotherapy resulted in additional alleviation of MF symptoms and splenomegaly in patients with MF (Yacoub. EHA2020. S216).
Aims: This phase 3, randomized, double-blind study (INCB 50465-313; NCT04551066), evaluates the combination of ruxolitinib and parsaclisib in patients with MF who are naive to Janus kinase (JAK) and PI3K inhibitor therapies.
Methods: Eligible patients are aged ≥18 years with a diagnosis of primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF, have a Dynamic International Prognostic Scoring System (DIPSS; Passamonti F, et al. Blood. 2010;115(9):1703–1708) risk of at least Intermediate (INT)-1, palpable spleen ≥5 cm below left subcostal margin, total symptom score ≥10 at screening, ECOG PS 0–2, and life expectancy ≥24 weeks. Patients will be excluded if they previously received therapy with any JAK inhibitor, any PI3K inhibitor, any experimental or standard drug therapy for MF≤ 3 months of first study dose and/or lack of recovery from all toxicities related to previous therapies to grade ≤1, have recent history of inadequate bone marrow reserve (eg, platelet count <50×10^9/L), or have inadequate liver or renal function at screening. Approximately 440 patients will be randomized (1:1) to ruxolitinib plus parsaclisib 5 mg QD or ruxolitinib plus matching placebo, with stratification at randomization by DIPSS risk category (high vs INT-2 vs INT-1) and platelet count (≥100×10^9/L vs 50 to <100×10^9/L inclusive). Treatment will begin on day 1, with starting ruxolitinib dose level determined by baseline platelet count, and will continue as long as treatment is tolerated and discontinuation criteria are not met. When the last enrolled patient has completed 24 weeks of treatment, the study will be unblinded and patients randomized to ruxolitinib plus placebo who have adequate hematology parameters will be able to crossover to receive parsaclisib together with continued ruxolitinib. The primary objective is the evaluation and comparison of spleen volume at week 24 for patients who received ruxolitinib plus parsaclisib versus ruxolitinib plus placebo. Secondary objectives include evaluation and comparison of patient-reported MF symptoms, overall survival, time to onset and duration of response in spleen volume, and safety and tolerability of ruxolitinib plus parsaclisib versus ruxolitinib plus placebo. Sites are opening across the United States, Europe, Asia, and New Zealand.
Results: Not applicable
Summary/Conclusion: Not applicable

PB1717 RELATIVE BIOAVAILABILITY AND DOSE LINEARITY OF FIVE STRENGTHS OF RUXOLITINIB EXTENDED RELEASE (XR) TABLETS

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Background: Ruxolitinib is currently dosed twice-daily using an immediate release (IR) formulation for the treatment of myelofibrosis, polycythemia vera, and acute graft-versus-host disease. An extended release (XR) formulation of ruxolitinib was developed to allow once-daily dosing. Five XR tablet strengths were developed, containing 10, 20, 30, 40, and 50 mg of ruxolitinib, free base equivalent.
Aims: To study the linearity in the pharmacokinetics (PK) of ruxolitinib following a single dose of each of the five strengths of ruxolitinib XR tablets.
Methods: This open-label, randomized, crossover study was conducted in healthy adult participants (n=12–15 per cohort) to evaluate the dose proportionality of the ruxolitinib XR formulation. The study also assessed the effect of a high-fat meal. Standard non-compartmental PK analysis was used. Dose proportionality of the ruxolitinib XR formulation was assessed by comparing dose-normalized, log transformed PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$). Food effect was evaluated by analysis of variance using a mixed effects model. Safety and tolerability were assessed by monitoring the frequency and severity of adverse events; performing physical examinations; and collecting vital signs, 12-lead electrocardiograms, and clinical laboratory data.
Results: The results of ruxolitinib XR dose proportionality analysis are summarized in Table 1. The geometric mean ratios with 90% CI (fed with a high-fat meal vs fasted) were estimated at 1.627 (1.367, 1.936), 0.903 (0.841, 0.970), and 0.912 (0.848, 0.981) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. The treatments were well tolerated and no new safety findings were observed with administration of ruxolitinib XR.

Table: Dose Proportionality Analysis Results of Ruxolitinib XR Tablets

Relative Bioavailability of Ruxolitinib XR Tablet Strengths Compared to 50 mg XR Tablet (Geometric Mean Ratios with 90% CI)			
	C_{max} (nM)	AUC_{0-t} (h*nM)	$AUC_{0-\infty}$ (h*nM)
10 mg XR	0.918 (0.773, 1.090)	1.026 (0.943, 1.118)	1.033 (0.949, 1.124)
20 mg XR	0.884 (0.745, 1.048)	1.034 (0.950, 1.126)	1.038 (0.954, 1.129)
30 mg XR	0.891 (0.755, 1.051)	0.958 (0.883, 1.040)	0.962 (0.889, 1.042)
40 mg XR	0.952 (0.803, 1.128)	1.000 (0.919, 1.088)	0.999 (0.920, 1.084)
Exponent (90% CI) on Dose from a Power Function Regression			
	1.069 (0.954, 1.164)	0.983 (0.935, 1.031)	0.978 (0.931, 1.026)

AUC_{0-t}, area under the plasma concentration-time curve from time zero to last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum plasma drug concentration; XR, extended release.

Summary/Conclusion: Dosage strength proportionality has been demonstrated across all five ruxolitinib XR tablet strengths (10 mg, 20 mg, 30 mg, 40 mg, and 50 mg), and they can be dosed without regard to food. No new safety concerns were observed with ruxolitinib XR.

PB1718 TUBERCULOSIS REACTIVATION FOLLOWING RUXOLITINIB THERAPY FOR MYELOFIBROSIS

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Background: Myelofibrosis is an uncommon myeloproliferative neoplasm, characterized by stem cell-derived clonal proliferation that is often accompanied by JAK2, CALR, or MPL mutations. It presents with marrow fibrosis, variable degree of splenomegaly, cytopaenias and constitutional symptoms, that significantly impact on quality of life and survival.
Aims: Ruxolitinib is a JAK 1/2 inhibitor that can decrease spleen size, relieve constitutional symptoms, reduce transfusion requirement and prolongs survival in some patients. Uncommon adverse reaction of Ruxolitinib includes reactivation of tuberculosis infection.
Methods: We are describing 4 patients of myelofibrosis who have had reactivation of tuberculosis, whilst on Ruxolitinib. Data was collected retrospectively. Patients were followed up actively during antituberculous treatment
Results: Age (yr) sex Diagnosis JAK2 CALR Ruxolitinib initi TB reactivation Site of reactivation ATT outcome
53 F SMF/PV + - Dec, 2013 15 months Abdominal 6 month Alive
33 F PMF + - Feb, 2016 14 months Pulmonary 6 months Alive 40 M PMF - + Apr, 2017 4 months Lymphnode 6 months Alive 54 M PMF + - Mar, 2017 11 months Pulmonary 6 months Alive
Summary/Conclusion: Tuberculosis infection was observed in 4 patients who were being treated with Ruxolitinib. This case series highlights the importance of screening for latent tuberculosis in patients from highly endemic areas before commencing on Ruxolitinib.

PB1719 A CASE OF POLYCYTHAEMIA VERA TREATED WITH ROPEGINTERFERON-2B DURING PREGNANCY

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Background: Polycythaemia Vera (PV), a myeloproliferative neoplasm (MPN), is usually diagnosed in patients ≥60 years. However, 15-20% of PV patients are less than 40 years of age at diagnosis. MPN patients have increased risk for pregnancy-related complications (miscarriage, thrombosis, haemorrhage, intrauterine growth restriction, pre-eclampsia and stillbirths). Hence the importance of a correct management during this time, including the employment of aspirin, low molecular weight heparin (LMWH), venesection and cytoreductive therapy when needed. When cytoreduction is necessary, in PV patients wishing to conceive, interferon alfa is the choice. The development of pegylated formulations, including ropeginterferon alfa-2b (Besremi®), has resulted in improved tolerability and easier administration.
Aims: To describe the clinical and analitical evolution of a PV patient treated with novel ropeginterferon alfa-2b during pregnancy.
Methods: We present the case of a 32-year-old woman diagnosed of PV in December 2018 and followed up at Guy's Hospital, who was on ropeginterferon alpha-2b during pregnancy, with adequate control and no complications.
Results: In December 2018, at the age of 29, she presented with numbness and intermittent paraesthesia in the right side of her face and body. She had had previous history of skin rash and bilateral conjunctival congestion. She had no history of thrombotic events. Neurological causes of her hyperviscosity syndrome were ruled out. Her leukocyte count was 25.2 $\times 10^9$/L (neutrophils 22.2 $\times 10^9$/L), with haemoglobin (Hb) of 175 g/L, haematocrit (Hct) of 0.57 and platelets of 859 $\times 10^9$/L. Abdominal ultrasound scan showed splenomegaly (16 cm). JAK2 V617F mutation was detected and PV, with bone marrow (BM) features of panmyelosis, no immature precursors and grade 1 fibrosis, was diagnosed according to WHO criteria.
She had several venesections and started aspirin 150 mg/day. Due to myeloproliferative features, treatment with peginterferon alfa-2a (Pegasys®), 90 mcg weekly, was added, with later increases up to 225 mcg weekly.
As she had no major response to peginterferon alfa-2a, with persistent high leukocyte and platelet counts (leukocytes 23.8 $\times 10^9$/L, neutrophils 21.2 $\times 10^9$/L, Hb 107 g/L, Hct 0.38 and platelets 926 $\times 10^9$/L), teardrop cells in the blood film and enlarged spleen (23 cm), in February 2020 another BM was performed, excluding progression to myelofibrosis. During this time she had the desire to concieve, but could not become pregnant. She was then switched to ropeginterferon alfa-2b, 350 mcg every other week.
In March 2020 she conceived, continuing ropeginterferon alfa-2b, as well as thromboprophylaxis with aspirin and enoxaparin 40 mg/day. She had several venesections during pregnancy, in order to maintain Hct <0.38 per BSH guidelines. She underwent local follow up with no special symptoms or signs of abnormal fetal development. Ultrasound scan in the third trimester demonstrated stability in spleen size.
The baby was delivered on 14th December 2020, at 38 weeks of gestation (weight 2.8 kg). The patient's most recent blood control in January 2021, after delivery, showed a leukocyte count of 19.1 $\times 10^9$/L (neutrophils 15.7 $\times 10^9$/L), Hb of 119 g/L, Hct of 0.42 and platelet count of 855 $\times 10^9$/L.

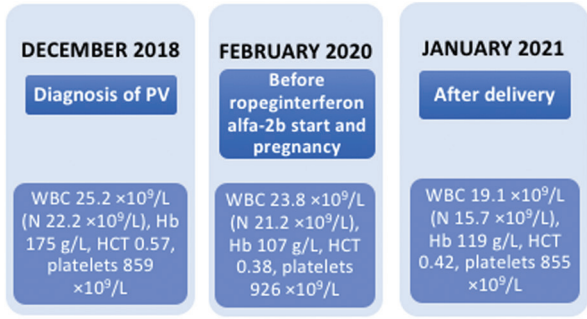


***Figure 1.** Evolution of blood counts since diagnosis of polycythaemia vera. Abbreviations: PV: polycythaemia vera. WBC: white blood cells. N: neutrophils. Hb: haemoglobin. HCT: haematocrit.*

Summary/Conclusion: To our knowledge, this is the first case in which ropeginterferon alfa-2b is used in a pregnant PV patient and also the first reported case where a patient with inadequate disease control with peginterferon alfa-2a attained sufficient response with ropeginterferon alfa-2b. An informed consent has been obtained from the patient to write this abstract.

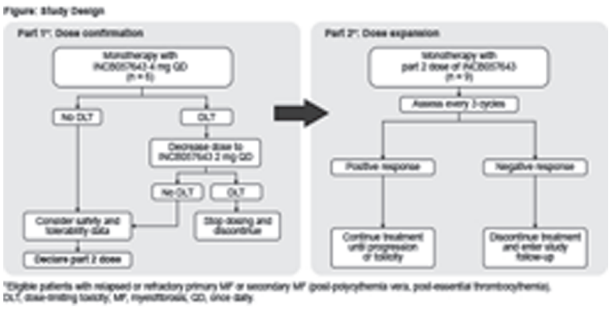
PB1720 A PHASE 1 STUDY OF INCB057643 MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY MYELOFIBROSIS (INCB 57643-103)

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Background: Many neoplasms including myelofibrosis (MF) are associated with activation of transcription factors that regulate oncogenic processes. These may respond to inhibition of bromodomain and extra-terminal domain (BET) protein. In the first-in-human study INCB 57643-101, the BET inhibitor INCB057643 was generally safe and tolerable as monotherapy, and demonstrated preliminary efficacy in a small number of patients with MF, as monotherapy or combined with the JAK inhibitor, ruxolitinib (Falchook G, et al. *Clin Cancer Res.* 2020).
Aims: This phase 1, open-label, two-part dose confirmation and expansion study further evaluates the safety and tolerability of INCB057643 monotherapy in patients with relapsed/refractory MF (INCB 57643-103; NCT04279847).
Methods: Eligible patients must be aged ≥18 years with histologically confirmed primary or secondary (post-polycythemia vera, post-essential thrombocythemia) MF, have received ≥1 prior therapy including ruxolitinib, have no known clinically beneficial therapy available, have intermediate-2/high risk disease by Dynamic International Prognostic Scoring System, have ECOG PS 0–2, life expectancy ≥24 weeks, and willing to provide a bone marrow biopsy and/or aspirate at baseline (or archival sample obtained after most recent therapy). Exclusion criteria include prior BET inhibitor or anticancer treatment within specified intervals before first dose; concurrent anticancer therapy; allogeneic hematopoietic stem cell

transplant (allo-HSCT) ≤6 months before enrollment; active graft versus host disease or immunosuppressive therapy after allo-HSCT ≤2 weeks before first-dose; significant and uncontrolled disease (eg, gastrointestinal, cardiovascular); history of bleeding disorders, high risk of bleeding, or abnormal hematologic, hepatic, renal, coagulation, or metabolic laboratory values. In part 1, ≤6 patients will receive oral INCB057643 4 mg once-daily continuously (Figure). Doses will be deemed tolerable if ≤2 patients experience dose-limiting toxicities (DLTs) and ≤2 patients discontinue due to treatment-related adverse events (TRAEs) during the DLT evaluation period. Part 2 will further characterize safety and tolerability as well as evaluate preliminary efficacy of INCB057643 in ≤9 patients. The starting dose will be 4 mg once-daily if tolerated in part 1, and 2 mg once-daily if not. Treatment may continue if clinically beneficial and discontinuation criteria are not met. The primary objective is to determine the safety and tolerability of INCB057643 monotherapy. Secondary objectives are to evaluate anemia response by International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet Consensus Report (ELN), transfusion dependence, spleen volume, rate and duration of spleen response by IWG-MRT and ELN, and impact on quality of life. Patients will be assessed every 3 cycles and will receive follow-up for safety for 30–35 days after last dose. Sites are opening in the United States and Europe.
Results: Not applicable



Summary/Conclusion: Not applicable

PB1721 CONSECUTIVE OCCURRENCE OF ACUTE MYELOID LEUKEMIA, CHRONIC LYMPHOCYTIC LEUKEMIA AND POLYCYTHEMIA VERA; EMERGENCE OF DRIVER MUTATIONS IN A CONTEXT OF CLONAL HEMOPOIESIS OF INDETERMINATE POTENTIAL.

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Background: Asynchronous occurrence of myeloid/lymphoid malignancies has been previously described. Multiple malignant clones can arise from a cancer cell but accumulation of genetic events is not fully elucidated. We describe a rare case of consecutive AML, CLL and PV in which extended genetic profiling has been performed.
Aims: To report the concurrent presence of three hematologic malignancies in the same patient
Methods: Flow cytometry, cytogenetics and molecular analysis.
Results: A 69 years old male presented 5 years ago with lymphocytosis (ALC 15.0 K/ul). His medical history revealed acute myeloid leukemia (AML) M2 FAB, diagnosed 20 years earlier. He had received intensive chemotherapy and achieved complete response. Karyotype was not performed at that time. Lymphocytosis investigation was initiated and flow cytometry revealed a clonal B cell population expressing CD5+, CD23+, CD43+, CD200+, ROR1+, CD20dim, FMC7-, CD79b- and weak surface light chain immunoglobulin. Hemoglobin and platelet counts were within normal range. There were no palpable spleen, liver or B symptoms. Small axillar lymph nodes were present and patient was diagnosed with chronic lymphocytic leukemia (CLL), stage Rai I, Binet A. Cytogenetic analysis demonstrated 47,XY,+del(5)(q13q33)[2]/46,XY [21]. No NOTCH1 or TP53 mutations were present. IGHV genes were 88.8% mutated bearing the VDJ rearrangement IGHV1-3/IGHD2-15/IGHJ3. Del(13)(q) was detected by FISH in 61% of the cells, while here was no 17p or 11q deletion or trisomy 12. Within two years the patient developed progressive splenomegaly and subsequently received 6 cycles of chemo-immunochemotherapy with Obinutuzumab-chlorambucil. He achieved partial response (marrow MRD 1.9%, splenomegaly partially resolved). During regular follow-up visits, gradual increase in hemoglobin was noted (RBC 6.65 x 10^9 K/ul, Hb=17.1 g/dl, Ht=51.4%). Polycythemia Vera was suspected and JAK2 V617F mutation was found. Bone marrow biopsy revealed 75% cellularity, erythroid and megakaryocyte hyperplasia with groups of megakaryocytes, and blasts <5%. A 10% B lymphocyte infiltration was also noted. No BCR/ABL transcript was found. He was put on hydroxyurea and salicylic acid. Concurrent follicular thyroid cancer was diagnosed. NGS analysis was performed with Sophia Genetics Myeloid Panel on 3 subsequent samples from: (i)AML (ii) CLL and (iii) PV diagnosis and the results are as follows: (i) FLT3-ITD, NPM1 type A and IDH2 Arg140Gln mutations, (ii) the AML mutations disappeared, KRAS and DNMT3A mutations and a 3% JAK2V617F clone emerged and (iii) KRAS, DNMT3A and JAK2V617F clones expanded contributed probably to the PV phenotype. Interestingly, 2 TET2 and CEBPA mutations were stable in all three timepoints, possibly as CHIP, indicating a single cell of origin.
Summary/Conclusion: Herein, for the first time to our knowledge, we report the concurrent presence of three hematologic malignancies in the same patient. Common genetic background with clonal hematopoiesis may confer genetic instability, upon which distinct driver mutations arise, contributing to distinct phenotype.

PB1722 ESSENTIAL THROMBOCYTEMIA IN THE YOUNG PATIENT: EXPERIENCE OF A SECONDARY HOSPITAL

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Background: Essential Thrombocythemia (ET) is a Philadelphia negative myeloproliferative neoplasia, which presents with persistent thrombocytosis, megakaryocytic hyperplasia in bone marrow and a tendency to both hemorrhagic and thrombotic complications. It predominates in female patients with a mean age of 60 years, with 15% being less than 40 years old.
Aims: The goal of our study was to describe our experience in patients with ET ≤ 40 years at diagnosis (dx).
Methods: A retrospective analysis was conducted based on the review of medical records of the adult patients diagnosed of TE in our centre from 2005 to 2020. Clinical and biological data were recorded.
Results: A total of 8 cases were detected (1 man and 7 women). in 38 total cases, which represents 21% (higher than that described in the literature). Mean age at dx: 34.5 [31-40] years.
- Reasons Consultation: Thrombocytosis + paresthesias (2), isolated thrombocytosis (5), thrombocytosis + headaches (1).
- Mutational status: CARL + (2), JAK-2 V617F + (4), not filiated (2).
- Thrombotic events (4/8): Abortion (2), PE (1), Portal Thrombosis (1).
- Thrombophilia study: MTHFR with increased Homocysteine (1), Gen 20210 Prothrombin (1). IPSET ET: High Risk (5), Low Risk (2), Intermediate (1).
- Treatment received: Hydrea + maintenance interferon (1/8), Anagrelide + antiplatelet (5/8), antiplatelet (ASA) (3/8), interferon due to pregnancy (1/8).
- Side effect: Heartburn + pain in lower limbs + headaches + heavy menstruation (1), hives + headaches + palpitations + asthenia + nausea (1), palpitations + dizziness + headaches + bruising + increased menstrual bleeding + pulmonary hypertension + pain in lower limbs (1), increased menstrual bleeding + alopecia + tachycardia (1) and nausea + headaches +palpitations (1).
- Intra-treatment thrombotic events (0/5).
- Treatment suspension (0/5).
- Evolution: Exitus due to breast neoplasia with metastases in a patient with previous Hydrea treatment (1/8).

Patient	Age	Sex	Reason for consultation	Mutational status	Treatment	Side effect	Thrombotic event	Thrombophilia study	IPSET ET
N° 1	31	Man	Thrombosis	JAK2	ASA	None	No	No	Interm
N° 2	32	Woman	Thrombosis	JAK2 - Rest of mutations not affiliated	Anagrelide + ASA	• Headache • Increased menstrual bleeding • Heartburn • Pain in lower limbs	Portal thrombosis	Homozygous MTHFR	High
N° 3	33	Woman	Thrombosis	JAK2	ASA	None	No	No	Low
N° 4	34	Woman	Thrombosis + headaches	JAK2	Anagrelide + ASA	• Headache • Palpitations • Hives • Asthenia • Nausea	No	No	High
N° 5	35	Woman	Thrombosis + Paraesthesia	CARL	Anagrelide + ASA	• Headache • Palpitations • Increased menstrual bleeding • Pain in lower limbs • Bruises • Dizziness • PH	Abortion	Heterozygous G20210A	High
N° 6	35	Woman	Thrombosis	CARL	Anagrelide/ Interferon + ASA	• Palpitations • Increased menstrual bleeding • Alopecia	Abortion	No	High
N° 7	36	Woman	Thrombosis	JAK2	Anagrelide + ASA	• Headache • Palpitations • Nausea	PE	Heterozygous MTHFR	High
N° 8	40	Woman	Thrombosis	Not affiliated	Hydrea/ Interferon + ASA	Not registered	No	No	Low

Abbreviations: ASA: acetylsalicylic acid, PE: pulmonary embolism, PH: pulmonary hypertension

Summary/Conclusion: - In our series 37.5% of the patients presented some thrombotic event / abortion as a precedent, the only etiology being ET 12.5%, given that the rest of the events were associated with prothrombotic mutations coinciding with the chronic myeloproliferative disorders.
- The common reason for consultation was thrombocytosis.
- Anagrelide therapy was acceptably tolerated, not being necessary to suspend treatment, and managed with dose adjustment.
- The most frequent side effects were: bleeding tendency, palpitations. The most serious side effect was pulmonary hypertension.

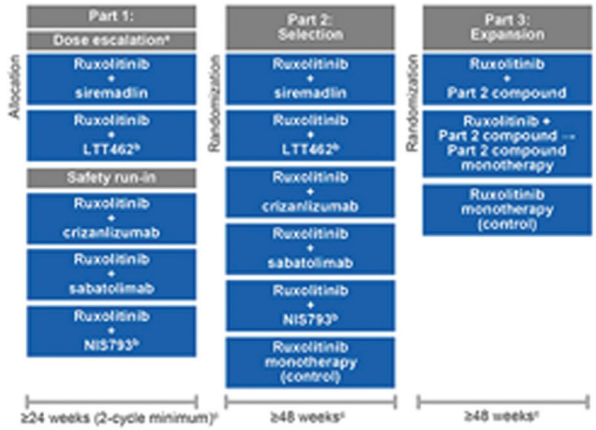
PB1723 ADORE: A RANDOMIZED, OPEN-LABEL, PHASE 1/2 OPEN-PLATFORM STUDY EVALUATING SAFETY AND EFFICACY OF NOVEL RUXOLITINIB COMBINATIONS IN PATIENTS WITH MYELOFIBROSIS

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Background: Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) that can develop de novo (primary MF) or from the progression of antecedent MPNs, in particular polycythemia vera (PPV-MF) or essential thrombocythemia (PET-MF). Ruxolitinib (RUX), a first-in-class JAK1/JAK2 inhibitor, is the standard of care for MF and demonstrated superiority over placebo (COMFORT-I) and best available therapy (COMFORT-II). However, RUX is not curative, cytopenias remain a challenge and some patients (pts) lose response or discontinue treatment due to adverse events. RUX combined with novel agents may offer superior disease control and transformative clinical benefits.
Aims: ADORE (NCT04097821) is a 3-part, open-label, multicenter, phase 1/2, platform study that will assess the safety and efficacy of RUX in combination with 5 novel compounds for the treatment of MF: siremadlin (HDM2 inhibitor), crizanlizumab (P-selectin inhibitor), sabatolimab (TIM-3 inhibitor) and, recently added to the study, LTT462 (ERK1/2 inhibitor) and NIS793 (anti-TGFβ antibody).
Methods: The study includes pts ≥18 years with primary MF, PPV-MF, or PET-MF, splenomegaly (a palpable spleen ≥5 cm from the left costal margin or spleen volume ≥450 cm^3 by MRI or CT scan), hemoglobin level <11 g/dL, and platelet count ≥75 × 10^9/L (≥50 × 10^9/L in Parts 2/3). Pts must have received RUX for ≥24 weeks and at a stable dose for ≥8 weeks prior to study entry.
Part 1 (phase 1b; Safety) includes a dose escalation arm to determine the recommended phase 2 dose for siremadlin + RUX and LTT462 + RUX, and a safety run-in for RUX + crizanlizumab, RUX + sabatolimab and RUX + NIS793. RUX will be administered at the same stable dose used prior to study entry. Pts will be treated for ≥24 weeks (8 cycles in NIS793 arm or 6 cycles in other arms). Part 1 primary endpoint is the incidence of dose-limiting toxicities within the first 2 cycles. Combinations evaluated as safe and tolerable in Part 1 may be selected for Part 2.
In Part 2 (phase 2; Selection), pts will be randomized to one of the selected combinations or RUX monotherapy (control) and treated for ≥48 weeks. After all Part 2 pts have completed 24 weeks of treatment, a futility interim analysis will determine which treatment will proceed to Part 3.
In Part 3 (phase 2; Expansion), pts will be randomized to the combination treatment, RUX cessation, or RUX monotherapy and treated for ≥48 weeks. Pts in the RUX cessation arm will be treated with combination therapy for 12 weeks, followed by novel agent monotherapy.
The primary endpoint for Parts 2 and 3 is the response rate (a composite of anemia improvement [increase in hemoglobin of ≥1.5 g/dL], no spleen volume progression, and no symptom worsening) at the end of cycle 8 (NIS793 arms) or cycle 6 (other arms) (24 weeks). The study will end 24 months after the last pt has initiated Part 3. A total of 240 patients are planned to be enrolled.
Results: Trial in progress.

Figure. ADORE Study Design



[a] Dose escalation required to determine Phase 2 dose for siremadlin and LTT462 arms.
[b] LTT462 and NIS793 added to study protocol in November 2020.
[c] NIS793 has a 21-day cycle; all other arms have 28-day cycles.
Part 1 dosing: ruxolitinib, 5 to 25 mg administered orally twice daily; siremadlin, 20 mg starting dose administered orally once daily on days 1 to 5 of a 28-day cycle; LTT462, 200 mg starting dose orally once daily in 28-day cycles; crizanlizumab, 5 mg/kg intravenously every 4 weeks; sabatolimab, 800 mg intravenously every 4 weeks; NIS793, 2100 mg intravenously every 3 weeks. Part 2/3: as per Part 1 except siremadlin and LTT462 which will use recommended Phase 2 dose established in Part 1.

Summary/Conclusion: As of January 2021, the study is open for enrolling into Part 1.

PB1724 CLINICAL CHARACTERISTICS AND SURVIVAL OF PATIENTS WITH PH NEGATIVE MYELOPROLIFERATIVE NEOPLASMS TREATED IN A REFERRAL HOSPITAL IN MEXICO CITY

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Background: Myeloproliferative neoplasms (MPNs) are heterogenous myeloid malignancies that include essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). There are few Latin American studies focused on these diseases.
Aims: In this work, we describe the clinical characteristics and frequency of the JAK2 V617F mutation, as well as the treatment patterns and survival of patients with the most frequent Philadelphia MPN neoplasms treated in a referral hospital in Mexico City.
Methods: A retrospective analysis of the medical history of patients with Ph negative myeloproliferative neoplasms treated at the National Cancer Institute of Mexico City was carried out to describe the variables considered for inclusion.
Results: Among the patients with essential thrombocythemia, 53% were men and 47% women, with a mean age of 51 years, 67% underwent

bone marrow biopsy, the JAK2 V671F mutation was detected in 47%, the mean platelet count at diagnosis was 1 016 x10^9/L (±SD 68 x10^9/L), 80% received treatment cytoreductive with hydroxyurea.
50% of the patients with polycythemia vera were women, the mean age at diagnosis was 63 years, 100% had a bone marrow biopsy, the JAK2 V617F mutation was found in 75%, the mean hemoglobin level at diagnosis was 18.6 g/dL (± SD 2.6 g/dL), 100% received treatment with hydroxyurea plus a low dose of aspirin.
Most of the patients with myelofibrosis were women (67%) and had a mean age at diagnosis of 68 years, a bone marrow biopsy was performed in 100% and the JAK2 V617F mutation was found in 67%, the mean hemoglobin level at diagnosis was 10.7 g / dL (± SD 4 g / dL), mean platelet count at diagnosis was 333 x109 / L (± SD 275 x109 / l), only 33% received treatment with JAK2 inhibitors.
Summary/Conclusion: Myeloproliferative neoplasms are rare in our environment, however, they present a behavior similar to that reported in other parts of the world. Efforts should be made to identify molecular alterations in our patients that could imply an improvement in access to novel treatments. Although our study has many limitations, it is expected to serve as the basis for the creation of a national registry that will help improve the study of patients with myeloproliferative neoplasms.

PB1725 SUCCESSFUL PREGNANCY OUTCOME IN ESSENTIAL THROMBOCYTAEMIA PATIENT AFTER MULTIPLE MISCARRIAGES WITH PLT NORMALISATION INDUCED BY GESTATIONAL THROMBOCYTOPENIA

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Background: Essential thrombocythaemia (ET) is a clonal stem cell disorder presented with elevated platelet counts. ET in young women can be challenging due to their childbearing potential. There can be increased risk of fetal and maternal complications. The most common pregnancy-related complication is spontaneous abortion during the first trimester.
Aims: We present here a high-risk ET patient 38y old with successful pregnancy and with gestational thrombocytopenia
Methods: Chart review of the case records of the hospital
Results: The patient has been followed by Hematologist since 2014 due to four miscarriages (2013, 2015, 2017 and 2018) but had normal pregnancy with healthy boy born in 2002. Her platelet (PLT) count started to increase from 2010 and in 2014 JAK2 positive ET was diagnosed. In 2017 patient reported heavy metrorrhagia caused by acquired von Willebrand disease with loss of high weight vWF multimers. Hemostasis analyses: APTT 47.7s (28-40), PT-INR 1.28 (0.8-1.2), fibrinogen 1.3 g/L (1.6-3.5), D-dimers 0.28 µg/l (<0.5), FVIII 37% (60-150), vWFAg 61% (50-160), vWFac 34% (46-146), vWFAg/ac ratio 0.55 (>0.7). Patient was consulted by genetics, prothrombin and factor V Leiden mutation were negative.
The highest PLT count was 1604x10^9/L before the last 6th pregnancy in 2019. During the first and second trimester PLT count was in range of 600x10^9/L and decreased to normal reference range before delivery (PLT 398x10^9/L). Patient was treated with LMW heparin Enoxaparin sodium and low-dose Aspirin (75mg) during the 2nd-3rd trimester and after delivery for 10 days. PLT count at week (w) 12 was 1122 x109/L, w22 600 x10^9/L, w36 475 x10^9/L and w39 398 x10^9/L. Hemostasis analyses in w36: APTT 31.6s (28-40), PT-INR 1.1 (0.8-1.2), fibrinogen 3.6 g/L (1.6-3.5), D-dimers 0.64 µg/l (<0.5), FVIII 122% (60-150), vWF 257% (50-160), vWFac 182% (46-146). Five weeks after the delivery PLT count increased again to 1099x109/L Patient had no bleeds during pregnancy and blood loss was 300 ml during delivery.
Summary/Conclusion: We conclude that the patient had pregnancy associated thrombocytopenia due to PLT count decrease of the 70% from base value. It has been reported PLT decrease up to 20% in patients with ET during pregnancy. However, PLT count decrease could also be a side effect of Enoxaparin treatment but PLT decrease was profound, more than 30-50% in which observed PLT change was unlikely caused by Enoxaparin treatment. Furthermore, clinical findings do not support drug-induced thrombocytopenia. Pregnancy outcome was successful without initially planned alfa-interferon therapy. VWF level normalized and during pregnancy increased to thrombosis state, but VWF was still dysfunctional with lack of high molecular weight multimers. Clinically there was no reports of bleeding during delivery and Enoxaparin therapy after the childbirth. Our patient's case refers to the need of individual person and situation specific guiding of pregnancy in patients with myeloproliferative neoplasms which can be challenging.

PB1726 MYELOFIBROSIS TREATMENT WITH RUXOLITINIB IN CLINICAL PRACTICE: AN ANALYSIS OF EFFICACY AND SAFETY OF A SINGLE CENTER

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Background: ruxolitinib is a potent *Janus Associated Kinase* (JAK) inhibitor that mediates the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. It acts by inhibiting dysregulated JAK signaling associated with myelofibrosis (MF). Also, it has been shown to be an effective drug in alleviating systemic symptoms and reducing spleen size with significant improvement in patients (pts) quality of life.
Aims: report the efficacy and safety of ruxolitinib in a cohort of MF pts treated in routine clinical practice.
Methods: we retrospectively analyzed a total of 16 pts with MF treated with ruxolitinib in our hospital, between 2015 and 2020. For toxicity grading (gr) we used CTCAE criteria v5.0.
Results: 62.5% were males and the median age at diagnosis was 69.5 years (22-77). Ten pts (62.5%) were diagnosed as primary MF, 4 (25%) as post-essential thrombocythemia MF and 2 (12.5%) as post-polycythemia vera MF. Ten pts (62.5%) were JAK2 V617F mutated, 1 (6.3%) was CALR and 5 (31.3%) were triple negative. When analyzing risk stratification, 50% were DIPSS intermediate II and 25% high risk. Indications for treatment were constitutional symptoms plus splenomegaly in 10 (62.5%) pts, splenomegaly alone in 5 (31.3%) and intolerance to hydroxycarbamide in 1 (6.25%). Median time from diagnosis to start of ruxolitinib was 32.9 months with a median initial dose of 30mg/day. At baseline of treatment, 75% pts experienced constitutional symptoms among which 58.3% had complete symptomatic resolution. An average reduction in the spleen length of 60.6%, with almost all patients having a spleen reduction, was observed. Seven pts (53.8%) required a dose reduction: 3 (42.9%) due to anemia gr4, 1 (14.3%) due to thrombocytopenia gr2 and 2 (28.6%) due to both anemia and thrombocytopenia gr3. Five pts (25%) discontinued ruxolitinib, 2 due to leukemic transformation, 2 due to anemia g4 and gr5 and 1 due to no response.
Summary/Conclusion: our analysis confirms the efficacy and safety of ruxolitinib outside clinical trials with more than half of treated pts achieving and maintaining a clinical benefit and most of them reporting relief from symptoms. Clinicians are usually more alert towards thrombocytopenia but in our series, anemia was the most frequent and serious toxicity having occurred in more than half of the cases. Although, we consider that it is manageable, we would like to propose more strict indications for ruxolitinib dose adjustment according to the hemoglobin cut-off value.

PB1727 RUXOLITINIB TREATMENT IN PATIENTS WITH MYELOPROLIFERATIVE DISORDERS (MPD) – A UNICENTER STUDY.

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Background: Ruxolitinib (RXL) is an inhibitor of JAK 1 and 2, used in the management of patients with MPD, leading to improvements in splenomegaly and constitutional symptoms.
Aims: to characterize the efficacy and toxicity of RXL in patients with MPD treated in our center.
Methods: retrospective analysis of the patients treated with RXL during the previous 5 years.
Results: 13 patients were included, 10 (71%) males, median age 63.5 yo (min 52; max 78). 7 (54%) patients had primary myelofibrosis (PMF); 4 (30%) patients had secondary myelofibrosis (SMF) - 1 post Polycythemia Vera (PV) and 3 post Essential Thrombocytosis (ET); 1 (8%) patient with PV and 1 (8%) patient with ET. Results are presented as follows:
PMF – at diagnosis 3 (43%) patients presented with intermediate-2 DIPSS score, 3 patients with intermediate-1 DIPSS score and 1 (14%) patient had low risk DIPSS. 4 patients were JAK2V617F+. As first line treatment, 3 patients were treated with ESA, 2 with HU and 1 patient received first line treatment with RXL. RXL was offered as 2nd line treatment in 3 patients, and as 3rd line treatment in 3 patients. Median duration of

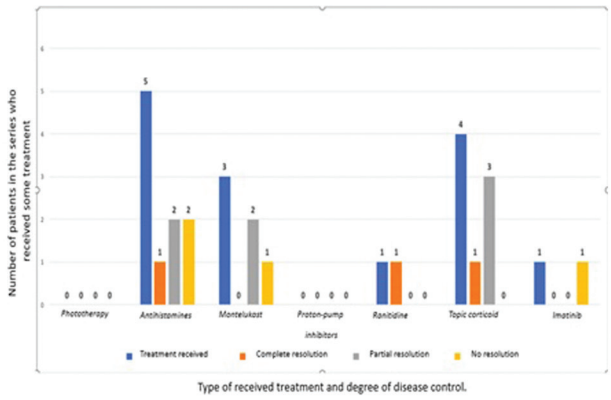
treatment with RXL was 15 months (min-9; max-54). No patient had PMF-related symptoms. Splenomegaly was present in 4 (57%) patients: 1 received RXL as first line treatment, 2 received RXL after 2nd line HU therapy and 1 received RXL as 3rd line of treatment (after HU and subsequent therapy with thalidomide + PDN). Response to RXL, including spleen reduction, was observed in the patient who received treatment as 1st line treatment, in 1 patient after 2º line treatment and in the patient treated as 3rd line of treatment. Overall, 4 (57%) patients had hematological toxicities and 1 (14%) patient had gastrointestinal adverse effects.
SMF – 3 patients had post ET myelofibrosis, all had received cytoreductive therapy as first line treatment; only 1 patient were JAK2V617F+ and had splenomegaly, and RXL was effective in reducing splenomegaly in this patient; the 2 other patients had no splenomegaly or JAK2V617F+ mutation and evolved with splenomegaly despite RXL therapy. Mean duration of treatment was 18 months (min 3; max 33). Hematological toxicity was registered in 2 patients. 1 patient had post PV myelofibrosis, was JAK2V617F+ and had splenomegaly responding to RXL treatment. There was no toxicity registered after a treatment duration of 10 months.
PV – 1 patient with PV received RXL due to intolerance to cytoreductive therapy; he was JAK2V617F+ and had splenomegaly at diagnosis. RXL was no able to reduce splenomegaly after 20 months of treatment. Hematological toxicity as thrombocytopenia has occurred.
ET – 1 patient with ET received RXL due to resistance to hydroxyurea; he was JAK2V617F+; had symptoms related to thrombocytosis, but no splenomegaly. RXL was effective in reducing symptoms but had no effect on the platelet count. No hematological toxicity was registered after 12 months of treatment with RXL.
Summary/Conclusion: Overall, response to RXL measured as spleen reduction or symptomatic control, was verified in 6 patients (46%) and 8 (61,5%) patients suffered toxicity, mainly hematological.

PB1728 CHARACTERIZATION OF ADULTS SERIES OF MASTOCYTOSIS CASES IN A HEALTH CARE CENTER IN CALI

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Background: Mastocytosis are neoplastic diseases of the myeloid line. They are characterized by pathological increase and accumulation of mast cells in one or more organs, most frequently involving the skin, bone marrow, liver and gastrointestinal tract. They may present as cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized mast-cell tumors. An annual incidence of up to 0.89 cases per 100,000 inhabitants has been reported for SM. There is no clarity on the therapeutic strategies, and several experimental treatments are still underway. In Colombia, there are only case reports; and so far, there are no more extensive studies.
Aims: To characterize a series of 7 patients with mastocytosis (both cutaneous and systemic cases) describing their clinical manifestations, paraclinical behavior and response to the medical treatment established in a reference center in the city of Cali (Colombia, South America).
Methods: A descriptive study of a series of cases in which it was carried out an active search for patients with a diagnosis of mastocytosis, whether cutaneous or systemic, from the total number of consultations in the period between June 2004 and June 2019, in the hematology-oncology reference center ("mastocytosis") in Cali. A total of 7 patients were found; their informed consent was obtained in accordance with the guidelines of the local ethics committee and the Helsinki act. Compliance with diagnostic criteria was verified according to existing WHO guidelines. The different sociodemographic, clinical, paraclinical and response to treatment variables were characterized, according to data from the clinical history. Qualitative variables were analyzed by frequencies and proportions, quantitative variables were measured by frequencies, averages and ranges.
Results: A total of 4 cases of CM and 3 cases of SM were identified. The most frequent clinical manifestations were skin lesions, which occurred in 100% of the patients; of these, the most frequent finding was hyper-pigmentary macules. 67% (2/3) of the SM patients presented gastrointestinal symptoms. Elevated serum tryptase (ST) levels were found in 67% (2/3) of MS patients. Both ST levels and the average absolute eosinophils values were higher in SM patients. The C-KIT mutation (D842B) was requested in only one patient (MC) in the series; this was positive. Only 28% (2/7) of the patients had complete resolution of symptoms with antihistamine treatment.



Summary/Conclusion: Regardless its presentations, mastocytosis is a rare disease, with little evidence to guide its diagnosis and management. A higher frequency of extracutaneous involvement, high levels of ST and eosinophils were found in SM patients; and in general, (there was) a very poor response to the established management in the two groups. The findings of this series are comparable to those reported in the world literature.

Platelets disorders

PB1729 OVERVIEW OF IMMUNE THROMBOCYTOPENIA MANAGEMENT IN CHILDREN, A SINGLE INSTITUTE EXPERIENCE

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Background: Immune thrombocytopenia (ITP) during childhood is usually characterized by acute onset of thrombocytopenia with around 75% of children having spontaneous remission within 6 months. Most children experience only mild bleeding in the form of bruising and Petechiae, with severe bleeding being rare even in children with persistent disease
Aims: To study demography, clinical, laboratory and treatment options of patients who were newly registered cases of immune thrombocytopenia referred to Children Welfare Teaching Hospital, Medical City, Baghdad.
Methods: A retro-prospective descriptive study was done on a newly diagnosed patients with ITP who were referred to Children's Welfare Teaching Hospital (CWTH) / Medical City / Baghdad from January 1, 2019 to April 30, 2020. The period of data collection and follow up started in September 2019 till December 2020
Results: A total of 107 patients were identified as having a presumptive newly diagnosed Immune Thrombocytopenia. Seven patients were excluded after being diagnosed as secondary ITP or other causes of thrombocytopenia during observation period. The mean age was 5.6 years (range 3 months-13.5 years). There were 56 (52.3%) boys, with a M:F ratio was 1.09:1. The mean duration of symptoms is 62 days. Sixty-four (59.8%) patients were managed as an outpatient only.
Sole cutaneous bleeding was reported in 55 (51.4%) patients while wet purpura was the leading cause of mucosal bleeding occur in 25 (23.3%) patients followed by epistaxis in 24 (22.4%) patients. According to grading, grade I/II was seen in 55(51.4%). The mean platelet's count was $15.7x10^9$/L, Platelet's count of <30 $x10^9$/L in 92 (86%) patients.
Seventy-eight patients (72.9%) reached CWTH without receiving any treatment while 29 (27.1%) patients received treatment elsewhere. The total number of patients kept under watchful waiting strategy was 44 (41.1%).
The mean and median platelets count at both time of diagnosis and time of last contact in the observation group were higher than that of the treatment group (24&19 vs 9.9&7 x 10^9/L at time of diagnosis; 210.6&246 vs 204.8&214 at time of last contact). There was significant

statistical correlation between each group and classification of grading (P value 0.0001).
Comparing severe thrombocytopenia (platelet's count < 30 x 10^9/L) and bleeding score among 2 groups; there was significant statistical correlation between bleeding grade at time of diagnosis and at time of last contact (P value 0.004).
Summary/Conclusion: The result of this study confirms the result of last year study in the same center which encourages the successful management of ITP by observation only and support the consensus that ITP is a benign and self-limited condition for the majority of affected children. The incidence on intracranial bleeding was 0.9%. The study observations support the emerging trend toward reserving drug therapy for ITP patients with major bleeding manifestations or troublesome impairment of quality of life.

PB1730 DENTOALVEOLAR PROCEDURES IN IMMUNE THROMBOCYTOPENIA; SYSTEMATIC REVIEW AND PRACTICAL RECOMMENDATIONS

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Background: Dentoalveolar procedures in immune thrombocytopenia (ITP) pose a risk of bleeding, due to thrombocytopenia, and infection, due to immunosuppressive treatments.
Aims: To systematically review the safety and management of dentoalveolar procedures in ITP patients in order to create practical recommendations.
Methods: Pubmed, Embase, Cochrane and Cinahl were searched. All original studies with surgical and non-surgical dentoalveolar procedures (including tooth extractions, scaling, and periodontal and endodontic surgery) in adult and pediatric patients with known primary ITP at the time of procedure were included. Details on bleeding- and infection-related outcomes were recorded, including the therapeutic strategies. Clinically relevant bleeding was defined as needing treatment or medical attention.
Results: Eighteen articles were included, of which twelve case reports/series. Overall, the quality of the available evidence was poor. Outcomes and administered therapies (including hemostatic therapies and prophylactic antibiotics) were not systematically reported. At least 118 dentoalveolar procedures in 94 ITP patients were described. The range of preoperative platelet count was 2-412*10^9/L. Two clinically relevant bleedings were reported in the same patient, of which one life-threatening. Strategies used to minimalize the risk of bleeding were heterogeneous and included therapies to increase platelet count, antifibrinolytics, local measures and minimal invasive techniques. Reports on the occurrence of bleedings due to anesthetics or infection were lacking.
Summary/Conclusion: It appears that clinically relevant bleeding complications after dentoalveolar procedures in ITP patients occur rarely, based on low quality data. Reported therapeutic strategies to prevent bleedings are heterogeneous. Prospective and controlled studies are needed to evaluate safety of dentoalveolar procedures in patients with low platelet counts and to investigate the efficacy of therapeutic interventions. We propose practical recommendations to manage dentoalveolar procedures in ITP patients based on the best available evidence and our single-center clinical experience.

PB1731 CLINICAL AND BIOLOGICAL PREDICTORS OF CHRONICITY OF IMMUNE THROMBOCYTOPENIA IN ADULTS

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Background: Immune thrombocytopenia (ITP) in adults is an auto-immune disease treated in first- line by corticosteroids and polyvalent immunoglobulins. This disease has frequently a chronic evolution. Risk factors for chronicity are not well defined and were explored in only a few studies.
Aims: The aims of this study were to report the clinical features of adult ITP, and to identify the clinical and biological risk factors predicting chronicity.
Methods: This was a monocentric retrospective study that collected data from adult patients followed for newly diagnosed ITP over a six year-period (2011 - 2017). Patients with platelets inferior to 30000/mm^3 were initially treated with corticosteroids. Second-line treatment consisted of splenectomy or danazol. Thrombopoeitin receptor agonists were not available in Tunisia during the period of the study.
Results: One hundred and fifty patients were included, with a median age of 43 (16-79). The median platelet count was 15000/mm^3 (0-88000). Response to corticosteroids was observed in 84,6% of patients with 71,5% of complete response. But recurrence of thrombocytopenia occurred in 27,2% of these patients.Chronic ITP was noted in 32,4%of patients, while newly diagnosed and persistent ITP were noted in 59,3% and 8,3% respectively.
Clinical and biological predictors of chronicity were studied. Clinical factors studied were: age, sex, the presence of bleeding symptoms,Khellaf score, the corticosteroid resistance, the time to response to corticosteroids, the duration between the response to corticosteroids and the recurrence of ITP. Biological factors studied were: the mean platelets count at baseline, the presence of antinuclear antibodies, the presence of antiphospholipid antibodies, the platelet-to-lymphocyte ratio at baseline (PLR). Only the presence of bleeding symptoms at diagnosis (p=0,033), the corticosteroid resistance (p=0,000) and the PLR <0.86 (p=0,031) were associated with a significant risk of progression to chronic ITP.
Summary/Conclusion: The progression to chronic ITP is frequent. The predictive markers of chronicity can be used to introduce promptly a second-line treatment and avoid prolonged courses of corticosteroids.

PB1732 NOT YET TO BE BORN – A CLINICAL CASE OF PSEUDOTHROMBOCYTOPENIA IN A PREGNANT WOMAN

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Background: Pseudothrombocytopenia (PTCP) is a platelet count (PC) erroneously below the reference value, usually under 150x10^9/L, due to platelet aggregation or platelet satellitism that happens *in vitro* triggered by the presence of an anticoagulant, mostly seen with EDTA. This phenomenon happens due to the binding of autoantibodies to glycoprotein IIb/IIIa in the presence of EDTA.
Aims: The authors present a clinical case of pseudothrombocytopenia.
Methods: 32-year-old pregnant woman, gesta 5, para 4, at 36 weeks and 2 days was admitted to the Obstetrics Emergency Room (OER) with complains of low back pain, cramps, chills, vomiting and nausea with 1 day evolution. The patient denied fever, cough, respiratory difficulty or urinary symptoms. There was no known epidemiological context for SARS-CoV-2 infection. Obstetric past history of 4 previous eutocic deliveries, 2 of them were preterm labours at 27th and 34th week of gestation. She had been medicated in outpatient care with vaginal progesterone. At clinical observation in the OER the patient was hemodynamically stable with no significant clinical changes, only showing a dubious right Murphy sign. Analytically, revealed thrombocytopenia of 126x10^9/L, lymphopenia of 0,34 x10^9/L and C-RP: 3,93mg/dL; the remaining inflammatory parameters were within reference values as well as renal function and liver damage analytes. Urine dipstick test revealed Ketone bodies: 150mg/dL; Proteins: 25mg/dL; Leucocytes: 100 cell/µL; Erythrocytes: 10 cell/µL; Nitrites: negative. SARS-CoV-2 RT-PCR test was positive. Cardiotocography (CTG) showed a normal pattern, with fetal heart rate of 150-160 bpm and irregular and sparse uterine contractility. The patient was proposed for hospitalization with CTG monitoring and started empirical antibiotherapy with cefuroxime for a presumed acute pyelonephritis. Prophylactic enoxaparin was started on the 2nd day. The pregnant woman remained clinically stable, analytically highlighting a progressive decrease in PC from the 2nd day on, with PC of 85x10^9/L. On the 4th day of hospitalization with thrombocytopenia of 11x10^9/L, a blood smear and the sFlt-1/PlGF ratio ongoing, a variety of different diagnosis were raised, such as pre-eclampsia, HELLP syndrome, autoimmune disorders, idiopathic thrombocytopenic purpura, heparin induced thrombocytopenia (HIT) or COVID-19-induced thrombocytopenia. At this point, our laboratory was contacted in order to confirm the low PC, since a labour induction was a possibility.
Results: HIT test proved to be negative and the blood smear revealed many and huge platelet aggregations. To confirm the PC our laboratory advised a new blood collection in a trisodium citrate solution (S-Monovette® *Citrate*) and in Mg^{2+} compound (S-Monovette® *ThromboExact*) collection tubes, which revealed a PC of 31x10^9/L and 123x10^9/L, respectively. On the 5th day she was discharged. After COVID-19 infection cure, the PC values remained significantly different

when measured in an EDTA and in Mg^{2+} compound collection tubes. The delivery happened, later, at 39 weeks of gestation.
Summary/Conclusion: The identification of a PTCP allowed us to avoid an iatrogenic preterm labour. When confronted with a patient with no signs or symptoms of bleeding or haemorrhagic dyscrasia and no past history of thrombocytopenia, PTCP should be considered as one of the differential diagnosis. It is estimated that approximately 0.1% of the whole population has antiplatelet autoantibodies triggered by EDTA. Early detection of this phenomenon may avoid an extensive investigation and unnecessary therapeutic procedures.

PB1733 PHASE III MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF RILZABRUTINIB, ORAL BTK INHIBITOR, IN ADULTS AND ADOLESCENTS WITH PERSISTENT OR CHRONIC IMMUNE THROMBOCYTOPENIA

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Background: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by immune-mediated platelet destruction and impaired production, leading to thrombocytopenia, a predisposition to bleeding, and diminished quality of life. Although initial response rates to standard therapy are generally high, long-term tolerability and durable remission remain elusive. Rilzabrutinib is an oral, reversible Bruton tyrosine kinase (BTK) inhibitor targeting mechanisms driving ITP. Preclinical studies of rilzabrutinib showed simultaneous rapid anti-inflammatory effects, along with neutralization and prevention of autoantibody signaling. In an ongoing phase I/II study of rilzabrutinib (± concomitant ITP therapy), 400 mg BID was identified as the optimal dose in patients with relapsed or refractory ITP. Preliminary results showed rapid, durable platelet response increases with a well-tolerated safety profile.
Aims: LUNA3 is a multicenter, randomized phase III study with open-label extension evaluating the efficacy and safety of rilzabrutinib vs placebo in adult and adolescent patients with persistent or chronic ITP (CT.gov: NCT04562766; EudraCT: 2020-002063-60).
Methods: Eligible patients must have primary ITP for a duration of >6 mo for adolescents (ages 12-17 y) or >3 mo for adults (age ≥18 y) and an average of 2 platelet counts <30×10^9/L (no single count >35×10^9/L) within 2 wk prior to treatment. Eligible patients should have a previous response (platelet count ≥50×10^9/L) to intravenous immunoglobulin/anti-D or corticosteroids that was insufficient or not sustained, or documented intolerance or insufficient response to any appropriate courses of standard-of-care ITP therapy. Randomization is carried out separately for the 2 age groups (12-17 y and ≥18 y). Within the 2 age groups, patients are stratified by splenectomy status (yes/no) and thrombocytopenia severity (platelet counts <15×10^9/L or ≥15×10^9/L). Patients are randomized 2:1 to oral rilzabrutinib 400 mg BID or placebo to receive double-blind treatment for up to 24 wk, followed by open-label treatment for 28 wk, and then a 4-wk safety follow-up. After 12 wk of double-blind treatment, non-responders will be given the option to receive open-label rilzabrutinib or discontinue from the study. Concomitant stable doses (maintained for at least 2 wk prior to study day 1) of ITP medication (corticosteroids and/or thrombopoietin-receptor agonists) are permitted. Patients who receive rescue medication may continue study treatment. The primary endpoint is the achievement of platelet counts ≥50×10^9/L for ≥8 of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue medication. Secondary endpoints include safety, duration of and time to platelet responses, rescue therapy use, and changes from baseline in bleeding scores (per ITP-BAT assessment). Responders may enter an additional 12-mo long-term extension.
Results: This is a recently-initiated, global clinical trial with the goal of enrolling approximately 194 patients.
Summary/Conclusion: The LUNA3 multicenter, phase III pivotal study is designed to evaluate the efficacy and safety of oral rilzabrutinib (± concomitant ITP therapy) vs placebo in adults and adolescents with persistent or chronic ITP who had insufficient response or were intolerant to previous ITP therapy. These study results will provide further support for a unique treatment mechanism via BTK inhibition to target the underlying pathology of ITP.

PB1734 REVISION OVER 15 YEARS EXPERIENCE OF MULTIPLE AUTOINMUNE CYTOPENIAS IN HEMATOLOGICAL AND NON-HEMATOLOGICAL DISORDERS

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Background: Inmune cytopenias (IC) are a frecuent finding that may occur either isolated or associated with autoimmune, neoplasic or infectious diseases. Anemia and thrombocytopenia are the most usual concomitant cytopenias and they even constitute a syndrome (Evans Syndrome-ES) themselves with specific characteristics and prognostic implications. Futhermore, when they are related with another medical condition, the presence of IC may affect unfavorably its treatment and evolution. However, it is not unusual that in some mild onsets this coexistence may be not detected until long time evolution because, for example, haemolytic activity is well-balanced and no anemia or thrombocytopenia are detected or neutropenia is unstable.
Aims: Get a global perspective of the variety of entities with multiple IC that had been referred to Haematology department for assessment and treatment evaluation. Identify those which fulfill classical ES criteria and their treatment and evolution.
Methods: We included 13 adult patients studied between 2006-2020 with autoimmune hemolytic anemia (AIHA) and/or immune thrombocytopenia (ITP) and/or immune neutropenia (IN) in the absence of any underlying cause. A revision of the diagnosis criteria and response to therapy was made according to International Consensus for Adult AIHA and the American Society of Hematology 2019 guidelines for inmune thrombocytopenia. Inmune neutropenia was define by neutrophil count <1,5x10E9/L on at least 2 separate determinations. Finally we defined ES as the concomitant or sequential confirmed presence of 2 of them: AIHA, ITP or IN.
Results: Thirteen patients with confirmed IC were included, 6 males and 7 females with a median age of 42 years at the diagnosis, and a median of 9 years of monitoring. Only 4 patients developed simultaneous cytopenias (2 ITP+IN, 2 ITP+AIHA) and the median of time between one cytopenia and another was 2'5 years. The most frecuent combination found was AIHA+ITP in 12 patients, with lower counts for ITP.
All AIHA were mediated by warm antibodies and antiglobulin test (DAT) IgG1+C3d in 85% of cases with only 1 case IgG+IgA. ITP presentation was moderated to severe in 12 cases. IN was not clinically relevant with a neutrophils nadir over 300x10E9 for all patients, and no recurrent or opportunist infections were documented even though there was 38% cases with significative hipogammaglobulinemia.
Additionally we detected antinuclear positive antibodies in 7 patients, and other types of autoimmune antibodies in 2 patients (antiphospholid and thyroid peroxidase antibodies) with higher titles in those with deeper cytopenias, specially AIHA, and mild to low titles in the rest.
ES criteria were accomplished by 8 patients, 5 AHAI+ITP, 3 ITP+IN. We describe their association with or without an underlying disorder as well as the therapeutic management in Table 1.
Finally, there was not any death related to this autoimmune disorder and 1 patient with secondary ES associated with lung cancer has died for this neoplasic disease.

	CYTOPENIA	1°/2	SIMUTANEOUS YES/NO	YEARS	ACUTE TREATMENT	CHRONIC TREATMENT	RESPONSE
Patient 1	AHAI+ITP	2°	No (1° ITP)	2'5	Corticosteroids+Igs+ Rituximab	No	Complete
Patient 2	AHA+ITP	2°	No (1° AHAI)	3	Corticosteroids+Igs+ Rituximab	Corticosteroids low doses	Complete
Patient 3	AHAI+ITP	2°	No (1°AHAI)	4'5	Corticosteroids+Igs	Revolade+ Corticosteroids low doses	Complete
Patient 4	AHAI+ITP	2°	No (1° ITP)	9	Corticosteroids+Igs	Romiplostin+ Corticosteroids low doses	Complete
Patient 5	AHAI+ITP	2°	N0 (1°ITP)	0'5	Corticosteroids+Igs+ Chemotherapy	Mycophenolate	Complete
Patient 6	ITP+IN	1°	Yes	-	Corticosteroids+G-CSF	No	Complete
Patient 7	ITP+IN	2°	Yes	-	Corticosteroids	Mycophenolate	Partial
Patient 8	ITP+IN	2°	No (1° ITP)	4	Corticosteroids+Igs	Revolade	Complete

Summary/Conclusion: ES in a rare and probably undiagnosed condition with a treatment traditionally based on corticosteroids. Nowadays combination with TPO-agonists is changing the rules and the prognosis of these patients.

Quality of life, palliative care, ethics and health economics

PB1735 HEALTH-RELATED QUALITY OF LIFE AMONG REFRACTORY/RELAPSED B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH KTE-X19: PHASE 2 RESULTS FROM ZUMA-3 TRIAL

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Background: Refractory/relapsed B-cell precursor acute lymphoblastic leukemia (r/r ALL) is an acute disease with poor prognosis with standard of care. The value of chimeric antigen receptor (CAR) T-cell therapies on not only overall survival but also health-related quality of life in r/r ALL warrants further study. The ZUMA-3 open-label, phase 1/2 multicenter trial (NCT02614066) was designed to evaluate the safety and efficacy of KTE-X19 in adult subjects with r/r ALL.
Aims: This analysis aimed to evaluate health-related quality of life as measured by the EQ-5D within the ZUMA-3 trial and how scores changed after treatment with KTE-X19 as compared to before treatment.
Methods: The EQ-5D 5 level version (EQ-5D-5L) was used to assess quality of life among patients in the Phase 2 portion of the ZUMA-3 trial at Screening, Day 28, Month 3, and every 3 months during long-term follow-up (up to 12 months). The EQ-5D visual analog scale (VAS) and Index scores (calculated using the US value set, with sensitivity analyses using crosswalk of UK, German, and French value sets) were described at screening, Day 28 and Months 3, 6, 9, and 12 with changes in scores from screening compared to thresholds for meaningful change (7 for VAS, 0.05 for EQ-5D indices). To handle missing survey response data, mixed-effects models with repeated measures (MMRMs) using a categorical variable for visit were applied under the missing-at-random assumption to estimate changes in scores in the full study population.
Results: Among 55 treated subjects in the Phase 2 modified intent to treat (mITT) study population, 51 patients completed the EQ-5D-5L survey at screening, 42 (41 for Index) at Day 28, 26 (25 for Index) at Month 3, 25 at Month 6, 10 at Month 9 and 14 at Month 12. Mean (SD) VAS scores at Screening, Day 28, Month 3, Month 6, Month 9, and Month 12 were 68.2 (21.8), 74.7 (17.9), 79.7 (12.2), 81.0 (17.6), 81.7 (23.1), and 86.9 (10.0) respectively. Most patients (min 70.0%, max 92.9%) had stable or improved VAS scores after treatment with KTE-X19.
Mean (SD) EQ-5D Index scores (US value set) were 0.82 (0.19) at screening with the highest score at Month 12 (0.91 [0.13]). Most patients had stable or improved EQ-5D Index scores after treatment with KTE-X19 (min: 57.5% [Day 28] max: 80.0% [Month 9]). Results were similar using UK, German, and French EQ-5D-5L index value sets. Based on MMRMs, estimated mean change in VAS exceeded clinically meaningful thresholds at Month 3 (mean [95% CI]: 9.6 [2.6, 16.5]), Month 6 (9.4 [2.5, 16.3]), and Month 12 (14.8 [7.0, 22.6]). Estimated mean change in EQ-5D-5L indices exceeded clinically meaningful thresholds at Month 12 (0.078 [-0.009, 0.164]) but confidence intervals overlapped 0. Similar to other patient outcome survey studies, results should be interpreted with caution due to missing follow-up data for some patients and small sample size.
Summary/Conclusion: Results showed that among R/R ALL patients participating in ZUMA-3, the majority of patients experienced improved or stable health-related quality of life as assessed by the EQ-5D scores, and this was more pronounced with the VAS score.

PB1737 PSYCHOLOGICAL DISTRESS IN OUTPATIENTS WITH LYMPHOMA DURING THE COVID-19 PANDEMIC

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Background: Cancer patients are a population at high risk of contracting COVID-19 and, also of developing severe complications due to the infection, which is especially true when they are undergoing immunosuppressive treatment. Despite this, they had still to go to hospital to receive chemotherapy during lockdown.
Aims: In this context, we have evaluated the psychological status of onco-hematological outpatients receiving infusion and not deferrable anti-neoplastic treatment for lymphoproliferative neoplasms, with the aim of both measuring the levels of post-traumatic symptoms, depression, and anxiety during the pandemic and also of investigating the perception of risk of potential nosocomial infection.
Methods: The Impact of Event Scale-Revised (IES-R) and the Hospital Anxiety and Depression Scale (HADS) were administered to all patients. Moreover, patients were investigated about their worries regarding the impact of COVID-19 on their lives as onco-hematologic patients.
Since the 2nd to the 29th April 2020 (during the first phase of the lockdown period in Italy) outpatients affected by lymphoma and needing an infusional chemotherapy/ immunetherapy were evaluated in the study. A multi-disciplinary approach to the patient was then activated, in order to provide a psychological support during the next phases of pandemy.
Results: 77 outpatients were prospectively evaluated. The mean age was 56.6 (range 22–85); 39 (50.6 %) were male and 38 (49.4 %) female. Diagnoses were distributed as: cHL n. 25 (32.5%); aggressive NHLS n. 15 (19.5%), of whom n. 9 had diffuse large B-cell lymphoma (DLBCL), n 5 mantle cell lymphoma (MCL), and n. 1 primary mediastinal large B-cell lymphoma; indolent NHLs n. 37 (48%), distributed as follicular lymphoma (FL) n. 28, marginal zone lymphoma (MZL) n. 3, hairy cell leukemia (HCL) n. 3, lymphoplasmacytic lymphoma n. 1, CLL/SLL n. 3. N. 6 (7.8%) were treated inside of a clinical trial. N. 52 (67.5%) of patients received infusion chemotherapy or immune-chemotherapy and n. 25 (32.5%) received immunotherapy. According to the line of treatment, n. 38 (49.3%) received induction therapy, n. 6 (7.8%) second line therapy, n. 13 (16.9%) were at the third or higher line, and n. 20 (26%) were receiving maintenance therapy.The mean age was 56.6 (range 22-85). Authors found that 36% of patients had anxiety (HADS-A), 31% depression (HADS-D), and 43% were above the cut-off for the HADS-General Scale; 36% fulfilled the diagnostic criteria for post-traumatic stress disorder (PTSD). Women and younger patients were found to be more vulnerable to anxiety and PTSD.
In the subsequent months, Authors planned a more structured psychological support, based on a screening offered to outpatients with lymphoma.
Summary/Conclusion: The study firstly analyzes the psychological impact of the COVID-19 pandemic on the frail population of patients affected by lymphoproliferative neoplasms, to underly the importance of screening patients for emotional and distress conditions and then offering them psychological support.

PB1738 REAL-WORLD COSTS OF FRONT-LINE TREATMENT FOR PERIPHERAL T-CELL LYMPHOMA IN FRANCE, GERMANY, AND THE UNITED KINGDOM

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Background: Peripheral T cell lymphomas (PTCL) are a rare and heterogenous group of aggressive non-Hodgkin lymphomas (NHL) that develop from mature T- and natural killer cells. They comprise approximately 10% of all newly diagnosed cases of NHL in Western populations
Aims: To estimate the cost of first-line treatment in patients with PTCL, from the government payer perspective, in France, Germany, and the UK
Methods: A cost calculator was designed to apply country-specific unit costs to treatments and other healthcare resource use collected in a retrospective medical chart review study conducted in France, Germany, and the UK. The study included PTCL patients diagnosed between January 1,

2014 and December 31, 2016, who received at least front-line treatment for PTCL. Medical chart data, including PTCL treatments, adjunctive therapies (e.g., antibiotics, antivirals, granulocyte-colony stimulating factor), radiotherapy, laboratory tests, inpatient and outpatient visits, and ancillary care, were collected. Unit costs for each type of resource used were sourced from tariffs in each country, and adjusted to 2020 values. Resource use was then multiplied by the corresponding unit cost to calculate the total cost by resource type, and the mean cost per patient was calculated. Results were stratified by country, PTCL subtype, front-line treatment regimen, age, and receipt of stem cell transplant.
Results: Data for a total of 165 patients (France, 53; Germany, 56; UK, 56) were collected in the chart review. The median age at diagnosis was 62 years, 81 % of patients had an ECOG status of 0-1 at diagnosis, and 72% had stage III/IV disease. Total costs of first-line therapy were €12,257 per patient in France, €22,392 in Germany, and €32,461 in the UK. The greatest proportion of costs was attributed to adjunctive therapies in France (€4,509) and Germany (€11,539), and stem cell transplant in the UK (€13,419). Of note, patients in the UK were more likely to have received a stem cell transplant (44.6%) compared to France (13.2%) and Germany (19.6%).
Summary/Conclusion: Adjunctive therapies and stem cell transplants are major cost drivers in patients with PTCL receiving front-line treatment.

PB1739 DETERMINING SATISFACTION WITH INTERPERSONAL RELATIONSHIP WITH NAVIGATOR MEASURE AMONG CAREGIVERS OF FILIPINO CHILDREN WITH CANCER IN A TERTIARY REFERRAL CENTER: A PATIENT NAVIGATION RESEARCH STUDY

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Background: Patient Navigators are trained to provide support and guidance to patients throughout the cancer care continuum. They help "navigate" through the maze of doctors' clinics, outpatient centers, insurance and payment systems, patient-support organizations, and other components of the health care system. Yet, there is no existing patient satisfaction tool to assess the patient navigation program in the Philippines for pediatric cancer.
Aims: This study aims to evaluate satisfaction with the patient navigation program using a validated Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers in a tertiary referral center for childhood cancer.
Methods: The tool was first translated for cultural appropriateness, translated and back translated into Filipino and the content validity and internal consistency were tested. Caregivers of Filipino children with cancer were then recruited to answer the survey and the results analyzed.
Results: The SN-I-Ph was modified for cultural appropriateness; content validity for all 9 items was acceptable with score of 4.5-5 and internal consistency showed satisfactory results with cronbach alpha of 0.9067. A total of 202 participants were recruited to join the survey. Results showed mean±SD of 42.6±7.8. All of the 9 items showed excellent satisfaction. The socio-demographic and clinical factors showed no clinical significance with p value showing >0.05.

Table 9. Socio-Demographic and Clinical Factors associated with Satisfaction among Caregivers of Filipino Children with Cancer

Factors	Very Satisfied (N = 187)	Somehow Satisfied (N = 15)	Odds Ratio	P-Value
Age (years)	36.8±8.9	35.6±7.3	1.01	0.594
Gender				
Female	157 (84.0%)	12 (80.0%)	Reference	Reference
Male	30 (16.0%)	3 (20.0%)	0.76	0.691
Relationship to the Patient				
Mother	151 (80.8%)	12 (80.0%)	Reference	Reference
Father	28 (15.0%)	3 (20.0%)	0.74	0.659
Others	8 (4.2%)	0	-	-
Educational Attainment				
College Level	79 (42.3%)	5 (33.3%)	0.58	0.351
Secondary Level	93 (49.7%)	10 (66.7%)	Reference	Reference
Primary Level	15 (8.0%)	0	-	-
Language Preference				
Bilingual (English/Filipino)	110 (58.8%)	5 (33.3%)	Reference	Reference
Filipino only	77 (41.2%)	10 (66.7%)	0.35	0.064
Employment Status				
Employed	42 (22.5%)	5 (33.3%)	0.58	0.342
Unemployed	145 (77.5%)	10 (66.7%)	Reference	Reference
Monthly Income				
Less than P 5000	152 (81.3%)	10 (66.7%)	Reference	Reference
More than P 5000	35 (18.7%)	5 (33.3%)	0.46	0.188
Health Insurance				
With Health Insurance	173 (92.5%)	15 (100.0%)	Reference	Reference
Without Health Insurance	14 (7.5%)	0	-	-
Diagnosis				
Hematologic Malignancy	138 (73.8%)	12 (80.0%)	Reference	Reference
Solid Tumor	49 (26.2%)	3 (20.0%)	0.70	0.599
Year of Diagnosis				
2013-2014	24 (12.8%)	3 (20.0%)	2.94	0.255
2015-2016	47 (25.1%)	2 (13.3%)	1.45	0.593
2017-2018	116 (62.1%)	10 (66.7%)	Reference	Reference

Summary/Conclusion: This study showed good satisfaction with the interpersonal relationship of the navigators among caregivers. Participants enrolled in the patient navigation program reported a positive overall experience with the medical care.

PB1740 DANISH PATIENTS WITH MULTIPLE MYELOMA REPORT NO CHANGE IN QUALITY OF LIFE DURING THE COVID-19 PANDEMIC

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Background: In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected for the first time in Wuhan, China, causing the coronavirus disease 2019 (COVID-19). Mortality rate in patients with multiple myeloma (MM) hospitalized due to COVID-19 has been reported to be 50% higher compared to non-cancer patients. The COVID-19 pandemic has resulted in adaption of myeloma care recommendations including key principles of limiting hospital visits by use of telemedicine communication and to use oral agents as much as possible and/or allowing treatment breaks. To mitigate the risk of COVID-19 spreading, extensive national lockdowns have been practiced and patients and caregivers have been encouraged to practice social distancing.
Aims: The aim was to investigate the impact of the first and second wave of the COVID-19 pandemic on quality of life (QoL) in Danish patients with MM.
Methods: The study was designed as a cross-sectional study comparing QoL in patients with MM using data obtained the year before the pandemic (pre-COVID) as a reference in comparison to the COVID period. In a Danish context, first wave was defined as April to June 2020 and the second wave as November 2020 to January 2021. The survey data originates from an ongoing cohort study, "Quality of life in Danish Multiple Myeloma patients" (QoL-MM), which is a Danish prospective, nationwide, observational survey, initiated in February 2017. Survey data are obtained at enrolment and subsequently at 12 follow-up time points over a two-year period including 24 QoL domains assessed by the European Organisation for Research and Treatment of Cancer Quality of life QLQ-C30, the Multiple Myeloma module QLQ-MY20, the Chemotherapy-Induced Peripheral Neuropathy module and the Short-form health survey version 2. The QoL data was analysed using mixed effects linear regression, with a year-period-interaction. Pre-COVID versus COVID mean domain score difference was considered evident, if the difference was *both* statistically significant (p-value <0.05) and clinical relevant using minimal important difference defined as 0.3 standard deviation of the mean score of all included 2019 answers. For data validation, the mean scores of the pre-COVID period were compared to the mean scores for 2018.
Results: In the study, 616 patients was included (63% newly diagnosed and 37% relapsed) with a mean age of 68.2 years (standard deviation 9.2). Females represent 40% of the population. Seventy-six percent were married/cohabiting, 24% single. The completion rates during the investigated periods were between 94% to 97%, and a total of 2,576 completed sets of questionnaires were included in the analyses. The Danish MM patients reported no statistical significant and clinical relevant difference in QoL during the first or second wave of the COVID-19 pandemic compared to one year earlier.
Summary/Conclusion: Patients with MM infected by COVID-19 are in increased risk of dying and the pandemic has to some extent affected the usual clinical care program and caused restrictions in their everyday living. However, the pandemic does not seem to impact the patients´ reporting's of QoL. A limitation, however, may be that the questionnaires used are not validated to capture psychosocial health during a pandemic. Still, our results is important as it documents that QoL collected in clinical trials during the pandemic allow interpretation without adjusting for the impacts of the pandemic.

PB1742 DISPARITIES IN ACCESS TO HOSPITAL-AT-HOME FACILITIES FOR MULTIPLE MYELOMA PATIENTS TREATED AS OUTPATIENTS WITH INJECTABLE CHEMOTHERAPY IN FRANCE – A NATIONAL HOSPITAL DISCHARGE DATABASE STUDY.

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Background: Multiple myeloma (MM) is the second most frequent hematologic malignancy. In the past few years, the approval of new drugs has significantly modified the management of this disease allowing outpatient care either in hospital-at-home or in outpatient hospital settings. However, little is known about the real-world management of MM patients in France and the factors influencing patients' orientation and use of the different hospital care facilities available.
Aims: To describe the real-world management of MM patients treated as outpatients with injectable chemotherapy. To assess determinants of being treated in each setting including patients related features and organization related features.
Methods: Methods: We conducted an observational, retrospective, cross-sectional study using the exhaustive national French hospital discharge database (PMSI). All myeloma patients with MM diagnosis (ICD-10 code=C90.0) having received at least one chemotherapy injection either in hospital at home or in outpatient hospital, in a hospital center offering both modalities of care, were included. The primary outcome was the proportion of patients having received at least one chemotherapy injection in the hospital at home setting in 2018. The following variables were collected: patient's age and gender, Charlson comorbidity index, time from MM diagnosis, distance from home to the hospital, number of inhabitants and median pre-tax annual income of the patient's city of residence, name of the chemotherapy when data available. To quantify the respective influence of each factor on access to hospital at home facilities, a logistic regression model was run on a 90% training set and assessed on a 10% test set.
Results: In 2018, 12,493 MM patients received at least one chemotherapy injection in France. 623 were excluded because of missing data and 8,245 because they had not been treated in center offering hospital at home chemotherapy. In total, 3,625 MM outpatients from 21 centers were included, of whom 1,180 (32.6%) had at least one chemotherapy injection delivered in the hospital at home setting. On average, those patients were 68 years (SD 11.3) old. Charlson comorbidity index was 5.5 (SD 2.6). Patients lived 26 kilometers (SD 29) away from the hospital. Time from MM diagnosis was 20.6 months (SD 14.9). The average size of the city of residence was 51,283 inhabitants (SD 67,097) and the median annual income was 22,702 Euros (SD 5,007). These patients were treated in 21 different centers, among which 9 teaching hospitals; 2,192 patients (60.5%) received bortezomib and 253 (7%) received carfilzomib.
After adjustment, the probability of having received at least one chemotherapy injection in the hospital at home setting was significantly higher for patients treated by bortezomib versus not treated by bortezomib (OR=21.3; 95IC=16.4-28.2) and living in more affluent cities (OR=1.07; 95IC=1.05-1.09). This probability was significantly lower for patients living further from the hospital (OR=0.99; 95IC=0.98-1.00) and in larger cities (OR=0.98; 95IC=0.97-0.98). The overall model fit was good (area under the ROC curve=0.83).
Summary/Conclusion: In this observational, retrospective, nationwide, real-world study in France, MM patients getting access to injectable chemotherapy in hospital at home facilities are more frequently treated by bortezomib and live closer to the hospital, in smaller and richer cities. These results suggest that organizational interventions could help reducing the observed disparities in access to hospital at home facilities.

PB1743 EXPERIENCES AND SUPPORT NEEDS OF CAREGIVERS OF PATIENTS WITH HIGHER-RISK MDS: QUALITATIVE INSIGHTS VIA ONLINE BULLETIN BOARD IN THE US, UK, AND CANADA

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Background: Higher-risk MDS pts and caregivers face many challenges in the course of disease management. Pts with advanced cancer and their caregivers can experience physical, emotional, social, financial, and functional issues. Research on the burden of caring for advanced cancer pts suggests that there is insufficient support for caregivers, likely due to the lack of knowledge about their needs and burdens. The overall experience of caregivers for MDS pts has not been evaluated to date.
Aims: Identify key challenges for caregivers of higher-risk MDS pts in the (1) caregiver role before, during, and after diagnosis; and along the disease journey; (2) Impact on the caregiver's life and well-being; consequently their areas of need for support; (3) Impact of decisions made, including treatments.
Methods: The OBB was the qualitative research methodology used. OBB enables data collection via a web-based platform. This innovative type of online focus group can generate more meaningful and impactful insights compared to traditional focus groups. A mix of moderator-led Q&A and participant discussion provides the caregiver insights as online dialogue. OBB is advantageous when participants are located in various geographic locations, time zones, and availabilities. Additionally, such a virtual platform meant the research was not disrupted despite being conducted during the COVID-19 pandemic. Inclusion criteria: (1) caregiver of adult pt with high- or very high-risk MDS as diagnosed per IPSS-R category or high-risk MDS as per IPSS, or intermediate-risk pts on hypomethylating agents, and (2) Proficiency in written English. Exclusion criteria: (1) Caregiver of pt with lower-risk MDS; (2) caregiver of pt in a clinical trial; and (3) Paid caregiver.
Results: 16 caregivers participated: 5 from the US, 6 from the UK, and 5 from Canada. A content analysis identified 7 key themes where caregiver burden was significant (Table).

Table: 7 Key Themes Experienced by Caregivers of Patients With Intermediate and Higher-Risk MDS

Themes	Categories That Fall Within the Theme
Caregiver role & burden	Adjusting to caregiver role, Adapting to patient's care needs, Boundary, Physical impact, Logistical burden, Financial impact, COVID-19 impact
Mental health	Emotional stress, Mindfulness, Masking, Adapting to life change, Coping mechanisms, Self-care, Social support networks
Family dynamics	Adjusting to new roles, Patient-caregiver dynamics, Co-caregiver dynamics, Impact on family relationships
Disease experience	Diagnosis, Prognosis, Watch and wait, Quality of life
Treatment experience	Treatment options, Decision-making, Experience of treatment
HCP interactions	Physician relationship, Physician communication, HCP care experience
Information & education	Disease awareness, HCP education, Sources of information/education

Abstract abbreviations: HCP, health care professional; IPSS-R, International Prognostic Scoring System-Revised; MDS, myelodysplastic syndrome; OBB, online bulletin board; Pts, patients.

Summary/Conclusion: The findings highlight a significant impact and burden on caregivers of pts with higher-risk MDS, which varies depending on the stage of the disease, the choice (or lack of choice) of treatments, and the personal situation of the caregiver. For example, although the caregiver role for more recently diagnosed pts is perceived as minimal effort, their role increases significantly if a stem cell transplant occurs, and/or if there are changes in the pt's health status (eg, infection, medication change, managing side effects). Emotional stress is pervasive, especially at diagnosis and prognosis stage, and when told to "watch and wait." This is amplified when HCPs are perceived to lack knowledge/expertise about MDS, resulting in additional burden to pts and caregivers as they seek more appropriate care. There is a strong need for mental health support for both pt and caregiver. The extent required depends on the personal situation and dynamics of the pt and caregiver. Additional stress factors include the uncertainty of employment and financial burden; the time burden when balancing other commitments; and the impact on their own health, particularly if they have their own health issues to manage. Most caregivers can manage the physical and functional aspects of care; however, many state that the bigger unmet need for both pt and caregiver is emotional support, which has not typically been part of the standard of care provided to MDS pts. There is thus an opportunity for healthcare systems to provide better support in these areas of emotional burden.

PB1744 'A DIFFERENT PERSON ENTIRELY': ADOLESCENT AND YOUNG ADULTS' EXPERIENCES RETURNING TO EDUCATION AFTER TREATMENT FOR HAEMATOLOGICAL MALIGNANCIES

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Background: Adolescent and Young Adults (AYAs) establish their independent, adult identities as part of their psychosocial development, a process largely informed by educational experiences. Not only is a cancer diagnosis disruptive to this process but AYA cancer survivors (AYACs) face barriers as they attempt to reintegrate into educational systems. .
Aims: This study explores the experiences of AYACs as they return to education. We do this to better understand the challenges they face, identify resources already available to this patient population and make recommendations that facilitate return of AYACs to education.
Methods: In-depth semi-structured interviews were conducted with AYA cancer survivors (n=8), aged 16-19 at time of diagnosis and 18-27 at time of interview. Interviews were transcribed verbatim and analysed using the principles of Giorgi's phenomenological analysis.
Results: Most participants were survivors of haematological malignancies (n=7, image 1). Four major themes were identified: AYAC survivors suffer from debilitating late effects (theme 1) post-treatment as they adjust to a loss of normality and other fundamental losses (theme 2) associated with a cancer diagnosis, such as irrecoverable future plans. The educational systems (theme 3) to which they return can be both accommodating, capable of making allowances, and uncompromising, unable to adapt to AYAC survivors' needs. Support (theme 4) is vital for successful return to education.

Table 1. Participant Demographics Table

AYA Participant	Gender	Age at diagnosis	Age at interview	Diagnosis
Pre-COVID lockdown measures: interviews conducted face-to-face				
AYA1	Male	17	21	Burkitt's lymphoma
AYA2	Male	19	22	Brain tumour
AYA3	Male	17	18	Hodgkin's lymphoma
AYA4	Female	18	25	Acute lymphoblastic leukaemia
Post-COVID lockdown measures: interviews conducted via online video calls				
AYA5	Female	19	21	Hodgkin's lymphoma
AYA6	Male	18	20	Hodgkin's lymphoma
AYA7	Female	17	27	Hodgkin's lymphoma
AYA8	Female	16	20	Lymphoblastic lymphoma

Summary/Conclusion: This study supports previous findings that late effects and systemic barriers can hinder return to education but further research focused on this age group is required. We believe that treating clinicians and specialist services can facilitate the return of AYAs to education by providing warning and comprehensive information about late effects, as early as possible prior to treatment completion, as well as effective information-sharing with educational institutions.

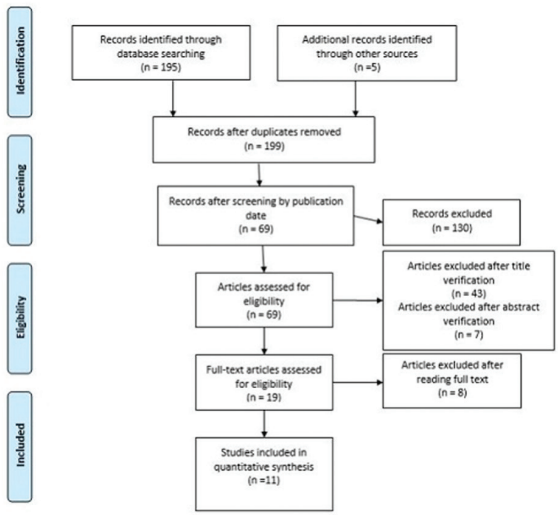
PB1745 SPIRITUALITY AND ITS INFLUENCE IN QUALITY OF LIFE IN HEMATOLOGICAL PATIENTS: A SYSTEMATIC REVIEW

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Background: Studies indicate that spirituality and religious practices can result in positive impacts in the quality of life (QOL) in many pathologies. From decreased anxiety or depression symptoms to a greater sense of peace and acceptance.
Aims: It is then questioned the spirituality impact in hematological patients QOL.
Methods: This systematic review included studies on the impact spirituality has in the QOL of hematological patients. Three electronic databases (SciELO, LILACS, PubMed) were consulted in search for articles published in the last ten years, in English, Spanish and Portuguese, using the following keywords searched in DeCs/ MeSH: spirituality, quality of life and hematology and its correlates in Portuguese and Spanish.
The initial online search led to the retrieval of 195 references and reviewers extracted data independently. A total of 11 articles were used in the review. The checklist of 27 items and 4-step flow chart (Table 1) indicated by the PRISMA methodology were used.
Results: It was observed that spirituality and religiosity have been associated with a better quality of life (QOL) in hematological patients. The study by Sirilla J, (2013) reported an improvement in QOL in patients who underwent bone marrow transplantation, as well as in the studies by Durner J, (2013), demonstrating improvement in patients with multiple myeloma and Thomas ML. (2012) in myelodysplastic syndromes. Rodin G. et al. (2013) found that spirituality is related to less symptoms of post-traumatic stress in patients with acute leukemia and Bediako SM et al. (2011) observed fewer hospital admissions among adults with sickle cell disease.
The study by Maheri A, et al. (2016) in adults with thalassemia affirms that spiritual growth is one of the most significant predictive factors of QOL, and emphasizes the importance of including spirituality in health care. Abdol Jabbari M, et al. (2018), observed that among parents of children diagnosed with cancer had developed spiritual tactics to deal with the disease, even under stressful conditions. According to Jabbari, reaching a certain spiritual level provided greater adherence to treatment and raised the hope.
Sheikhzakaryaee, et al. (2018) also explores the experiences of parents with children with cancer and their spiritual strategies. The results obtained were reduction of anxiety, depression and loneliness of patients and increase in QOL, with an expansion in positive and pleasure feelings.
The research carried out by Prince, et al. (2015) reports that patients subjected to allogeneic hematopoietic stem cell transplantation with greater spiritual well-being achieved a better QOL, while those who reported lower spiritual well-being affirmed emotional and QOL damage.
The study by Kiyancicek, (2017) with family members who assisted cancer patients obtained the following results: of 230 participants, 47.1% believed exercising spirituality helped them to deal with stress; 35% affirmed that after the diagnosis they dedicated more time to spiritual practices. In contrast, 30% affirmed that they spent less time exercising spirituality and 35.6% said nothing had changed.

Table 1 - PRISMA 4-step flow chart



Summary/Conclusion: The analyzed studies showed that spirituality has great potential in improving QOL for hematological patients and their relatives. However, despite the fact that complementary medicine has been gaining ground in helping various hematological diseases treatments, for spirituality to be truly added in daily practices, further studies should be strongly considered. In addition, health professionals must recognize the value of patients' psycho spiritual well being.

PB1746 EFFECTS OF ISOLATION DURING THE COVID-19 PANDEMIC ON TEENAGERS WITH SICKLE CELL DISEASE IN ITALY: THE EXPERIENCE OF A DEDICATED TELEPHONE SERVICE FOR PSYCHOLOGICAL SUPPORT

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Background: In the past year the COVID19 Pandemic and the repeated lockdown measures have disrupted people's life. Teenagers with chronic illness, such as Sickle Cell Disease (SCD) present special health care and educational needs during the delicate phase of transition to adulthood compared to their peers. The Veneto Region, in North East Italy, was one of the first red zones areas in Europe since February 26th 2020 with Phase 1 of strict lockdown until April 30th 2020; Phase 2 with progressive reopening of activities during the summer; Phase 3 since September 2020 with initial high school opening but successive implementation of risk zones across the country with regional limitation of movements, economical activities, social life and education according to the diffusion of COVID19 in the area. Since November 2020 high school students were forced to stay at home and perform virtual classes; only individual sports were allowed.
Aims: We analyzed the psychological impact of the restrictions and isolation measures on teenagers and young adults with SCD in the Veneto Region of Northern Italy during the 3 different phases of lockdown while offering a dedicated telephone service of psychological support.
Methods: A dedicated telephone service was organized since March 2020 by a Psychologist of the SCD Team to contact families and offer support. Adolescents and young adults were contacted directly. Telephone calls occurred during Phase 1 (strict isolation), phase 2 (progressive reopening) and the current phase 3 (alternation of openings and closures) and were characterized by a set of standardized questions tailored to the phase followed by an open dialogue. A qualitative description is presented.
Results: 28 adolescents responded to the phone calls and agreed to be called again. Psychological experiences differed according to the phase of the lockdown. In phase 1, in which the limits to personal freedom were high, they felt equal to the general population and felt confident that this painful period would soon end. In phase 2, due to loosen restrictions, greater concerns and anxiety emerged: the need to coexist with the virus and the continuous changing of the rules generated a greater perception that a sudden painful event could break into their life at any time, increasing personal discomfort and undermining the quality of life. Phase 3 showed further different responses. 23/28 stated that they resumed school or work activities, although in different ways (virtual classes or smart working). All reported feeling accustomed to, and therefore less anxious, about covid-19. All claimed to respect the rules, to know them well, and to apply them. 20/28 patients reported spending most of their time at home, were not interested in going out and didn't have social interactions. 6/28 teenagers requested specific psychological support in the form of weekly phone calls or zoom calls with the SCD psychologist, which is still ongoing. Most of them are girls who asked for help in managing their anxiety and the fear that they won't be able to realize their expectation in professional or family life.
Summary/Conclusion: The dedicated telephone service for psychological support was well received by teenagers with SCD with a subgroup requesting a repeated intervention. The qualitative results of our experience demonstrate the need for psychological support during the pandemic in patients with chronic disease; remote support has proven to be an effective tool.

PB1747 USE OF THE EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE MULTIPLE MYELOMA QUESTIONNAIRE (EORTC QLQ-MY20): A REVIEW OF THE LITERATURE 25 YEARS AFTER DEVELOPMENT.

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Background: The EORTC QLQ-MY20 was originally developed in 1996 to assess health-related QoL (HRQoL) in multiple myeloma (MM) patients. Since its development, the use of multiple new myeloma treatment options has had a major impact on prolong survival in MM patients. The continuous introduction of new Myeloma combination agents is likely to have further implications on HRQoL outcomes and its measurement.
Aims: In the era of new therapies the aim of this review was to explore the use and performance of the QLQ-MY20 in clinical studies, the population characteristics (i.e the number of treatment lines patients had received), therapy types, positioning to support randomised controlled trial (RCT) endpoints and psychometric performance.
Methods: Original research (1996-June 2020) that used the QLQ-MY20 in a clinical study or that assessed the psychometric properties of the questionnaire was identified through an electronic database search. Abstracts were screened to remove irrelevant results and duplicates. Data were extracted from full text publications/conference abstracts and checked by a second rater.
Results: 66 clinical studies and 9 validation studies were identified. The QLQ-MY20 had been used in RCTs (n=19, 29%), clinical trial-single arm (n=3, 5%), cross-sectional observational (n=26, 39%), and longitudinal/cohort observational (n=18, 27%) studies. The publication of QLQ-MY20 data in clinical trials increased over time from 2006-2010 (n=1), 2011-2015 (n=8) and 2016-2020 (n=13). Clinical trials most frequently included relapsed MM patients (n=15, 68%), and assessed a range of combinations therapies with Steroids (n=18, 82%), Proteasome inhibitors (n=13, 59%), immunomodulatory IMiDS (n=12, 55%) and Chemotherapeutic drugs (n=10, 46%). QLQ-MY20 subscales were most frequently defined as secondary (n=12, 55%) or exploratory (n=7, 32%) trial endpoints. The subscales most frequently used to support trial endpoints were Disease Symptoms (DS; n=16, 72%) and Side Effects (SE; n=16, 72%). Validation articles demonstrated that all domains were performing well in terms of internal consistency reliability (>0.7), test-reset reliability (intraclass correlation coefficient >=0.85) and internal and external convergent and discriminant validity. The DS, SE and Future Perspectives (FP) domains were performing well with respect to floor and ceiling effects however four articles reported a high percentage of ceiling effects in the Body Image (BI) domain.
Summary/Conclusion: Overall the results showed that the EORTC QLQ-MY20 remains a widely used and psychometrically robust instrument. An update to prospectively optimize this EORTC QLQ MY20 is currently underway in a European trial, to keep up the conceptual relevance in reporting QOL with survival outcomes using new therapies.

PB1748 INPATIENT CARE OF PATIENTS WITH EARLY-RELAPSED DIFFUSE B-CELL LYMPHOMA (DLBCL): AN ECONOMIC PERSPECTIVE

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Background: Immunochemotherapy-regime R-CHOP is the standard firstline (1L) treatment for patients (pts) with diffuse large B-cell lymphoma, approximately 30 - 50% of pts will not be cured by 1L. Especially pts with an early relapse <12 months (m) after 1L have a poor prognosis for cure. Only limited information exists on clinical outcomes, treatment patterns, resource consumption and costs in routine care of early-relapsed DLBCL-pts in Germany.
Aims: Therefore, we initiated a study to provide information on aforementioned variables.
Methods: Retrospective single center observational feasibility study. Data sources were claims data and data from medical records (2007-2018) from a German tertiary teaching hospital. Early relapse was defined as <17m after initial diagnosis (ID). Treatment-patterns were analyzed in regimens per line. Outcome-parameter: resource-use (inpatient stay; cumulated over patient career), costs (cumulated over patient career) and documented death (dd). Costs were evaluated from statutory health insurance perspective. Inclusion criteria: age ≥18 years, diagnosis of relapsed DLBCL (ICD: C83.3). Exclusion criteria: age <18 years, additional active malignancies.
Results: We identified 84 pts with relapse after 1L. In total 44 pts (52%) relapsed within 17 m after ID. Mean age at ID: 59 y (median: 63); n = 26 (59%) were male. Ann-Abor stage at ID: 15 pts I-II; 29 pts III-IV. 28 pts were in 2L; 14 pts received 3L, 1 pt in 4L and 1 pt 5L. Outcomes for 2L pts: 17 in complete remission incl. follow-up (CR), 11 documented deaths (dd). 3L pts: n=8 in CR, 6 dd. 4L: n=1 in CR. 5L: n=1 dd. Mean duration of inpatient stay per patient (ppt) in 2L was 45 days (median:

43; range 3 – 132); in 3L: 74d (80; 33 – 122); 4L: 137d; 5L: 183d. Following treatment-patterns refer on pts in 2L (n=28): 10 pts received Immuno-chemotherapy (I-chemo), 6 pts I-chemo + autologous-stem cell transplantation (auto-SCT), 4 pts a chemo, 4 pts a radiation, 2pts a chemo + auto-SCT and 2 pts a I-chemo + radiation. Mean total costs (€) ppt in 2L: 47.300 (median: 40.300; 6.500 – 166.000); 85.000 for 3L pts (77.300; 33.700 – 214.000); 4L: 200.000 and 5L: 163.000.
Summary/Conclusion: The results show that an early-relapse results in a high patient and economic burden: various therapies, long inpatient-stay, significant costs and documented deaths. The highly individual treatment approaches or the huge ranges in costs are indicators that it is difficult to calculate DLBCL-treatment with averages in variables. Comprehensive cost and outcome analyses in DLBCL treatment are needed. The presented costs may underestimate the total hospital costs for patients with DLBCL treatment, because exclusively inpatient claims data from the hematology/oncology department were taken into consideration. Costs from the radiation center and the outpatient center are not included.

PB1749 HEALTH –RELATED QUALITY OF LIFE OF PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Patients with acute myeloid leukemia are treated with intensive chemotherapy, and usually have long hospitalizations and severe treatment side effects that may have a negative influence on the health-related quality of life.
Aims: The aim of this work was to study the health –related quality of life of acute myeloid leukemia survivors in complete remission.
Methods: Arabic translations of the SF-36 and the Hospital-Anxiety-Depression Scale (HADS) questionnaires were used. The patients replied to these questionnaires during their medical consultation.
Results: Thirty –nine patients were included in the study with a median age of 42. Twenty one patients had acute myeloid leukemia (AML) and 18 patients had acute promyelocytic leukemia (APL). The median duration after the diagnosis was 74 months (13-190). All these patients were in complete remission. The SF-36 results showed no difference in physical or mental scales compared to the population norms. The mean physical score found was 71,5. The mean mental score was 70,9. The scores of the different domains were also similar to the population norms, ranging between 61,6 and 85,8. The lowest score was associated with the domain of fatigue.
The HADS questionnaire results showed a pathologic score (>= 11) in 14% of patients in the domain of anxiety. The anxiety score was doubtful (ranging from 8 to 10) in 17% of patients. No pathologic results were found in the domain of depression, but the score was doubtful in 17% of patients.
Summary/Conclusion: Survivors of acute myeloid leukemia have normal global health-related quality of life. But they suffer often from anxiety disorders and still require counseling.

PB1750 COST-EFFECTIVENESS OF RUXOLITINIB FOR PATIENTS WITH MYELOFIBROSIS: A REVIEW OF THE LITERATURE

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Background: Myelofibrosis (MF) is a rare (annual incidence estimated to be 1/100,000 in Europe), chronic hematologic disorder associated with morbidity and mortality as well as the risk of evolution to acute myeloid leukemia. Ruxolitinib (Jakavi®, Novartis) is the first JAK 1/2 inhibitor approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011 for the treatment of patients with MF. Ruxolitinib is considered a high-cost and life-time treatment. UK-based estimates of the cost of treatment are in the region of £43,000 per patient, per year. The work was completed in partial fulfilment of an MSc in Applied Economics for Healthcare Decision Making from the University of South Wales. The research was deemed as low risk and as such was reviewed by the Low Risk Ethical procedure at the Faculty of Life Science and Education, University of South Wales and granted approval.
Aims: Against the background of the challenge of treatments for rare diseases reaching cost-effectiveness thresholds, this study identified, synthesized and appraised the available evidence on the cost-effectiveness of ruxolitinib in the treatment of MF.
Methods: A systematic approach was taken to conducting the literature review. Databases searched included PubMed, EMBASE, MEDLINE, and the Cochrane Library based on search terms informed by Population, Intervention, Comparator and Outcomes (PICO): myelofibrosis, ruxolitinib, best available therapy/standard of care, and cost-effectiveness/cost-utility/pharmacoeconomics. The search was limited to studies published in the English language. Narrative synthesis was used to evaluate included studies and the CHEERS checklist to explore quality of reporting of the cost-effectiveness analysis.
Results: The narrative synthesis included five studies conducted in the UK, Portugal, Chile, Canada, and Finland. All cost-effectiveness analyses used data obtained from the same two large, randomized controlled, double-blind, phase III studies (COMFORT-I and -II) that led to the regulatory approval of ruxolitinib. Ruxolitinib was compared to best available therapy (BAT), including hydroxyurea, no medication, and prednisone/prednisolone. Perspectives and included costs varied among analyses. Markov models and discrete state cohort models were used to evaluate cost-effectiveness and clinical benefit was measured in quality-adjusted life years (QALY) or life years (LY) gained.
These analyses estimated the base case incremental cost-effectiveness ratios (ICER) per QALY of (converted into USD, if appropriate, at the historic average annual exchange rate) 44,905 GBP in the UK (in 2013; USD 70,2262), 40,000 EUR in Portugal (in 2016; USD 44,272), 54,500 USD in Chile (in 2016), 61,444 CAD in Canada (in 2012; USD 61,474), and 42,367 EUR in Finland (in 2015; USD 42,027). Based upon the cost-effectiveness thresholds applied in each of these countries, ruxolitinib was found to be universally cost-effective, albeit with price adjustments as part of the wider pricing and reimbursement processes used in these countries.

	Wade et al., 2017[4]	Vandewalle et al., 2016[7]	Rojas et al., 2016[8]	El Ouagari et al., 2012[9]	Hahl et al., 2015[10]
Country	The UK	Portugal	Chile	Canada	Finland
Publication type	Full-text	Full-text	Abstract	Poster	Abstract
Comparator	BAT	BAT	BAT	BAT	BAT
Economic model	Discrete state cohort	Discrete state cohort	Markov cohort state transition	Markov	Survival decision
Time horizon	35 years	Lifetime	Lifetime	Lifetime	Lifetime
Discount rate	3.5%	5%	3%	NA	3%
Types of costs included	Drug acquisition costs, disease management costs, adverse event costs, costs associated with leukemic transformation, end of life costs	Treatment costs, AE costs, costs related to AML transformation, splenic irradiation, splenectomy, resource use	NA	Costs related to drug administration, the management of AEs, other medical costs, and indirect costs	Drug costs and healthcare resource cost
Perspective	NHS and PSS	National health service	NA	Societal	Payer
Incremental cost	NA	€97,052 (Ruxolitinib: €188,967 BAT: €91,915)	$54,856 (Ruxolitinib: $101,926, BAT: $47,070)	CAD 73,104 (Ruxolitinib: CAD 494,859, BAT: CAD 421,755)	€102,802
Incremental QALY with ruxolitinib	+2.51 (Ruxolitinib: 3.99 BAT: 1.48)	+2.43 (Ruxolitinib: 5.39 LY BAT: 2.96)	+0.98	+1.19 (Ruxolitinib: 4.01 BAT: 2.82)	+2.43
ICER	£44,905/QALY	€40,000/LY	USD 54,500/QALY	CAD 61,444/QALY	€42,367/QALY
Sensitivity analysis	Probabilistic sensitivity analysis: £44,625/QALY gained The probability of being cost-effective £30,000: 0.33% £50,000: 95.02%	Probabilistic sensitivity analysis: The probability of being cost-effective €50,000: > 95%	The probability of being cost-effective $20,000: 0% $60,000: 73.6%	One-way sensitivity analysis and probabilistic sensitivity analysis: The mean ICER was CAD 59,216/QALY	The model was found to be robust to changes in inputs based on sensitivity analysis
Conclusion	Cost-effective at a £50,000 threshold	Cost-effective option with a WTP of €50,000	Cost-effective option with a discount	Cost-effective option at a threshold of CAD 100,000	Acceptable QALYs and costs

AE, adverse event; AML, acute myeloid leukaemia; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LY, life years MF, myelofibrosis; NA, not available; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-year; TTO, time-trade-off; UK, United Kingdom; WTP, willingness-to-pay

Summary/Conclusion: Ruxolitinib was found to be cost-effective for the treatment of patients with myelofibrosis informed by different types of models and from different perspectives; however, there was some uncertainty around available data due to a very limited data source.

PB1751 THAI-VERSION OF THE MD ANDERSON SYMPTOMS INVENTORY FOR ACUTE MYELOID LEUKEMIA/ MYELODYSPLASTIC SYNDROME (MDASI-AML/MDS): THE PSYCHOMETRIC PROPERTIES INVESTIGATION IN ADULT AML PATIENTS

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Background: The MD Anderson Symptoms Inventory for acute myeloid leukemia/myelodysplastic syndrome (MDASI-AML/MDS) is one of the specific patient-reported outcome measure (PROM) and widely used to assess the quality of life of acute myeloid leukemia (AML) patients. We translated the original version into Thai (Thai MDASI-AML/MDS) and evaluated its psychometric properties.
Aims: To evaluate the psychometric properties of Thai MDASI-AML/MDS in AML patients.
Methods: After receiving permission, the original MDASI-AML/MDS was translated and cross-culturally adapted to Thai. Sixteen of AML patients were included in the study. Internal consistency was evaluated using Cronbach's alpha and test-retest reliability was analyzed using intraclass correlation coefficient (ICC). Spearman's rank correlation was used to investigate among the subscales of Thai MDASI-AML/MDS and Thai EQ-5D-5L.
Results: All subscales of Thai MDASI-AML/MDS showed an acceptable Cronbach's alpha (0.64-0.92). The test-retest reliability of each subscale was good (ICC = 0.89-0.98). The core symptoms subscale in the Thai MDASI-AML/MDS strongly correlated to the anxiety/ depression subscale in the Thai EQ-5D-5L (r = 0.65, p = 0.0044). The strong correlation was demonstrated between the interference's subscale of the Thai MDASI-AML/MDS and the usual activities subscale of Thai EQ-5D-5L (r = 0.79, p = 0.0002). A weak correlation was found between the MDS/AML specific symptoms subscale in the Thai MDASI-AML/MDS and the pain subscale in the Thai EQ-5D-5L (r = 0.59, p = 0.0121). The Thai MDASI-AML/MDS had strong correlation with Thai EQ-5D-5L (r = 0.76, p = 0.0005).
Summary/Conclusion: The Thai MDASI-AML/MDS provides adequate internal consistency in all subscales as well as good construct validity and reliability for Thai patients.

PB1752 ECO-HEALTH LITERACY ASSOCIATED WITH LEUKEMIA AMONG TUNISIAN YOUTHS AND PROSPECTS FOR EMPOWERMENT

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Background: Given the increasing blood cancer incidence in Tunisia and recent discoveries proving the involvement of environmental factors, the empowerment of youths to the complexity and multi-causality of this disease constitute an essential objective of health promotion and education.
Aims: This study examined the eco-health literacy of Tunisian secondary school students concerning blood cancer, their interest in knowing about it, and their emotional and behavioral attitudes towards leukemia risk.
Methods: This is a quantitative study; a cross-sectional survey was conducted among Tunisian youths. Data collection took place in five representative public secondary schools in the north, center, and south of Tunisia. Students completed a paper and pencil questionnaire and described their literacy level about blood cancer, as well as their attitudes and interest in the disease. Statistical software (SPSS, v.25.0) was used to analyze the data.
Results: The results indicate low eco-health literacy scores concerning leukemia. Lack of knowledge and confusion about the causes, symptoms, and diagnosis of leukemia is a common finding at all school levels surveyed. Most youths failed to identify all the carcinogenic (except tobacco) and non-carcinogenic risk factors. Pesticide use and exposure to electromagnetic radiation are not considered risk factors. Living in a polluted urban area or near a roadway in high traffic does not constitute a real risk situation for youths. The leukemia risk perception and the fear level differed according to gender, with higher sensitivity among teenage girls. Despite these low scores, most participants were interested in having more information about leukemia and cancers in general.
Summary/Conclusion: This investigation shows a lack of knowledge about leukemia and these environmental factors. Low scores, interest, and an information need for expressed by youths who should incite educational actors and curriculum designers to optimize content and innovate ICT adapted to this eco-health challenge.

PB1753 UNCERTAINTY ABOUT THE FUTURE: INSIGHTS FROM OLDER PATIENTS WITH ACUTE MYELOID LEUKAEMIA (AML) ON DIFFERENT TREATMENT PATHS

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Background: AML is a haematologic cancer primarily affecting older people (median age 68 at diagnosis). Prognosis is poor, with median survival ranging from 2 to 10 months from diagnosis, depending on patient health, age, and treatment path. Some patients described struggling with uncertainty about the future, but it is unclear how this differs across patients and treatment paths.
Aims: This study explored the experiences of AML patients (≥65 years old, not receiving intensive chemotherapy), their close relatives, and independent clinicians. Specifically, patient expectations for the future and how these varied by treatment path and by time since diagnosis were investigated.
Methods: A total of 28 AML patients (aged 65-83; median 74), 25 relatives, and 10 clinicians from the US, UK, and Canada each took part in a 60-minute, semi-structured telephone interview. Open-ended questions were used to elicit spontaneous content, followed by focused questions when needed.
Results: Patients had diverse treatment histories: 13 no treatment, 14 with experience of non-intensive chemotherapy (NIC) including 3 who discontinued treatment, and 1 on best supportive care (BSC). At time of interview the mean time since diagnosis was 5 (range 2 to 9) months for patients with no treatment experience, and 8 (range 2 to 19) months for those with treatment experience. The BSC patient was diagnosed 9 months prior to interview.
Patients discussed positive and negative expectations for the future related to: physical functioning; treatment; life expectancy; ability to do hobbies, spend time with family, and go on vacation. In the no treatment group, there was evidence that expectations about the future became more negative over time. Few patients (n=4/13) recalled having negative expectations about the future at diagnosis, while most (n=10/13) did at time of interview. In contrast, patients with treatment experience appeared to have increasingly positive expectations. Most of these patients (n=11/14) recalled negative expectations when diagnosed, whereas at interview most (n=9/14) felt hopeful about future events. Further, of patients with treatment experience, almost all those diagnosed ≥6 months prior to interview had positive expectations about their future (n=6/7), while under half of those diagnosed <6 months prior (n=3/7) did. Clinicians (n=7/10) further highlighted that patient expectations changed over time depending on treatment success.
Additionally, patients (n=15/28) and relatives (n=15/25) discussed feeling uncertain throughout the AML journey, reporting unknowns around life expectancy, what they would be able to accomplish, and future plans. Uncertainty was a consistent experience regardless of treatment history, with similar proportions of patients not on treatment (n=7/13) and those with NIC experience (n=7/14) reporting the sentiment. Additionally, recently interviewed patients (n=7/13) and relatives (n=7/10) noted that the ongoing COVID-19 pandemic contributed to experiences of uncertainty and difficulties planning for the future.
Summary/Conclusion: There were key differences between patients not on treatment and those with experience of NIC, as patients with treatment experience demonstrated more hope for the future. Regardless, uncertainty is a key element of the AML journey. For some patients, this was exacerbated by the COVID-19 pandemic. These findings highlight

the importance of ensuring all patients are provided with emotional and spiritual support to help them process their diagnosis and plan for the future, both during this pandemic and beyond.

PB1754 MEASURING HEALTH RELATED QUALITY OF LIFE OF CHRONIC MYELOID LEUKEMIA PATIENTS ON NEWER GENERATION TKIS USING THE FILIPINO VERSION OF THE FACT-LEU QUESTIONNAIRE

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Background: Significant attention has been placed on recognizing impact of symptom burden and treatment-related toxicities on patients' health-related quality of life (HRQoL) since these would have an effect on treatment tolerability and adherence. In the Philippines, the only locally available TKIs are Imatinib and Nilotinib. Access and sustainability for the newer TKIs such as Dasatinib, Ponatinib and Bosutinib as second- or third-line agents is made possible with the help of The Max Foundation via their Max Access Solutions (MAS). There is paucity of published local data on HRQoL outcomes on Filipino CML patients treated with newer-generation tyrosine kinase inhibitors (TKIs).
Aims: This study determined the HRQoL of Chronic Myeloid Leukemia (CML) patients on newer-generation TKIs using the Filipino-version of the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) Questionnaire©.
Methods: A single-center, cross-sectional study included CML patients, aged 19, with stable comorbidities, taking newer-generation-TKIs as second-or-third line treatment (Dasatinib, Ponatinib and Bosutinib) for 3 months. HRQoL was assessed using the Filipino-version of the FACT-Leu© questionnaire. Descriptive statistics was used to summarize patients' demographic and clinical characteristics. Independent sample T-test and one-way analysis of variance was used to test significant difference between groups. STATA 13.1 was used for data analysis.
Results: All 33 patients were in chronic-phase. Newer-generation TKIs used were: Dasatinib (54.55%), Bosutinib (30.30%) and Ponatinib (15.15%). Mean scores: Trial Outcomes Index (106.15 ± 12.27), FACT-G score (94.79 ± 10.74) and FACT-Leu score (151.58 ± 17.25) showed good HRQoL. There was no significant difference between HRQOL with sex, marital status, educational attainment, employment, adverse drug event with concomitant dose adjustment and newer-generation TKI used (p-value 0.786, 0.764, 0.764, 0.944, 0.864, 0.554); and insufficient evidence to conclude a correlation between overall FACT-Leu score to age, CML and treatment duration (p-value 0.7389, 0.4738, 0.6984).
Summary/Conclusion: HRQoL evaluation is a vital part of disease management. This study demonstrated that Filipino CML patients using newer-generation TKIs as second or third-line therapy showed good HRQoL regardless of age, sex, marital status, educational attainment, employment, CML duration, treatment duration, presence or absence of adverse drug event with concomitant dose adjustment and newer-generation TKI used.

PB1755 NATIONAL REGISTRY-BASED SURVEILLANCE ON HEMOGLOBINOPATHIES IN TURKEY

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Background: The National Hemoglobinopathy Registry of the Turkish Society of Hematology (TSH) includes all resident patients in Turkey.
Aims: It aims to assess the efficacy of the national hemoglobinopathy control program (HCP), the changing pattern of the epidemiology, and the standardization of high-quality health care overall in Turkey.
Methods: The registry has been approved by the ethics committee of the Ege University. Participating physicians recorded patients' data into the database after receiving informed consent from the patients/legal representatives. The data collected during the last 18 months were extracted onto an Excel spreadsheet for analysis in January 2021.
Results: The table shows the characteristics of the 3554 patients. Overall, 81.5% of patients had thalassemia, and 18.5% sickle-cell disorders (SCD). A comprehensive HCP was activated, in Turkey, in 2002. A total of 1262 affected births were registered in the database since 2003. While 40% of the parents of affected births had a pre-marital screening, only 50% of those couples stated having appropriate genetic counseling. Eighty percent of couples having genetic counseling did not get a prenatal diagnosis (PND). The rest (20%) gave birth to affected babies despite PND. Notably, 30% of patients had at least one affected sibling born before the patient's birth, and 24% of patients had at least one affected sibling after the patient's birth. Although there has been a 33% reduction in the number of affected subjects (~52/year) since 2015, compared to the prior 5-year cohort (~80/year), the rate is still high, and this declining pattern requires further confirmation. The registry also includes 428 affected children from refugee families, of whom 30% were born in Turkey during the last decade. Overall, 295 patients (13 refugees) with thalassemia and 9 (1 refugee) with SCD, aged 8.7±5.4 (median 7.0), had bone marrow transplantation (BMT). The majority (82%) of BMTs were performed after 2010. The 2-year overall survival was 98%, and event-free survival was found 89% in those (MSD 179, MFD 29, UD 29) followed at least 2-years after BMT. Cardiac failure and arrhythmias were the most common causes of death in thalassemia until the last decade. The rate of cardiac deaths in the "at-risk" population significantly decreased, while the mean age of deaths was increased in the decades following (p=0.02), and infections, particularly in association with transplantation, have replaced cardiac deaths in the period between 2010-2019. Cardiac and infectious complications were also the leading causes of death in patients with SCD. Acute chest syndrome, renal failure, and thrombosis comprised other frequent causes of death in this group. Survival analysis of patients with thalassemia & SCD by 10-year intervals demonstrated that >90% of patients were alive in each 10-year cohort since 1960.

Table. Demographics of patients with Thalassemia and SCD in Turkey

Hemoglobinopathies	All	Thalassemia	SCD
Number of patients	3554	2898	656
Turkish	3126	2486	640
F/M	1554/1572	1219/1267	335/305
Age ± SD (year)	23 ± 14	20 ± 12	32 ± 15
DT <2003	1864 (60%)	1338 (54%)	526 (82%)
DT≥2003	1262 (40%)	1148 (46%)	114 (18%)
*Refugees**	428	412	16

Summary/Conclusion: Turkey is a country with a high young patient burden of hemoglobinopathies. As shown by the present data, these

patients will survive by using the advantages of full access to conventional treatment. Despite good outcomes, BMT as a curative approach has remained limited to a suitable donor. Therefore, a more effective HCP should be in place to reduce the economic burden on the healthcare system. The program should offer prenatal testing in couples of the immigrant population. The longitudinal hemoglobinopathy registry is needed for national surveillance to organize healthcare resources properly.

PB1756 PRIORITISATION OF RELEVANT COCHRANE REVIEW TOPICS IN THE FIELD OF HAEMATOLOGY

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Background: Cochrane Haematology produces, publishes and maintains systematic reviews in the field of haematology. The group wants to ensure that their limited resources and efforts are being used to produce Cochrane reviews addressing topics that are of utmost importance to their end-users. According to one of Cochrane's key principle 'striving for relevance' the group initialised their first priority setting exercise engaging stakeholders worldwide to identify the top priority topics for Cochrane Haematology reviews.
Aims: To identify the top ten priority topics for review updates and the top five priority topics for new Cochrane Haematology reviews as part of Cochrane Haematology's priority setting exercise.
Methods: The priority setting exercise consisted of two phases. In phase one, potential priority topics were generated by identifying trends (analysing review metrics) and gaps (screening for priority topics of the American Society of Hematology (ASH), the European Hematology Association (EHA), the German Society for Hematology and Oncology (DGHO) and the James Lind Alliance (JLA) in the field of hematology) in the current review portfolio. In the second phase, the identified topics were then prioritised by various stakeholders in an online survey. Respondents were asked to select the topics they deemed to be of high priority and rank them afterwards from highest to lowest priority. An average score was then calculated for each ranked topic. Topics with the highest average score were identified as being the top priority topics.
Results: The online survey was open between July 6th 2020 to August 28th 2020. A total of 160 responses were collected, of which 63 respondents (39%) provided complete responses. Most of the respondents identified themselves as physician (34%), someone who is or has been affected by haematological disease (31%), or researcher (24%) and were distributed across 21 countries. The highest number of respondents resided in the United Kingdom (n = 72), Germany (n = 20) and Canada (n = 11). The top ten priority topics for reviews that need updating were related to interventions in multiple myeloma, hodgkin lymphoma and topics from the areas of stem cell transplantation and supportive care for haematological diseases. The top five priority topics for new reviews addressed mainly myelodysplastic syndrome (MDS), relapse of disease post-haematopoietic stem cell transplant and long-term survival in cancer.
Summary/Conclusion: The priority setting process engaged various stakeholders and identified the most relevant review topics, published on Cochrane Haematology's website. These topics, some of them are open to new authors, will now guide the group's future scope of work and ensure that the most important reviews are updated. New priority reviews will close gaps within the review portfolio of Cochrane Haematology.

PB1757 ENHANCING THE ACCESS OF COAGULATION FACTORS TO PATIENTS WITH HAEMOPHILIA IN ESTONIA

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Background: Estonia, located in the shores of Baltic Sea has a population of 1,3 million with population density of 29,8 inhabitants per km^2 (2011). There are 2 major islands which are accessible from mainland by ferry or airplane. After the restruction of the hospital network 19 hospitals remained, incl. 3 regional, 4 central and 11 county hospitals.
Aims: Patients with haemophilia live everywhere. Replacement factors are distributed from regional hospitals, two are located in Tallinn (population 500 000) and one in Tartu (population 100 000). The network of retail pharmacies is very well established. The social support in rural parts of the country is suboptimal; from the other hand the pharmacy services are developing rapidly, including the door-to-door deliveries.
Methods: It was one of Kreuth III recommendations to establish a national roundtables to develop the treatment of coagulation disorders. Estonian Hemophilia Society (EHS) initiated a meeting in September 2013 where high-level stakeholders – from Ministry of Social Affairs, Health Insurance Fund, Estonian Hematology Society's working group on coagulation disorders – supported the improvement in treatment access. It was proposed that 20% of the coagulation factors will remain for hospital use in case of emergencies and surgeries and 80% will be included to the reimbursement list and can be obtained from retail pharmacies as prescription drugs.
Results: Some of the coagulation factors were included to the reimbursement list and became available in retail pharmacies in early 2015. However, as the regional hospitals had economically favorable tender contracts which tied the sale of the donated plasma to the purchase of plasma-derived factors, the system change was not fully implemented. EHS continued the work for better access. National tender and better access to replacement factors was supported by WHF-EHC-EAHAD joint visit to Estonia in October 2015. The major breakthrough took place in July 2019 when new medicines were included to the reimbmursement list by Health Insurance Fund. Also all plasma derived products, long acting coagulation factors, recombinant factors, aPCC are included to the list, which are prescribed electronically by physicians.
Summary/Conclusion: The delivery to pharmacies takes place within 24 hours. The door-to-door delivery to patients is developing as well. The new coagulation factor delivery system has reduced patients' financial burden, travel time and has brought high satisfaction among Haemophilia community in Estonia.

PB1758 A PRECEDE - PROCEED MODEL APPROACH IN ESTABLISHING A HEMOPHILIA CENTER IN A TERTIARY MEDICAL INSTITUTION: A DESCRIPTIVE STUDY.

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Background: Hemophilia is an inherited bleeding disorder due to "clotting factor" deficiency which requires lifelong management and support. This is the first study created to address the needs of this special population of patients in the country.
Aims: To provide a comprehensive framework that can be offered for hemophilia care.
Methods: The researcher used the PRECEDE-PROCEED framework to assess the current status of hemophilia care by evaluating the epidemiology, beliefs, environmental factors, including medical, surgical, psycho-social aspects based on the retrospective data evaluation in the PRECEDE phase. The Haemo-HQOL questionnaire was used to evaluate the current status of patients as part of the PROCEED phase.
Results: A total of 202 patients were seen in the institution over the past three years. Important factors identified were the ability to manage bleeding episodes at home, challenges due to limited supply of factor concentrate and cost of treatment. The availability of patient support groups and provision of donated factor concentrates provided improvement in the care of persons with hemophilia (PWH).

The PROCEED phase evaluated the current status of care with the use of a validated Haemo-HQOL which showed the different dimensions of interest according to age group.
Summary/Conclusion: The study provided a comprehensive framework of care and service that can be offered to PWH. Evidences regarding the importance of creating a specialized treatment center to cater hemophilia patients despite the difficult political, socio-economic, behavioural and environmental problems of PWH confirmed that interventions may improve the quality of life of this population. Moreover, continuous monitoring and reevaluation will provide a good system to guide our pediatric hematologists regarding the practice of treating hemophilia patients.

PB1759 THE IMPACT OF COVID-19 ON PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: THE MIXED-METHOD ANALYSIS OF AN ISRAELI NATIONAL SURVEY

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Background: The COVID-19 pandemic required reevaluation of the therapeutic approach and added emotional stress for patients with hematological malignancies at high risk of contracting the virus.
Aims: We aimed to evaluate how it affected such patients during the second lockdown in Israel.
Methods: This national survey included Hebrew-speaking patients with hematological malignancy. This included three tools with 28 items of socio-demographic and medical baseline characteristics, management of hematological disease, and evaluation of emotional coping during COVID-19 pandemic; the Hebrew version of the Patient Health Questionnaire 9; and 3 qualitative open-ended questions. Data was analyzed by mixed methods which combined both quantitative and qualitative thematic analyses.
Results: 408 patients responded to the survey. The management of their hematological disease included a decrease in the number of visits to the hematology clinic (37.0%), delay of some treatment schedules (9.1%), and prescription of replacement therapies permitting less visits to the clinic (2.2%). The frequency and intensity of "feeling afraid" regarding COVID-19 infection was increased (mean±SD: 4±1 to 5±2 in a 1-7 Likert scale), and a high rate of depression was recorded, which appeared to be more evident in patients with chronic myeloid leukemia (CML) ($p<0.001$).
Summary/Conclusion: The management of hematological malignancies during pandemics should always take into consideration patients' fears, as well as the development of depression related to isolation and loneliness, in addition to the high risk of severe disease. Patients with CML had a high rate of depression which obviously needs to be managed very carefully during and after the COVID-19 pandemic.

Sickle cell disease

PB1760 THE PHARMACOKINETIC PROFILE OF DEFERIPRONE IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Repeated blood transfusions are a mainstay treatment for the management of sickle cell disease (SCD), but often cause transfusion-dependent iron overload (TDI) in patients. Deferiprone (Ferriprox®) is an oral iron chelator indicated for the treatment of TDI due to thalassemia and has been investigated as a treatment for TDI in patients with SCD and other anemias. Unlike other chelation therapies, deferiprone is well tolerated in patients with decreased renal function, a common complication in SCD patients (Nath and Hebbel 2015). Previous studies in healthy adult volunteers have characterized the pharmacokinetic (PK) and safety profiles of deferiprone and its metabolite, deferiprone 3-O glucuronide, but the PK of deferiprone in SCD patients has not been established.
Aims: The present study aims to characterize the PK profile of deferiprone in patients with SCD and evaluate whether alterations in its metabolism and excretion necessitate dosing adjustments.
Methods: In this phase I, single-center, non-randomized, open-label, single-dose study (NCT01835496), patients with a diagnosis of SCD were administered a single 1500 mg dose of deferiprone under fasting conditions. Blood and urine samples were collected pre-dose and over a 10-hour post-dose period for PK assessments of deferiprone and deferiprone 3-O glucuronide. Patients were monitored throughout the study for adverse events (AEs) and returned to the study site 7 ± 3 days for a final follow-up and safety assessment.
Results: Eight patients with SCD (3 males and 5 females) were enrolled and completed the study. All patients were black, with a mean ± SD age of 33.0 ± 5.9 years. Following drug administration, serum levels of deferiprone and deferiprone 3-O-glucuronide rose rapidly with maximum concentrations (C_{max}) reached at 1.0 and 2.8 hours post-dose, respectively. The mean ± SD C_{max} for deferiprone was 17.6 ± 5.8 mg/mL and for deferiprone 3-O- glucuronide was 33.0 ± 11.8 mg/mL. The peak in serum levels of deferiprone and deferiprone 3-O-glucuronide were followed by a rapid decline with a half-life of 1.5 and 1.6 hours, respectively. Less than 4% of administered drug was excreted unchanged in urine samples, while the majority was metabolized and excreted as deferiprone 3-O-glucuronide. Two patients reported mild AEs. One patient experienced sore throat, headache, fatigue, and fever and the other patient reported abdominal pain. None of the AEs were considered related to the study drug. Furthermore, vital sign measurements and laboratory test results found no indications of clinical concern.
Summary/Conclusion: The pharmacokinetics of deferiprone in SCD patients were consistent with values reported in previous PK studies in healthy adult volunteers, suggesting no special dosing adjustments are indicated. The safety profile of deferiprone and deferiprone 3-O glucuronide, was found to be favorable with no safety concerns. Because the sample size is small the latter results should be interpreted with caution. However, these findings provide insight for the treatment of TDI in SCD patients with limited chelation therapy treatment options.

PB1761 GBT1118, A VOXELOTOR ANALOG PROTECTS RED CELLS FROM POLYMERIZATION-INDUCED DAMAGE DURING SEVERE HYPOXIA

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Background: In Sickle Cell Disease (SCD) sickle hemoglobin (HbS) can polymerize in its deoxygenated form, leading to perturbations of Red Blood Cells (RBC) biochemical, morphological, and mechanical properties. RBC membrane damage due to hypoxia-induced polymerization causes hemolysis leading to hemolytic anemia and other complications linked to elevated cell-free Hb levels and heme toxicity.
Aims: The FDA recently approved voxelotor (Oxbryta; Global Blood Therapeutics) for treatment of SCD in patients 12 years of age and older, shown to increase patient Hb levels in a pivotal phase 3 trial. In this study, we assessed the effect of GBT1118, a voxelotor (Oxbryta) analog on hypoxia-induced RBC membrane damage (lethal and sublethal) using standardized assays.
Methods: Blood was from steady state homozygous SS SCD patients of Children's Hospital of Michigan (n=4; HbS=62-85%). Informed consent was obtained per protocol approved by Wayne State University IRB. RBC Mechanical Fragility (MF), a metric indicative of existing RBC membrane damage and prospective hemolysis, was measured using a proprietary system comprising an electromagnetic bead mill and fiber-optic spectrophotometry detection. Non-invasive probing of sample agitated with a magnetic bead at 5 Hz allowed determination of MF indices (MFI), representative of RBC resistance to induced hemolysis. MFIs were assessed for most labile RBC fraction (induced hemolysis ab. 20%, MFI_1) and for total induced hemolysis over 10 minutes agitation time (MFI_10). RBCs were assessed at normoxia, before and after three cycles of hypoxia, with deoxygenation induced via protocatechuate/protocatechuate dioxygenase oxygen scavenging system (< 5% oxygenated-Hb) and re-oxygenation under normoxic conditions (close to 100% RBC recovery).

Results: Whole blood samples supplemented with 1mM GBT1118 in DMSO (0.9% final concentration) were compared *in-vitro* to those with equal volume of DMSO-containing buffer. For control samples, three cycles of hypoxia with follow-up reoxygenation resulted in significant increase in RBC MF indices (MFI) for all samples with changes for labile fraction being more pronounced. Supplementation with GBT1118 did not result in statistically significant changes in RBC MFI_1 or MFI_10 as compared to control samples pre-hypoxia. Following GBT1118 treatment, MFI_1 and MFI_10 showed significantly less increase after the hypoxia-reoxygenation cycles with the averages unchanged from MFIs' pre-hypoxia values. (Figure 1). Average (mean ±SD), for the 4 samples, percent change from pre-hypoxia after the 3 cycles of hypoxia was 47%±28% (MFI_1) and 25%±20% (MFI_10) for the control samples compared to 0%±20% (MF_1) and 5%±7% for (MFI_10) for samples supplemented with GBT1118. Changes in pre-existing (existing prior to stress application) sample hemolysis due to hypoxia cycles were not significant for any of the samples.

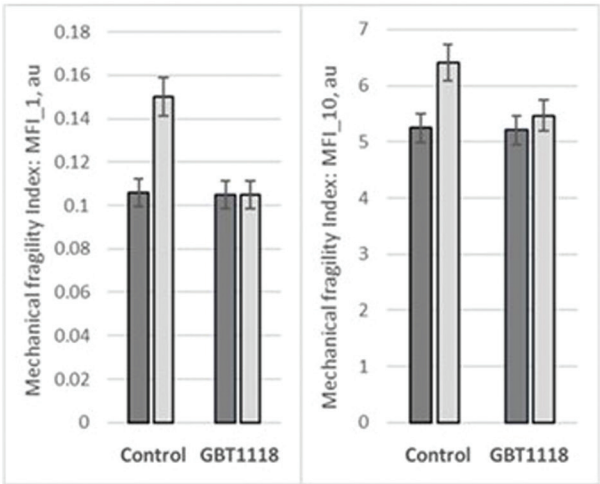


Fig.1 RBC MF at normoxia before (■) and after (□) three cycles of hypoxia with and without GBT1118.

Summary/Conclusion: Cycles of severe hypoxia followed significantly damage RBC membranes making cells more susceptible to lysis under flow-induced mechanical stress. With no history of hypoxia, GBT1118 did not affect membrane stability under normoxic conditions. However, when present during hypoxia, GBT1118 significantly reduced membrane damage as shown by reduced RBC propensity to lyse. That highlights the potential of GBT1118, a voxelotor (Oxbryta) analog, to prevent sub-lethal RBC membrane damage likely leading in increased RBC survival in circulation

PB1762 IMPACT OF SICKLE CELL DISEASE ON DAILY LIFE IN PATIENTS MANAGING VASO-OCCLUSIVE CRISES AT HOME VS THE EMERGENCY ROOM/HOSPITAL: RESULTS FROM THE INTERNATIONAL SICKLE CELL WORLD ASSESSMENT SURVEY (SWAY)

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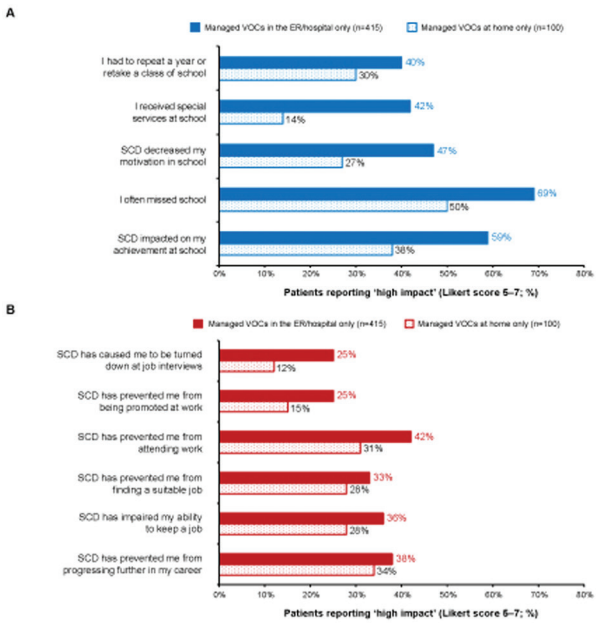
Background: Sickle cell disease (SCD) is a group of blood disorders with a range of clinical complications, mostly driven by hemolytic anemia and vaso-occlusion. Vaso-occlusive crises (VOCs) are the hallmark of SCD and the most common cause of patient (pt) hospitalization. Despite the potential severe consequences of VOCs, many pts manage them at home. Previous reports from SWAY showed that 24% of pts managed their VOCs at home (not exclusively), primarily because of a poor prior experience in the emergency room (ER)/hospital (Osunkwo I *et al.* ASH 2019; abstract 2297).

Aims: To assess whether pt-reported impact of SCD on daily life in SWAY differs between pts who reported managing their VOCs exclusively in the ER/hospital vs exclusively at home in the 12 months prior to survey completion.

Methods: SWAY was developed by international SCD experts, pt advocacy groups and Novartis. Pts with SCD aged ≥6 years completed the survey between April and October 2019 (completion by proxy [parent/guardian/caregiver] was required for pts aged 6–11 years, optional for older pts). In SWAY, VOCs were defined as 'severe pain crises' and were self-reported by the pt or relevant proxy. Responses to questions on the impact of SCD on daily life were classified on a 1–7 Likert scale (1=not severe/strongly disagree, 7=worst imaginable/strongly agree; 5–7 indicated high impact/agreement).

Results: 2145 pts from 16 countries across six regions were included in SWAY; 11,317 VOCs were reported in the 12 months prior to survey completion. Of these pts, 29% (n=629) reported managing their VOCs in the ER/hospital (mean age, 24.6 [SD 12.4] years; female, n=331 [53%]; median of 3 [IQR 1–4] VOCs) and 6% (n=134) reported managing VOCs at home (mean age, 27.5 [SD 13.6] years; female, n=71 [53%]; median of 2 [IQR 1–4] VOCs). A greater proportion of pts who reported managing their VOCs in the ER/hospital (n=629) vs at home (n=134) reported a high negative impact of SCD on their emotional wellbeing (61% vs 49%). Of pts managing their VOCs in the ER/hospital, 49%, 45% and 49% rated their level of agreement with the statements *'I feel stressed'*, *'I feel depressed'* and *'I worry about dying'*, respectively, in the high impact range, compared with 37%, 33% and 36% of pts who managed their VOCs at home. A greater proportion of pts who reported managing their VOCs in the ER/hospital vs at home reported a high impact of SCD on aspects of their daily life, including family/social life (37% vs 27%), relationship with their spouse/partner (33% vs 17%), sexual desire/activity (33% vs 19%) and, to a lesser extent, household daily activities (eg housework, childcare; 32% vs 25%). Self-reported impact of SCD on aspects of schooling and employment also appeared to be higher in pts who managed their VOCs in the ER/hospital vs at home (Figure).

Figure. Proportion of pts reporting a high impact (Likert score 5–7) of SCD on their schooling (A) and careers (B) stratified by VOC management location



Summary/Conclusion: Pts managing their VOCs in the ER/hospital reported a greater impact of SCD on daily life than pts who managed them at home. This may indicate that pts visited the ER/hospital because their pain was too severe to manage at home. Pts experiencing a high impact of SCD on daily life may also seek ER/hospital care for VOCs for psychological support. Equally, visiting the ER/hospital for VOC management may itself be a detriment to pts' daily lives. Differences in access to healthcare facilities amongst participating countries in SWAY, as well as differing numbers of pts who managed VOCs in the ER/hospital vs at home – possibly influenced by pts' varied geographic location – may also contribute to the observed differences in this analysis.

PB1763 IMPACT OF COVID-19 ON SICKLE CELL DISEASE IN LEBANON; MILD DISEASE AND ONE CASE OF DEEP VEIN THROMBOSIS.

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Background: Novel coronavirus SARS-CoV-2, COVID-19, infection was first reported in December 2019, and then spread dramatically around the world. Sickle cell disease is caused by a mutation in the beta globin gene resulting in the production of sickled hemoglobin that alters its shape upon deoxygenation to form an elongated rigid sickled erythrocyte that leads to vaso-occlusion. To date, there have been limited published data on how COVID-19 may affect morbidity and mortality in SCD patients. A review of the literature showed that SARS-CoV-2 infection should be considered to be an important triggering factor of sickle cell crisis. Most investigators report mild disease in children and moderate disease in many SCD adults.
Aims: The aim of this report is to describe the clinical features of 11 confirmed cases of COVID-19 in patients with SCD in Lebanon.
Methods: 11 SCD patients, were infected with COVID-19. Data concerning the age, gender, weight, and genotype were collected. In addition to medications received and chronic transfusion. Information about the course of COVID-19 is reported regarding: complications, type and duration of symptoms as well as therapy.
Results: In this series median age was 22.2 years (range 14-40 years), only 2 are females and 8 patients had HbSS, 2 HbS beta + thalassemia, and 1 HbSC. 3 patients weighed >70kg the others were all below 70 kg. Ten patients were on long term hydroxyurea (HU) and in one it was initiated for only 1 week before infection. 1 patient was receiving Voxelotor and 1 Crizanlizumab in addition to HU. None were on chronic transfusion. Two patients had previously been started on Aspirin. One was on acencoumarolum, for a previous pulmonary embolism. One patient had asthma and was a smoker. Nine patients had moderate to severe symptoms and 2 had mild symptoms. 2 patients underwent PRBC transfusion for pain and anemia and one had erythrocytopherisis to control severe pain. Three patients required oxygen but none were admitted to a critical care unit. The mean number of days with symptoms was 14.1 days. Of the 11 patients 7 experienced pain crisis. None developed acute chest syndrome. 3 patients received corticosteroids and 5 patients received low molecular weight heparin (LMWH) 2 received therapeutic dose and 3 prophylactic dose.
A 16 years old male with HbSS genotype developed multi system inflammatory syndrome and was admitted to regular floor for 26 days. He had prolonged high grade fever, epigastric pain, sore throat in addition to maculopapular rash. He had elevated D-Dimers >3000 ng/ml. He received PRBC transfusion, IVIG, corticosteroids, LMWH and antibiotics. Another 18 year old male with HbSS, developed extensive right lower limb deep vein thrombosis (DVT) 20 days after recovering from very mild COVID-19 infection. This patient had been on aspirin for 6 years after recovering from a catheter provoked DVT.
Summary/Conclusion: This is one of the first reports on COVID-19 in patients who are not of African descent. In our patients COVID-19 was manifested mainly as fever and pain crises. Most patients required transfusions. Overall the symptoms were mild or moderate, similar to what was reported by others. Of concern were the development of multi system inflammatory syndrome in one patient and the development of delayed extensive DVT in another.

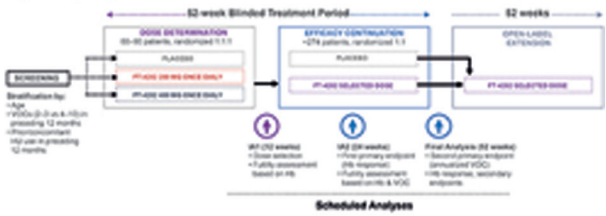
PB1764 HIBISCUS, AN ADAPTIVE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTICENTER STUDY OF ORAL FT-4202, A PYRUVATE KINASE ACTIVATOR IN PATIENTS WITH SICKLE CELL DISEASE

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Background: The hallmark of sickle cell disease (SCD) is hemoglobin S (HbS) polymerization upon deoxygenation, resulting in red blood cell (RBC) sickling, hemolysis, and vaso-occlusion. Exacerbating the pathogenesis of SCD, the HbS RBC has increased (↑) levels of 2,3-diphosphoglycerate (2,3-DPG), resulting in reduced (↓) Hb oxygen affinity (↑P50), and ↓ATP, essential for RBC homeostasis. FT-4202 is a selective, and orally bioavailable allosteric activator of erythrocyte pyruvate kinase (PKR) that increases PKR activity, resulting in ↓2,3-DPG levels and ↑ATP levels in RBCs. Preliminary data from an ongoing phase 1 study (NCT03815695) indicate that FT 4202 is well-tolerated, has no effect on steroidogenesis, and exhibits linear and time-independent pharmacokinetics and associated pharmacodynamic responses (↓2,3-DPG and ↑ATP). Treatment of patients with SCD for 14 days with once-daily FT-4202 resulted in ↑Hb O2 affinity, ↓RBC sickling, improved RBC deformability, and improved hematologic and hemolytic parameters (Brown, ASH2020_ abstract_#134269).
Aims: Hibiscus (NCT04624659) is a phase 2/3, randomized, double-blind, placebo-controlled global study to investigate the safety and efficacy of FT-4202 in patients with SCD.
Methods: Adult and adolescent patients with SCD (all genotypes) will be enrolled in a Dose Determination (DD) group and an Efficacy Continuation (EC) group using an adaptive design. Eligible patients must have had ≥2 vaso-occlusive crises (VOCs) in the past year, baseline Hb ≥5.5 and ≤10 g/dL, and if receiving hydroxyurea (HU), be on stable therapy for the previous 90 days. Patients with >10 VOCs in the past year, hospitalized for sickle cell crisis/other vaso-occlusive event within 14 days of consent, receiving routine RBC transfusions, significant hepatic/renal dysfunction, history of unstable or deteriorating cardiac or pulmonary disease, or overt stroke within 2 years will be excluded. Co-primary endpoints are Hb response rate (RR) at Week 24 (increase from baseline >1 g/dL) measured as the percentage of treated population achieving the endpoint, and annualized VOC rate during the blinded treatment period based on adjudicated VOC review. Secondary endpoints include measures of hemolysis, time to first VOC, and the Patient Reported Outcome Measurement Information System fatigue scale. Safety endpoints will also be assessed. Patients will be stratified by number of VOCs in the preceding 12 months, prior/concomitant HU use and age, and randomized 1:1:1 to 200 or 400 mg (once-daily) FT-4202, or placebo in the DD group. At interim analysis (IA) 1, one FT-4202 dose level will be selected based on safety and Hb RR at Week 12 in the first 60 patients. EC group patients will be randomized 1:1 to the selected FT-4202 dose or placebo. Once 110 patients randomized to the selected dose or placebo complete 24-weeks blinded treatment or drop out, IA2 will assess Hb RR (first primary endpoint). At final analysis (52-weeks blinded treatment) annualized VOC (second primary endpoint), 24-week Hb RR and all secondary endpoints will be evaluated. Patients may then enter a 52-week open-label extension period at the selected FT-4202 dose. Futility assessments will be conducted (Weeks 12 and 24).
Results: Recruitment is ongoing; planned enrolment: ~344 patients with SCD (DD group, n=60–90; EC group, n~274).

Figure: Study Design



Summary/Conclusion: This study will evaluate the safety and efficacy of oral, once-daily FT-4202 in adult and adolescent patients with SCD.

PB1765 ECOCARDIOGRAPHIC EVALUATION OF CARDIOVASCULAR COMPLICATIONS IN PEDIATRIC SICKLE CELL DISEASE PATIENTS: MORE THAN MEETS THE EYE?

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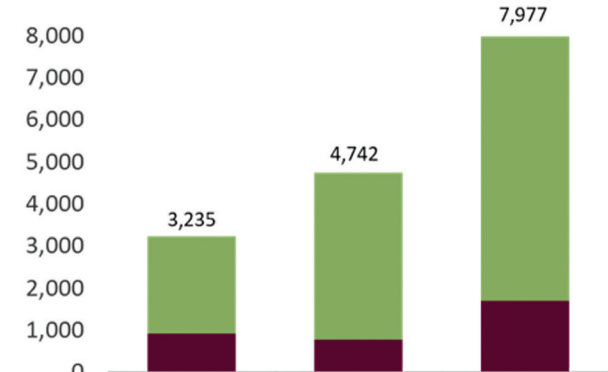
Background: Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the gene encoding the hemoglobin subunit β. The number of SCD cases is expected to increase in the next decades and new therapies led to an increase in patients' life expectancy. Thus, it has become essential to define screening and prevention programs for the long-term complications. Among these, cardiovascular involvement has a significant impact on morbidity and mortality in SCD. Although cardiovascular complications have been well described in the adult population, few studies are currently available regarding the pediatric setting.
Aims: This study aims to investigate the impact of cardiac complications in a pediatric cohort and the role of clinical and laboratory markers as predictors factors to identify at-risk patients.
Methods: This is a retrospective observational monocentric study on a pediatric SCD population followed at the Bambino Gesù Childrens' Hospital in the last 5 years (2015–2020). We have analyzed the data regarding 64 SCD patients (37 Males and 27 Females, median age 10) who undergone a routine transthoracic echocardiogram. Echocardiograpic evaluations were performed by a pediatric cardiologist, blinded to the clinical status and biological data. We collected personal information, medical history, and laboratory data referring to 2 years prior to echocardiogram. Statistical analysis was performed and data considered with statistical significance were those with p-value <0.05 and are therefore the ones presented in the results section.
Results: Globally, 46 (72%) patients had at least one cardiac abnormality. Left atrial dilatation (LAD) was present in 41 (65%) patients and left ventricular hypertrophy (LVH) was found in 29 (45%) patients. Only 5 patients had systolic disfunction, and no patient had indirect signs of pulmonary hypertension. No differences were found in the different age groups. Patients with LAD showed lower median Hb level (p=0,009), higher absolute reticulocyte count (p=0,04), higher conjugate bilirubin level (p=0,01) and alanine transaminase level (p=0,009). LVH was negatively correlated with median Hb value (p=0,006) and positively with reticulocyte count (p=0,03). Interestingly, we found that patients with cardiac anomalies had a higher transfusion needs and a lower frequency of pain crises. Among other complications, we found a correlation between left ventricular hypertrophy and splenectomy (p=0,03).
Summary/Conclusion: In our setting, cardiac involvement has a high prevalence in a pediatric cohort, involving the majority of patients. In the adult setting it's known that elevated right ventricular pressure and left diastolic dysfunction are independent predictors of worst clinical course and early death. As suggested from other studies, left diastolic dysfunction, the prominent echocardiographic finding in adult, may take time to develop. Our findings suggest that cardiac complications are not only associated with specific laboratory findings, but also with a specific clinical phenotype, characterized by chronic significant hemolysis, severe anemia, high transfusion need and other complications related to chronic volume overload due to chronic anemia. The current guidelines do not recommend a screening echocardiogram in the asymptomatic pediatric population, we think further studies are needed on the impact of cardiac anomalies in the young age since their burden and clinical significance may be currently understated.

PB1766 THE GREATALYS (GENERATING REAL WORLD EVIDENCE ACROSS ITALY IN SCD): EPIDEMIOLOGY AND DISEASE BURDEN IN ITALY

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Background: Epidemiological 2010-2050 predictions of increasing global burden, make SCD an emerging problem of public health. The distribution of SCD patients in Italy has severely changed in the last decade due to a combination of migration fluxes and increased survival of the endemic population.
Aims: To understand the evolution of SCD disease burden in Italy, we designed a non-interventional retrospective cohort study with secondary use of administrative data (GREATalyS; CSEG101AIT01). Our objective is to collect representative data generalizable to the total Italian population to estimate prevalence and incidence rates of SCD in clinical practice settings.
Methods: An observational retrospective analysis was conducted by integrating administrative NHS databases for healthcare resources consumption from a geographically distributed sample of Italian Regions and Local Health Units (LHUs) comprising approximately 15.3 million health-assisted subjects (about 25% of the whole Italian population). Patients with at least one hospitalization (day hospital or regular admission) with a main or secondary discharge SCD diagnosis (identified by ICD-9-CM codes) were included in the analyses (period: January 2010-December 2018). Analyses of prevalence and incidence were stratified by age, sex and presence/absence of crisis (based on diagnosis at inclusion). Data were then projected to the total Italian population.
Results: Out of 15.3 million health-assisted subjects, 2,347 patients fulfilled the inclusion criteria during the full study period. The calculated SCD prevalence in 2018 was around 13 cases per 100,000 health-assisted subjects (around 11 cases per 100,000 males and 15 per 100,000 females were observed). SCD prevalence in young (<18 years old) and adult population was 17.2 and 12.4 cases per 100,000 health-assisted individuals, respectively. When projected to the total Italian population, 7,977 SCD patients were estimated in 2018 (1,690 young and 6,287 adult patients) (Figure 1).
Incidence rates slightly fluctuate over the years (from 2.00 per 100,000 health assisted in 2011 to 0.93 per 100,000 in 2018 corresponding to 567 new diagnosis in 2018).
Approximately two third (74%) of the patients had at least one hospitalization during study without a concomitant diagnosis of crisis (5,894 without/1,279 with, 804 unspecified), thus suggestive of a high disease burden beyond severe VOC. SCD "With crisis" prevalence was higher in patients aged <45 years, ranging from 2.45 (age group 35-44) to 3.04 (age group 25-29) and decreased significantly after 54 years to a minimum of 0.34 in patients aged 75-84 years. Geographical stratification showed a "population without crisis" almost doubled in the Southern areas (12.44 cases per 100,000) compared to the North (6.93 cases per 100,000) and Center (4.34 cases per 100,000) areas.



	M	F	TOT
>=18 yy	2,316	3,971	6,287
<18 yy	919	771	1,690
Total	3,235	4,742	7,977

Summary/Conclusion: GREATalyS identified a high SCD incidence and prevalence resulting in a total of 7,977 Italian SCD patients estimated in 2018, when considering the long observation period. The discrepancy between the prevalence herein reported with previous SCD epidemiology analysis (around 2,000 SCD patients in Italy) might be explained by the real world setting of our analysis which considers also patients not referred to specialist centers, potentially underreported in Italy. Hence, this data represents the highly variable presentation of SCD and shed light on the management of patients not generally described in the literature.

PB1767 IN SICKLE CELL DISEASE WITH CHRONIC RETINAL COMPLICATION CAN HAEMATOLOGICAL PARAMETERS BE USEFUL AS A STRATIFYING RISK TOOL?

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Background: Sickle cell associated retinopathy is a well established chronic complication in sickle cell disease. There can be proliferative retinopathy (PR) and non-proliferative retinopathy (NPR). Although the risk of retinal changes is higher in heterozygotes SC (SC) disease followed by sickle-beta-thalassemia disease (S-tal) and homozygous sickle cell disease (SS), its exact incidence is unknown since most patients are asymptomatic.
Aims: Our study's goals are, firstly to characterise sickle cell retinopathy in patients with SS, SC and S-tal disease and secondly understand if haematological parameters (such as hemoglobin level, haematocrit, mean corpuscular volume and percentage of haemoglobin S and F) can be used as a stratifying risk tool regarding presence of NPR and PR in SS patients.
Methods: We included 106 patients followed between January/2017 and December/2019. Retinal evaluation was performed with binocular indirect ophthalmoscopy, fluorescein angiography (FA) and optical coherence tomography angiography (OCTA). In order to compare haematological parameters in the PR and NPR groups, we carried out a descriptive analysis of the variables and verification of normality. We resorted to the t-test of 2 independent samples for normal variables and the Mann-Whitney U test for variables without normal distribution. Subsequently, the existence of variables with an impact on the type of retinopathy was analysed through logistic regression
Results: We found 26 from 35 patients asymptomatic, however 13 (37.1%) had already fundoscopic changes, whilst 22 (62.9%) had no changes. Further ophthalmological evaluation with FA and OCTA, found that 29 patients (82.9%) had retinopathy. According to the Goldberg's classification, 17 patients (58.6%) had NPR and 12 (41.4%) had PR. These patients included all with SC and S-tal disease (5 and 2, respectively) and 22 (78.6%) with SS disease.
Regarding the SS retinopathy group, these patients had higher levels of Hb S (69.2% vs. 67.21%) and lower levels of Hb F (9.54% vs. 13.47%). Statistical analyses revealed that the two populations PR and NPR, are similar, without significant statistical differences and with no specific associated parameters.



Summary/Conclusion: Our preliminary results reinforce that retinopathy is frequently clinically silent. Unfortunately, it is a well established under-diagnosed complication in sickle cell disease. Retinal complications should always be stratified with ophthalmological imaging techniques, since haematological parameters apparently are not a good stratifying risk tool. There is a minor difference regarding the amount of Hb S and F, but further work with a larger cohort of patient is needed. Therefore, our preliminary results reinforced that periodic ophthalmological evaluation is mandatory for all sickle cell disease patients and not only for the high-risk group sickle cell associated retinopathy.

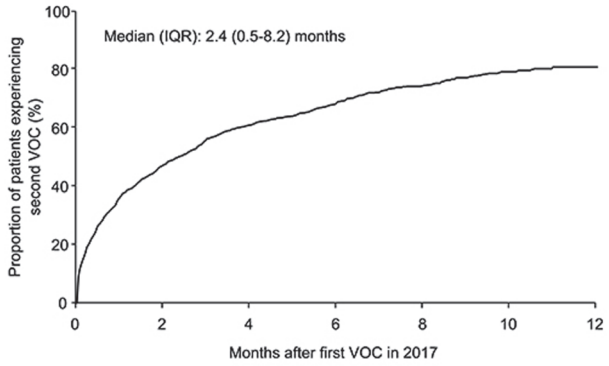
PB1768 CLINICAL CHARACTERISTICS AND THE RISK OF VASO-OCCLUSIVE CRISES IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited disorder affecting the red blood cells that causes lifelong complications. Vaso-occlusive crises (VOCs), which result from blood vessel obstruction, are clinical hallmarks of SCD. VOCs are associated with intense pain and can lead to potentially irreversible organ damage, and thus can represent a significant clinical burden.
Aims: To assess the risk of VOC by age in patients with SCD using data from a retrospective database analysis.
Methods: The IBM MarketScan Commercial Claims and Medicare Supplemental Claims databases (July 1, 2013 to June 30, 2018) were used for a retrospective analysis of patients with SCD. Patients with ≥2 SCD diagnoses (ICD-9 CM and ICD-10 CM) on separate claims between July 1, 2013 and January 1, 2017, who were ≥6 years of age on January 1, 2017, and had continuous enrollment throughout a 1-year analysis period (January 1, 2017 to December 31, 2017) were included in this analysis. Patients with >100 inpatient or outpatient VOC-related days, as of January 1, 2017, were excluded from the analysis. Patient demographics and clinical characteristics were assessed using descriptive statistics. In addition, the monthly VOC risk by age, proportion of VOCs experienced by clinical setting, and time to second VOC were evaluated.
Results: All inclusion criteria were met by 8174 patients. The median (interquartile range) age was 42 (24–55) years and 36.5% of the patients were male. A total of 1659 (20.3%) patients had ≥1 VOC diagnosis during the 1-year study period. The mean (SD) Charlson Comorbidity Index was 0.6 (1.3) and the most common component conditions were chronic pulmonary disease (n=1117 [13.7%]), mild to moderate diabetes (n=608 [7.4%]), renal disease (n=445 [5.4%]), and cerebrovascular disease (n=438 [5.4%]). Patients experienced VOCs in both the outpatient and inpatient setting, and the mean (SD) proportion of VOCs experienced in an outpatient setting was 0.74 (0.34). The mean (SD) monthly VOC risk was 0.07 (0.19). Patients aged ≥20 and <30 years (n=939) had the highest mean (SD) monthly VOC risk (0.16 [0.28]). Among the 1659 patients with ≥1 VOC, 1161 (70.0%) experienced a second VOC during the study period. The time from first to second VOC for all patients with ≥1 VOC within the 1-year study period is shown in Figure 1.

Figure 1. Time from first to second VOC in patients experiencing ≥1 VOC from January 1, 2017 through December 31, 2017



Number of patients experiencing second VOC						
0	766	968	1065	1124	1156	1161
Number of patients at risk						
1659	818	530	358	217	100	3

Abbreviations: IQR, interquartile range; VOC, vaso-occlusive crisis.
Second instance of a VOC during the study period was defined as the second instance of a VOC (defined by diagnosis codes) in 2017 after the first VOC experienced on or after January 1, 2017.

Summary/Conclusion: The findings of this study show that patients with SCD often experience recurring VOCs and that younger patients appear to be at greater risk of VOC events.

PB1769 PEDIATRIC PATIENT REPORTED OUTCOMES IN PATIENTS RECEIVING VOXELOTOR FOR SICKLE CELL DISEASE

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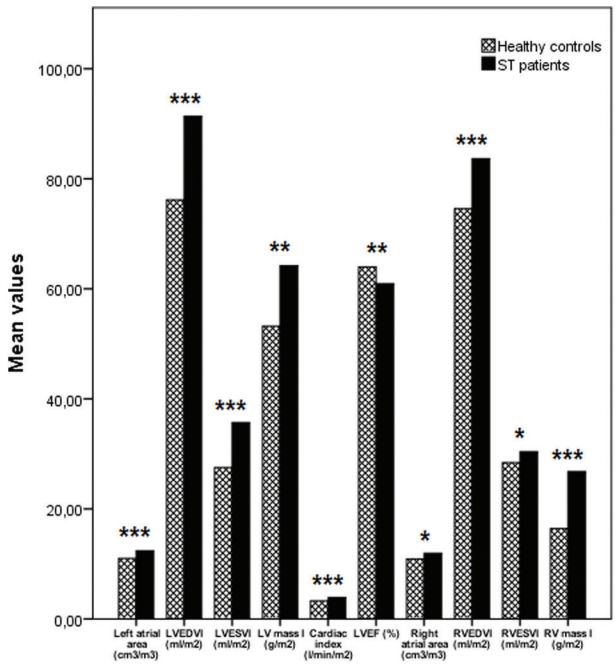
Background: Sickle cell disease (SCD) describes a group of chronic, inherited blood disorders resulting from mutations that reduce or abolish normal hemoglobin production. The most common clinical manifestations of SCD are related to hemolytic anemia and vaso-occlusion, which can cause acute and chronic pain and end-organ damage. Voxelotor is a first-in-class sickle hemoglobin–polymerization inhibitor, FDA approved for patients with SCD aged ≥12 years, that modulates hemoglobin oxygen-affinity, prevents sickling of red blood cells, and possibly interrupts the molecular pathogenesis of the disease. It is currently being investigated in patients aged 4-11 years. Incorporating the patient voice into drug development is increasingly important to regulators; thus, collecting qualitative data to gain patient and caregiver insights alongside clinical data can aid in understanding treatment benefits in this patient population.
Aims: The purpose of this study is to collect qualitative data to understand patient experiences with voxelotor, as reported by pediatric patients and their caregivers. Specifically, the study aims to understand how the treatment affects symptoms and related impacts, and overall health-related quality of life (HRQOL).
Methods: This qualitative study will involve interviewing children with SCD (aged 4-11 years) and their caregivers to be recruited from multiple sites in the US. Eligible patients will have been taking voxelotor for ≥4 weeks at the time of the interview. Concept elicitation interviews are to be conducted via telephone by experienced qualitative researchers using a semi-structured interview guide. Interview transcripts will be analyzed with MAXQDA software. This will allow theme identification using an induction-abduction approach, enabling the analysis to remain grounded in the data. Inter-coder reliability will be established early in the coding process by having two analysts independently code the same transcript.
Results: The interviews are ongoing. Changes in symptoms, effects on daily life, and other impacts to HRQOL reported by patients and their caregivers will be presented.
Summary/Conclusion: This will be the first study to report qualitative experiences of pediatric patients treated with voxelotor.

PB1770 CARDIAC INVOLVEMENT IN SICKLE Β-THALASSEMIA PATIENTS BY MAGNETIC RESONANCE IMAGING

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Background: Sickle β-thalassemia (Sβ-thal) is a hereditary hemoglobinopathy resulting from the combined heterozygosity for sickle cell and β-thalassemia genes. Cardiac involvement in Sβ-thal patients has been poorly investigated.
Aims: We aimed to evaluate myocardial iron overload and cardiac function by cardiovascular magnetic resonance (CMR) in patients with Sβ-thal.
Methods: One hundred and eleven Sβ-thal patients consecutively enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) network were studied and compared with 46 sickle cell disease (SCD) patients. Bi-atrial and biventricular function CMR parameters of Sβ-thal patients were compared with those of 111 healthy volunteers, matched by gender and age. Myocardial iron overload (MIO) was assessed by T2* technique. Cine images were acquired to quantify biventricular function. Macroscopic myocardial fibrosis was evaluated by late gadolinium enhancement (LGE) technique.
Results: In Sβ-thal and SCD patients morphological and functional MR parameters were not significantly different, except for left atrial area and SVI (p = 0.023 and p = 0.048, respectively) that were significantly higher in SCD patients. No significant differences between the two groups were found in terms of myocardial iron overload and macroscopic myocardial fibrosis. When compared to healthy subjects, Sβ-thal patients showed significantly higher bi-atrial and biventricular parameters except for LVEF that was significantly lower (Fig.1).



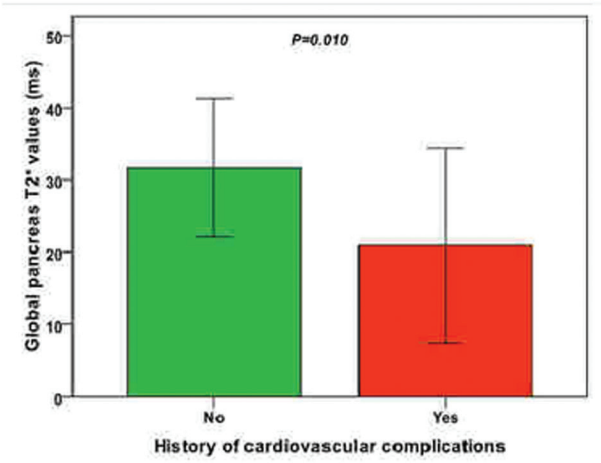
Summary/Conclusion: The CMR analysis confirmed that Sβ-thal and SCD patients are phenotypically similar. Since Sβ-thal patients showed markedly different morphological and functional indices from healthy subjects, it would be useful to identify Sβ-thal/SCD-specific bi-atrial and biventricular reference values.

PB1771 PANCREATIC IRON IS A MARKER OF CARDIOVASCULAR COMPLICATIONS AND IN SICKLE CELL DISEASE

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Background: A strong association between pancreatic iron burden and cardiac complications was found in patients with thalassemia major. There is no study evaluating this issue in sickle cell disease (SCD).
Aims: The objective of this multicenter study was to systematically explore the link between pancreatic iron and cardiovascular complications in a cohort SCD patients enrolled at baseline in the prospective Extension-Myocardial Iron Overload in Thalassaemia (E-MIOT) project.
Methods: We considered consecutively enrolled 63 patients: 44 with sickle beta thalassemia, 18 with sickle cell anemia (SCA), and one with hemoglobin SC disease (HbSC). Mean age was 36.6±14.4 years and 29 patients were females. T2* measurements were performed over pancreatic head, body and tail and global value was the mean. Myocardial iron overload (MIO) was quantified using a T2* segmental approach.
Results: SCA and sickle beta thalassemia patients were comparable for age, sex, hematochemical parameters, and cardiac and pancreatic T2* values.
Transfusion dependent (TD; N=44) and no-TD patients showed comparable global pancreas T2* values (29.8±11.4 ms vs 32.2±8.0 ms; P=0.414), but were more frequently chelated (79.1% vs 52.6%; P=0.034).
Nineteen patients (30.2%) showed a pathological global pancreas T2* value (<26 ms) while no patient had significant myocardial iron overload (global heart T2*<20 ms).
Seven patients (11.1%) had at least one cardiovascular complication: two supraventricular arrhythmias, one heart failure, one heart failure + pulmonary hypertension, one myocardial infarction, one deep vein thrombosis, and one leg ulcer. Frequency of cardiovascular complications was comparable among the forms of SCD, but all complications occurred in regularly transfused patients.
Patients with cardiovascular complications showed significantly lower global pancreas T2* values than patients free of cardiovascular complications (20.9±13.5 ms vs 31.7±9.6 ms; P=0.010) (Figure 1) but comparable global heart T2* values (38.4±5.6 ms vs 40.6±4.7 ms; P=0.257). Patients with pancreatic iron overload were more likely to have cardiovascular complications [odds ratio=7.5 (95%confidence intervals=1.3-43.1); P=0.024].



Summary/Conclusion: Pancreatic iron overload is associated with an increased risk of cardiovascular complications in SCD patients. If a patient has pancreatic iron overload, it would be prudent to start or intensify iron chelation therapy to prospectively prevent cardiac damage.

PB1772 EFFECT OF HYDROXYUREA ON ADHESION MOLECULES IN YOUNG PATIENTS WITH SICKLE CELL BETA THALASSEMIA

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Background: Hydroxyurea (HU) is a cytotoxic drug that is used in sickle cell disease (SCD) in order to ameliorate disease's severity. Induction of HbF is reported as the main mechanism of action, however, other mechanisms contribute to its beneficial effect, given that some patients present with clinical improvement without an HbF increase. Sickle erythrocytes and activated circulating neutrophils contribute to vaso-occlusion by adhering to inflamed endothelium. B2-Integrins (CD11a, CD11b, CD11c and CD18), which are transmembrane adhesion receptors, are expressed exclusively on leukocytes. A number of studies have shown that HU decreases leucocyte adhesion, but the role of HU on B2 integrins expression has not been clarified. Moreover, there is conflicting data on the role of HU in decreasing CD36 - an adhesion receptor with increased expression on sickle reticulocytes and immature sickle erythrocytes.
Aims: Aim of present study was to evaluate the effect of HU on erythrocyte and leukocyte adhesion molecules in young patients with Sickle cell beta thalassemia.
Methods: Eleven young patients with Sickle cell beta thalassemia aged 3.5-18 years participated in the study. HU was given at a daily dose that ranged from 14.5 to 19 mg/kg, with a mean of 16.3mg/kg, for a 3year period. Expression of CD11a, CD11b, CD11c and CD18 on neutrophils, and of CD36 on reticulocytes was evaluated by flow cytometry.
Results: Before HU initiation all patients presented with normal expression of the CD11a, CD11b, CD11c and CD18 integrin subunits and increased expression of CD36. Following 3 years of therapy, expression of CD11a, CD11b and CD18 integrin, as well CD36 expression, were not found to be significantly altered. Of interest is the finding of a significant increase in the expression of the CD11c integrin subunit (p=0.034) (Table 1).

	Prior to HU initiation	Following HU treatment	p-value
CD11a (%)	94.70±3.67	94.46±5.06	0.859
CD11b (%)	94.42±4.35	96.28±4.03	0.091
CD11c (%)	85.97±7.34	90.64±8.75	**0.034**
CD18 (%)	99.43±1.33	99.90±0.1	0.952
CD36 (%)	0.97±0.46	0.91±0.99	0.213

Summary/Conclusion: The present study failed to reveal an effect of HU on most of the adhesion molecules studied. In order to better interpret study results, evaluation in larger cohorts of Sickle cell beta thalassemia patients is warranted.

PB1773 EPIDEMIOLOGICAL CHARACTERS OF ADULT: EGYPTIAN SICKLE CELL ANEMIA PATIENTS: A SINGLE CENTER EXPERIENCE

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Background: Sickle cell anemia (SCA) is a chronic problem with growing with ages consequences. It starts with birth & continues to add complication throughout the patient's life. During his childhood the patient develop a psychological bond with his treating team which makes it traumatic to him when he is transferred to adult hematology service

which might lead to loss of interest in receiving treatment and skipping follow up visits which eventually leads to increased complications and either stopping treatment or developing treatment related adverse events.
Aims:
This is a descriptive study regarding Adult (above the age of 18) SCA patients on follow up with the clinical hematology unit Oncology center Mansoura University, Dakahlia, Egypt who had recorded follow up visits on our System in the period between 2005 and 2020 regarding their age at diagnosis, sex, baseline criteria, presence of crisis or not method of diagnosis and their follow up regimen.
To outline the Demographic characters of Egyptian SCA patients on regular follow up at an adult academic hematology center in Egypt and the characters of their disease
Methods: This is a descriptive study regarding Adult (above the age of18) SCA patients on follow up with the clinical hematology unit Oncology center Mansoura University, Dakahlia, Egypt who had recorded follow up visits on our System in the period between 2005 and 2021 regarding their age at diagnosis, sex, baseline criteria, presence of crisis or not method of diagnosis and their follow up regimen.
By reviewing the data on our system over the period of 1-1-2005 and 1-1-2020 we found that we have 39 SCD anemia patients with 19 males (48.7%) and 20 females (51.3%) as shown in figure 1, Four patients had a less than six months follow up so they were excluded from the final analysis.By reviewing the data on our system over the period of 1-1-2005and 1-1-2020 we found that we have 39 SCD anemia patients with 19 males(48.7%) and 20 females (51.3%) as shown in figure 1, Four patients had aless than six months follow up so they were excluded from the final analysis.
Results: By reviewing the data on our system over the period of 1-1-2005 and 1-1-2021 we found that we have 39 SCD anemia patients with 19 males (48.7%) and 20 females (51.3%), The average age at referral to our center was 24 years with the range of 14.6 – 37.4 years, The median follow up of our patients was 114.8 months (357 – 6).Out of our 35 patients twenty five (71.4 %) were referred to us from the pediatric service while the remaining ten (28.6 %) were newly diagnosed at our unit. Using Hemoglobin electrophoresis twenty eight patients (71.8 %) had done this investigation which showed that 11 (39 %) had sickle-thalassemia while the rest were pure SCA. Spleen was surgically removed in 7 (17.9 %), Non-visualized in 8 (20.6 %) while the remaining 22 had spleen measurable by ultrasonography. 12 (30.7 %) patients had HCV infection, Twenty four (61.5 %) were non transfusion dependent while the remaining 11 (28.2 %) required monthly transfusion. As regard all our 39 patients were accounted for at the time of data analysis
Summary/Conclusion:
Children with SCA need a more smooth transfer from their pediatric service to adult service to help them to be more adherent Children with SCA need a more smooth transfer fromtheir pediatric service to adult service to help them to be more adherent to follow up instead of showing up when they have a problem, require transfusion or in need of a grave intervention and on the other hand all SCA patients require more thorough chelation therapy and supportive measures to avoid end organ damage.

Stem cell transplantation - Clinical

PB1774 THE RELATIONSHIP OF SERUM GROWTH DIFFERENTIATING FACTOR 15(GDF15) TO HEPCIDIN IN POST TRANSPLANT ADULT EGYPTIAN PATIENTS AND ITS PROGNOSTIC SIGNIFICANCE

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Background: Hepcidin is a small peptide that is produced in the liver that is most likely the major regulator of iron. Based upon the importance of iron, multiple mechanisms exist for the regulation of hepcidin. Iron levels, inflammation, erythropoiesis and the combined effects of several proteins expressed on hepatocyte membranes are involved. Growth differentiation factor 15 (GDF15) is a member of the transforming growth factor-b (TGF-b).GDF15 expression level is usually low in resting cells but may be substantially increased following response to diverse cellular stress signals, such as hypoxia, inflammation, acute tissue injury and during cancer progression
Aims: The aim was to assess the relationship of serum Growth Differentiating factor 15(GDF15) to hepcidin in post transplant adult Egyptian patients as an assessment for iron overload and their relationship to post transplantation complications
Methods: Serum GDF15 and hepcidin were measured using ELISA in 45 post allogenic(23 patients) and autologous(22 patients) bone marrow transplanted patients 1 year posttransplantation in comparison to 15 healthy controls recruited from Bone Marrow Transplantation Unit, Ain Shams University Hospitals
Results: Serum level of GDF15 and hepcidin level were elevated 1 year post allogenic and autologous transplantation in comparison to control group with a statistically significant difference between patients and control($P<0.001$). GDF15 and hepcidin were positively correlated with ferritin level($p<0.001$). GDF15 and ferritin were positively correlated with acute GVHD and chronic GVHD($P=0.004$ and 0.002 respectively), but hepcidin did not show any significant correlation with acute GVHD(($P=0.110$). Also, GDF15, hepcidin and ferritin were positively correlated with serum levels of ALT and AST in both autologous and allogenic transplanted patients. But, GDF15, hepcidin and ferritin were not correlated with bacterial or viral infections in both allogenic and autologous group of patients
Summary/Conclusion: Both GDF15 and hepcidin are useful biomarkers for iron overload late post allogenic and autologous bone marrow transplantation and both can be used as a predictor for posttransplantation complications

PB1775 SYSMEX XN 1000 CAN PREDICT THE TIME OF STEM CELL COLLECTION WITH NEW COMPLETE BLOOD COUNT PARAMETERS: SINGLE CENTER EXPERIENCE FROM TURKEY

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Background: Hematopoietic stem cell transplantation is widely perfomed for the treatment of hematological malignancies. Hematopoietic stem cells are mostly collected from peripheral blood. A minimum of $2x10^6$ CD34+ cells/kg is needed for a successful transplant. The amount of CD34+ cells in peripheral blood must be 20/µl in order to collect this amount. The optimal time for stem cell collection varies between patients and the time of initiating stem cell collection should be determined according to peripheral blood stem cell count. The gold standard method for determining the amount of peripheral blood stem cells is flow cytometry. However, this method is expensive and time laboring. In Sysmex XN 1000 (Sysmex Corporation, Kobe, Japan) automatic complete blood count (CBC) analyzers; immature granulocytes(IG) are counted in white blood cell differential (WDF) channel and nucleated red blood cells (NRBC) are counted in white cell nucleated (WNR) channel with fluorescent flow cytometry method. IG is expressed as the sum of metamyelocytes, myelocytes and promyelocytes and NRBC reflects the increase in erythropoietic activity.
Aims: In this sudy; we compared IG and NRBC counts, the routine components of our CBC parameters,with peripheral blood CD34+ cell counts and aimed to find the role of these parameters in determining the time of stem cell collection.
Methods: 86 patients who underwent stem cell mobilization between October 2018 and August 2020 were included in the study. Mobilization and stem cell collection records were evaluated retrospectively. Peripheral blood CD34+ cells were analyzed with flow cytometer (Becton Dickinson Biosciences FACS Calibur, California,US) according to ISHAGE guidelines. The time of analyzes were determined according to white blood cell count.(WBC) IG and NRBC analyzes were performed by Sysmex XN 1000 (Sysmex Corporation, Kobe, Japan) on the same day with flow cytometry which was also the first day of stem cell collection. Patients were divided into 2 groups according to periheral blood CD 34+ cell count/µl (≤20= group 1 vs >20= group 2). IG ratio was calculated with the formula of IG count x 100 / WBC count and NRBC ratio was calculated with the formula of NRBC count x 100 / RBC count.
Results: The median age was 56 years and 48.8% were female. The diagnosis were multiple myeloma in 56, non Hodgkin lymphoma in 18, Hodgkin lymphoma in 8, plasma cell leukemia in 2, amyloidosis in 1 and

multiple plasmositoma in 1 of the patients. Mobilization regimens were cyclophosphamide + G-CSF in 55, DHAP + G-CSF in 7, ICE + G-CSF in 12, hyperCVAD + G-CSF in 5, plerixafor + G-CSF in 2, G-CSF alone in 4 and etoposide + G-CSF in 1 of the patients. When we compared CBC parameters we found that only IG ratio, NRBC ratio and NRBC counts were different between 2 groups ($p< 0.001$, $p= 0.011$ and $p= 0.012$, respectively). IG ratio, NRBC ratio and NRBC counts were positively correlated with peripheral blood CD34+ cell counts. The index formulated with multivariate logistic regression analysis was -1.7 + (IG% x 0.12) + (NRBC% x 2) and the cut off was zero. According to these results, the parameter with the highest diagnostic accuracy was the new index with an AUC of 0.766 (0.665 – 0.867). The sensitivity of the index was 76% and specifity was 72% with a cut off of zero.
Summary/Conclusion: In conclusion, the new index formulated from the CBC parameters can predict the time for beginning stem cell collection with a more fast and less expensive way compared with the gold standard flow cytometry. However, this data must be validated with larger multicenter prospective studies.

PB1777 PATIENT-CENTERED FACTORS IN EVALUATION OF ELIGIBILITY AND PROGNOSTICATION IN HEMATOPOIETIC STEM CELL TRANSPLANTATION IN OLDER PATIENTS WITH HEMATOLOGIC MALIGNANCIES – A SYSTEMATIC REVIEW

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Background: Hematopoietic stem cell transplantation (HSCT) represents a cornerstone in individualized treatment algorithms in blood cancer. However, assessment of eligibility and outcome prediction remains challenging, particularly at advanced age.
Aims: This systematic review investigates the relevance of patient-orientated scores in decision-making in HSCT.
Methods: We performed a systematic review with a literature search on MEDLINE and Web of Science on the use and prognostic relevance of patient-centered scores in allogeneic and autologous HSCT in adult patients with hematologic malignancies.
Results: After screening 2326 studies, we identified 59 studies using at least one validated score to determine eligibility for HSCT, including 57 studies assessing performance status (PS) and three studies using comorbidity scores. Prognostic relevance of comorbidities was analysed in 128 studies, of PS in 67, of functional activities in three, of nutritional status in ten and of health-related quality of life (HRQOL) in six studies. Based on uni-/multivariate analyses, predictors of overall survival in allogeneic HSCT included comorbidities in 42/72 (58%) and in 39/58 (67%), PS in 20/33 (61%) and 30/37 (81%), nutritional status in 1/3 and 3/5, functional activities in 2/3 and 2/2 and HRQOL in 2/3 and 2/2, respectively. Likewise, comorbidities were predictors of reduced survival in autologous HSCT in 3/9 (33%) and 4/7 (57%) and PS in 4/5 (80%) and 4/6 (67%), respectively.
Summary/Conclusion: To date, validated patient-centered scores have been rarely used to evaluate eligibility for HSCT. The prognostic impact of comorbidities and of PS was demonstrated in a relevant proportion of studies and the results for the relevance of functional activities and HRQOL are encouraging. Thus, the relevance and further integration of patient-orientated scoring in decision-making in HSCT is underlined.

PB1778 IS THE USE OF DEFIBROTID EFFECTIVE ON GRAFT VERSUS DISEASE (GVHD) IN ALLOGENEIC STEM CELL TRANSPLANTATION?

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Background: Hepatic sinusoidal obstruction syndrome (SOS) is one of the complications of allogeneic stem cell transplantation (allo-SCT) due to endothelial dysfunction. Defibrotide (DF) is used effectively in SOS prophylaxis and treatment because of its endothelial protective and thrombocytic-fibrinolytic regulatory effects. On the other hand, graft versus host disease (GVHD), regardless of whether acute chronic or overlap syndrome, is the most important cause of morbidity and mortality in ASCT.
Aims: Here, we retrospectively investigated the use of DF and its effect on the development of GVHD in our allogeneic transplant patients.
Methods: Eighty-one patients with various diagnoses (including myeloid and lymphoid hematological malignancies and aplastic anemia), who underwent allo-SCT at the Hematology Department of Adnan Menderes University between 2014-2020 were included. Of the patients, 34 used DF as a prophylaxis (25mg/kg/day, intravenously, 21 days) while 47 patients did not. Acute and chronic GVHD and overlap syndrome assessment were performed at +30/100th day and throughout the life of the patient, respectively. The data were evaluated using SPSS 21 software program (Chicago, IL, USA). Chi-square test was used to demonstrate the difference between categorical variables. A p value below 0, 05 was the cutoff for statistical significance.
Results: The results for the patients are presented in Table 1. Thirteen patients (38%) in the DF group and 16 patients (34%) in the non-DF group received myeloablative conditioning regimens containing busulfan. The rest of the patients in both groups received non-myeloablative or reduced intensity conditioning regimens. Acute GVHD was more common in patients who received DF, compared to patients who did not receive it (82% vs 61%). Although rates of chronic GVHD differ among DF users compared to non-users (31% vs 19%); it did not reach a statistically significant value (p: 0,274). While no patient died in the group that did not use DF, 5 patients died in the first 100 days in the group using DF. Overlap GVHD was observed in 4 patients. We observed that 1 patient in the non-DF group developed SOS according to the European Bone Marrow Transplantation (EBMT) criteria.

	DF (+) N: 34	DF(-) N:47	p
Mean age	39.5±10	45±11	>0.05
Sex Female	15	17	
Male	19	30	>0.05
Disease type			
-Myeloid	25	28	
-Lymphoid	7	18	0.028
-Aplastic anemia	2	1	
Conditioning regimen			
-MAC	13	16	0.043
-non MAC	5	17	
-RİC	16	14	
Transplantation type			
10/10 related	11	39	0.001
10/10 unrelated	11	3	
9/10 related	2	2	
9/10 unrelated	7	1	
Haploidentical	3	2	
Acute GVHD			
-without	6	18	0.047
-with	28	29	
Chronic GVHD			
-without	20	38	0.274
-with	9	9	
Overlap GVHD	2	2	
SOS development	-	1	

Table 1: Comparison of patients according to defibrotide use

Summary/Conclusion: In our study, DF use was evaluated in terms of the development of acute and chronic GVHD and we noted the development of more acute GVHD with the use of DF. There was no difference in the development of chronic GVHD. There are few studies in the literature evaluating the relationship between DF use and GVHD. In an in vitro study on mice, DF use was shown to be effective in acute GVHD through T lymphocyte and neutrophil interaction. In another experimental study, it was shown to suppress acute GVHD by inhibiting the "endothelial cell line" activation. In contrast to our study, acute GVHD was less common in another clinical study by Tekgündüz et al (46, 5% vs 82%). To the best of our knowledge, this is the first study evaluating the effect of DF on both acute and chronic GVHD in the adult population. The use of DF for prophylaxis is mostly preferred in high risk patients. Development of GVHD is also important for this risk group. These risks may explain the higher rate of acute GVHD in the DF group in our study. The effects of DF use on GVHD will be clarified with studies in which both the use of DF and risk subgroups of GVHD development are evaluated using a high and homogeneous number of patients.

PB1779 CLINICO-HEMATOLOGICAL PREDICTORS OF RESPONSE DEEPENING AFTER STEM CELL TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA

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Background: The effectiveness of multiple myeloma (MM) patients' treatment is dependent on the response to therapy including the stage of autologous stem cell transplantation (AutoSCT). The importance of predictors associated with the quality of response after AutoSCT is due to the possibility to change the option and intensity of condiioning regimen and/or posttransplantation consolidation.
Aims: To determine the frequency of MM cases without the improving of response after AutoSCT and evaluate the possibility to predict the effectivence of AutoSCT using clinical and hematological parameters.
Methods: Retrospective analyses of 84 patients' data have been done. Total number of performed AutoSCT was 112 including 84 the first and 28 the second transplantation. The response was determined according to IMWG criteria.
Results: Before the first AutoSCT the number of patients with complete (CR), very good partial (VGPR) and partial (PR) response were 31, 19 and 33 accordingly. One patient has MM stabilisation. Improving of the response depth after the first AutoSCT was recorded in 29/53 (54.7%) patients. Frequency of CR was higher in patients with previus VGPR than PR: 11/19 (57.9%) vs 6/33 (18.2%); p=0.005; OR=6.19, 95%CI 1.7-22. In the group without improving of response the number of patients received additional drugs to standard schemes with bortezomib and lenalidomide was higher than in the group with depeening of response: 29.2% vs 13.8%; difference not significant. The same situation was in relation to Mel200 conditioning regimen: 65.6% vs 79.3%.: difference not significant. The effectiveness of the second AutoSCT was evaluated in 2 patients with VGPR and 6 patients with PR. All patients with VGPR and 1 patient with PR had CR and 1 patient with PR reached VGPR. 4 patients with PR did not improve their response after the seconf AutoSCT.
Summary/Conclusion: Reaching of CR after AutoSCT in patients with MM is dependent on the quality of previous response, scope of induction therapy and intensity of conditioning regimen.

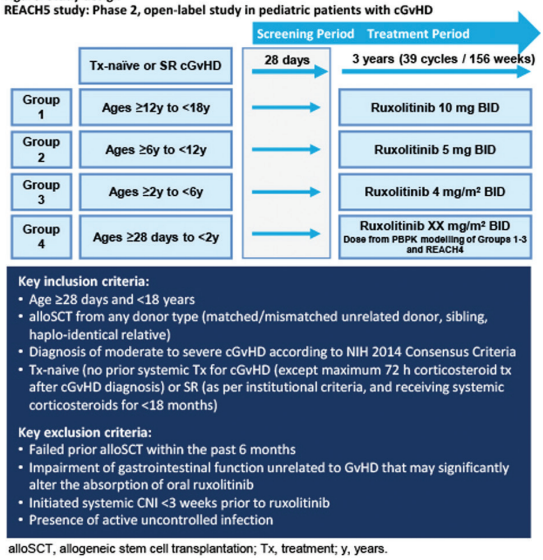
PB1780 A PHASE 2 OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF RUXOLITINIB ADDED TO CORTICOSTEROIDS IN PEDIATRIC SUBJECTS WITH MODERATE/SEVERE CHRONIC GVHD AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (REACH5)

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Background: Graft-vs-host disease (GvHD) may significantly impair the success rate of allogeneic stem cell transplantation. In pediatric patients, chronic GvHD (cGvHD) can lead to considerable morbidity, impaired quality of life and transplant-related mortality (Inagaki 2015). Although systemic corticosteroids are the standard of care in initial stages of moderate to severe cGvHD, there is little controlled trial evidence to indicate the best initial or second-line treatment strategy. In recently reported data from the phase 3 REACH3 study, ruxolitinib improved overall response rate (ORR) versus best available therapy in adults and adolescents (≥12 years of age) with steroid-refractory (SR) or steroid-dependent cGvHD (Zeiser ASH 2020 [abstract 77]; NCT03112603). Furthermore, ruxolitinib has demonstrated encouraging activity in SR cGvHD pediatric patients in case series and a single center study (González Vicent 2019, Moiseev 2020). These data, combined with knowledge of the role played by janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling in cGvHD pathophysiology, support the investigation of ruxolitinib in the pediatric cGvHD patients.
Aims: The REACH5 study will assess the safety, efficacy, and pharmacokinetics (PK) of ruxolitinib in pediatric patients with moderate to severe treatment-naive or SR cGvHD.
Methods: REACH5 is a Phase 2 open-label, single-arm, multicenter study of pediatric patients aged ≥28 days to <18 years divided into four age groups (see **Figure** for details). Patients are eligible for inclusion if diagnosed with moderate to severe cGvHD (National Institutes of Health [NIH] 2014 Consensus Criteria) and are either treatment-naïve or SR (as per institutional criteria and still receiving systemic corticosteroids). Patients will be treated for up to approximately 3 years (39 cycles/Week 156). The primary objective is to evaluate the activity of ruxolitinib twice daily (BID) added to corticosteroids +/- calcineurin inhibitor (CNI) measured by ORR at Week 24. Secondary endpoints include ruxolitinib safety, PK in treatment-naive and SR cGVHD, percentage of participants with ≥50% reduction from baseline in daily corticosteroid dose at Cycle 7 Day 1, duration of response, best overall response and failure-free survival. The study will enroll a minimum of 5 evaluable patients in Groups 1, 2 and 3, no minimum number of evaluable subjects in Group 4, and no cap to enrollment in any group. Group 1 patients will be treated at 10 mg BID, which is already considered the recommended phase 2 dose for this age group. Based on a review of PK data in the same aged group of patients treated in the pediatric acute GvHD study REACH4 [NCT03491215], the Group 2 dose has been confirmed at 5 mg BID and Group 3 dose at 4 mg/m² BID. Enrollment initiation into Group 4 will be subject to the availability of data in this age group from REACH4, as well as a review of available PK, safety, and activity data generated from Groups 1 to 3 in the current study.
Results: Trial in progress.

Figure. Study design
REACH5 study: Phase 2, open-label study in pediatric patients with cGvHD



alloSCT, allogeneic stem cell transplantation; Tx, treatment; y, years.

Summary/Conclusion: As of February 2021, 25 patients have been enrolled. Enrollment is ongoing for Groups 1 and 2, with Group 3 opening in 2021 (ClinicalTrials.gov: NCT03774082).

PB1781 EFFECT OF CYP3A5 GENE POLYMORPHISMS ON TACROLIMUS CONCENTRATION AND ADVERSE EVENTS IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL

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Background: Acute graft-versus-host disease (aGVHD) is one of the major life-threatening complications after HSCT. Prevention of severe aGVHD is crucial to the success of HSCT.
Aims: To investigate the relationship between CYP3A5 gene polymorphisms and tacrolimus concentration and acute graft versus host disease (GVHD) in patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods: Retrospective analysis the clinical data of 35 Chinese adult patients received allo-HSCT from 2019.7 to 2020.2. Bone marrow samples were collected before transplantation for CYP3A5 genotyping. Intravenous infusion of tacrolimus and short course of methotrexate (MTX) ± mycophenolate were used to prevent GVHD. The initial concentration was monitored on the second or third day of tacrolimus administration, followed by 2-3 times a week. The drug dose was adjusted according to the target blood concentration (10-15ng / ml). The incidence of III-IV aGVHD in patients with CYP3A5*1 alleles was higher than that in patients with CYP3A5*3/*3 gene (26.3+10.1% vs 6.2+6.1%, P=0.115).
Results: In 16 HSCT patients with CYP3A5 * 3 / * 3 gene, the initial concentration of tacrolimus (9.82 vs 8.53 ng / ml), the initial concentration / dose (C / D) ratio (5.72 vs 4.26 ng / ml / mg), and the median C / D ratio in the first two weeks after HSCT (5.29 vs 4.61 ng / ml / Mg, 5.65 vs 4.56 ng / ml / mg) were significantly higher than 19 patients with at least one CYP3A5 * 1 allele (P = 0.026, 0.001, 0.037, 0.045).
Summary/Conclusion: CYP3A5 genotype directed administration may help to achieve the target blood concentration of tacrolimus after HSCT more quickly, reduce the incidence of severe aGVHD and improve the efficacy of transplantation.

PB1782 ANTIGENIC DIVERSITY OF THE MAJOR HISTOCOMPATIBILITY COMPLEX AMONG RECIPIENTS, RELATED DONORS AND HEMATOPOIETIC STEM CELL DONORS OF THE REGISTRY OF THE REPUBLIC OF BELARUS

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Background: Modern trends in hematopoietic stem cell transplantation with high donor requirements (10/10 HLA-matching of donor and recipient, infectious status, young donor age) require new approaches to the operation of registries and donor centers. There are various strategies not only to attract more potential HSC donors, but also to increase the diversity of HLA phenotypes. The allele frequencies of the HLA system are specific for populations, which limits the number of different phenotypes that we obtain when typing new potential donors.
Aims: to analyze antigenic diversity in the population of siblings, patients and HSC donors of the registry.
Methods: The analysis included the results of HLA typing of 216 patients and 289 siblings, 27 885 phenotypes HSC donor of the registry of the Republic of Belarus.
Results: The results of the study of the frequency of occurrence of antigens in patients, siblings and HSC donors of the registry presented in Table 1.

Table 1
Comparison of the frequency of occurrence of antigens in the phenotypes of patients, siblings and HSC donors of the registry.

	patient	sibling	registry	p-value corrected for multiple comparisons		
				patient vs sibling	patient vs registry	sibling vs registry
A26	14 (3,2)	18 (3,1)	5581 (5,5)	>0,99	0,103	0,045
A33	13 (3)	11 (1,9)	1119 (1,1)	0,346	0,001	0,207
A68	15 (3,5)	19 (3,3)	553 (0,5)	>0,99	<0,001	<0,001
B14	13 (3)	18 (3,1)	1720 (1,6)	>0,99	0,078	0,026
B15	26 (6)	37 (6,4)	1348 (1,3)	0,918	<0,001	<0,001
B40	28 (6,5)	55 (9,5)	1284 (1,2)	0,108	<0,001	<0,001

Summary/Conclusion: Taking into account the results obtained, it can be concluded that there are differences in the phenotypes of related and unrelated HSC donors. The revealed differences in the frequency of occurrence of antigens suggest the formation of unique phenotypes that differ from the general population, the inclusion of which in the information base will increase the antigenic diversity of the main histocompatibility complex in the population of HSC donors of the registry, which will increase the number of suitable donor-recipient pairs.

PB1783 COMPARATIVE EFFECTIVENESS OF DIFFERENT CONDITIONING REGIMENS WHEN PERFORMING AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS

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Background: The principal role of autologous stem cell transplantation (AutoSCT) in patients with multiple myeloma (MM) is dependent primarilly on cytoreductive action of conditioning regimen (CR). There are different approaches to strengthen antimyeloma exposure of CR and one of them is adding a new drug to standard used melphalan
Aims: The aim was to compare the effectiveness of standard used CR with melphalan (Mel) monotherapy with combination of Mel with thiotepa (Mel/Thio) and combination of Mel with carfilzomib (Mel/Carfil). Progression free survavl (PFS) was chosen as a measure of CR effectiveness
Methods: Response to therapy before AutoSCT was identified with IWG criteria. PFS was calculared from the data of AutoSCT in patients without MM progression during the first 3 months. Thre groups of patients were formed: the first group of 27 patients with CR Mel200/140, the second group of 9 patients with CR Mel/Thio and the third one of 8 patients with CR Mel/Carfil
Results: Median age of patients in the group one, two and three was 54y, 59y and 57.5 y accordingly. The number of patients with comple, very good partial and partial response was 10, 7 and 10 in the first group, 1, 4 and 1 in the second group and 1, 1 and 6 in the third group. The patients' follow-up period was 14 (3-40), 13 (10-26) and 11.5 (3-18) months in the groups accordingly. The median PFS was 40 mo, 13 mo and not achived in the groups accordingly: p=0.833. Difference in the data of PFS between indidvidual groups has not been found too
Summary/Conclusion: Despite the lack of distinction, the trend towards improved PFS in the group with the pre-eminent number of MM patients with partial response treated with regimen Mel/Carfil possibly reflects a more pronounced antimyeloma effect of this CR. A longer period of observation is needed for the final conclusion

PB1784 USE OF RECOMBINANT SUPEROXIDE DISMUTASE IS THE EFFECTIVE METHOD TO REDUCE TOXIC COMPLICATIONS IN PATIENTS WITH MULTIPLE MYELOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: It is well known that high dose chemotherapy may lead to the strengthening of oxidative stress that may be an additional factor of internal injuries and deteriorating of the patients' condition. It has been shown previously that increased oxidative stress after conditioning regimen with melphalan in patients with multiple myeloma (MM) can be considered as a reason of worthening of quality of life too.
Aims: To evaluate the influence of recombinant superoxide dismutase (Rexod®) (SOD) on some parameters of oxidative stress in MM patients during autologous stem cell transplantation (AutoSCT).
Methods: 6 VV patients with median of age 50 y (39-60) were included in the trial after signing the informed consent. Levels of SOD, total SH-groups, active oxigen species, malondialdehide (MDA) were studied. 9.6 - 16x10/6/U of recombinant SOD was infused IV within 10-15 minutes at -2, +1, +7 and +14 days.
Results: Baseline level of SOD was reduced in 2 and more times compared to the norm. Futher decline of SOD was fixed on +7 day in 4 patients. Level of SOD did not change in 2 other patients. Baseline level of active oxygen species was increased (by maximum of 20 times) or decreased (by 1.3-1.8 times) in 5 patients. Levels of MDA and SH-groups did not differ from the norm. Postinduction reactions were not fixed in any case. One episode of febrile neutropenia took place in (16%) patient. Short-term

elevation of transaminases of grade 1 was detected in 2 (33%) patients. Median time of neutrophils and platelets engraftment was 12 (10-15) and 14.5 (13-17) day accordingly. On day +14 restoring of SOD and active oxygen species levels to the indicators corresponding to AutoSCT were fixed. Despite the positive dynamics of significant markers of oxidative stress, they did not reach the norm in any patient.
Summary/Conclusion: The use of Rexod®, which has anti-inflamatory properties, leads to a decrease in undesirable toxic effects. It is possible that an increase in the dose and duration of Rexod® using will give a more pronounced positive effect.

PB1785 THE RESULTS OF THERAPY IN PATIENTS WITH B-CELL LYMPHOID MALIGNANCIES WITH MUTATIONS IN THE TP53 GENE

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Background: Mutations in the *TP53* gene in lymphoid malignancies occur in about 19,3% of cases. Patients are carrying mutations in *TP53* do not benefit from intensive chemotherapy regimen and have poor prognosis. The only approach to achieve long-term remission is to use cell therapy in the first line: allogeneic hematopoietic cell transplantation and CAR-T cell therapy. The use of targeted therapy does not allow achieving long-term remissions and is justified only as a bridge to cell therapy.
Aims: To evaluate the prognostic value of mutations in the *TP53* gene in patients with B-cell lymphoid malignancies and the results of therapy in this group of patients.
Methods: During the period from 2016 to 2021, 95 patients with B-cell lymphoid malignancies were included in the prospective study: 47 pts - mantle cell lymphoma, 16 pts - primary mediastinal lymphoma, 12 pts - diffuse large B-cell lymphoma, 8 pts - "double-hit" lymphoma, 7 pts - follicular lymphoma grade 3, 3 pts - Burkitt's lymphoma, 1 pt – plasmablastic lymphoma, 1 pt - chronic lymphocytic leukemia. Sanger DNA sequencing and NGS carried out analysis of mutations in the *TP53* gene.
Results: *TP53* mutations were detected in 18 of 95 patients (19%): 11 pts – mantle cell lymphoma, 2 - diffuse large B-cell lymphoma, 1 pt - "double-hit" lymphoma, 1 pt - Burkitt's lymphoma, 1 pt - primary mediastinal lymphoma and 1 pt – plasmablastic lymphoma. In our study of eight patients with mutations in the *TP53* gene underwent haploidentical (4), matched unrelated (3), mismatched related (1) allo-HCT between 2016 and 2021.
Five out of 8 patients before allo-HCT received targeted therapy: 4 patients as a bridge to allo-HCT after previous chemotherapy (3 pt - MCL, 1 pt – DLBCL), 1 pt with PL - in combination with induction chemotherapy (mNHL-BFM-90 + lenalidomide) and 1 patient with CLL - in as a first-line therapy ibrutinib with venetoclax was administered before allo-HCT.
Five out of 8 patients remain in complete remission of the disease without signs of GVHD with follow-up from 1 to 52 months: 3 pt – mantle cell lymphoma, 1 pt - plasmablastic lymphoma, 1 pt - chronic lymphocytic leukemia.
Three out of 8 patients died after allo-HCT: 1 pt - due to severe toxic and infectious complications (DLBCL), 2 pt – due to progression disease (MCL).
One patient with «double-hit» lymphoma underwent CAR-T cell therapy. With a follow-up period of 6 months, the patient remain in complete remission.
Among other patients five died of disease progression (4 pts – MCL, 1 pt – BL, 1 pt – PML), despite the use of various chemotherapy regimens and targeted therapy. Four patients are currently undergoing therapy.
Summary/Conclusion: The presence of mutations in the *TP53* gene is characterized by an extremely unfavorable impact on the prognosis and survival of patient with lymphoid malignancies. *TP53* mutations should be considered for risk models in all B-cell lymphoid malignancies. Allo-HCT improves outcomes for patients with mutant *TP53*. CAR-T cell therapy can serve as an alternative approach to the therapy of patients with B-cell lymphoid malignancies with mutations in the *TP53* gene.

PB1786 PREEMPTIVE VS SALVAGE RUXOLITINIB TREATMENT FOR STEROID-INSENSITIVE ACUTE GRAFT-VERSUS-HOST-DISEASE (SI-AGVHD): WHICH APPROACH IMPROVES CLINICAL OUTCOMES?

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Background: Ruxolitinib (RUX) has been approved for second line treatment of acute graft-versus-host disease (aGVHD). However, the optimal timing for steroid-insensitive aGVHD (SI-aGvHD) remains unclear.
Aims: In this context, our multi-center retrospective study aimed to assess the benefits and risks of initiating RUX treatment for aGvHD poorly responsive to corticosteroid therapy within 7 days (preemptive strategy) compared to that longer than 7 days (salvage strategy).
Methods: The study was a multi-center retrospective study to compare the efficacy and safety profiles of preemptive versus salvage RUX treatment. A total of 49 patients were included, with 32 receiving preemptive RUX within 7 days when fail response to prior steroid and 17 patients treated with salvage RUX longer than 7 days.
Results: The two cohorts were well-matched demographically. Although the baseline condition of aGVHD in both groups were more than half are stage II and mainly with skin involvement, more patients (71.9% vs 35.3%, p==0.015) achieve CR in preemptive cohort which also led to a better survival outcome. The median time to response was shorter in patients treated with preemptive RUX (7 days vs 14 days, p=0.157). The risk of adverse events was comparable between the two groups (SAEs: 25% vs 24%, symptom of Cytopenia:43.8% vs 35.3%, viral reactivation:50% vs 23.5%). No adverse events led to treatment discontinuation and no viral infections had been documented. The mortality rates were low in 2 cohorts (21.9% vs 23.5%, P=0.582), mainly due to opportunistic infections and aGVHD progression.
Summary/Conclusion: It became more common to prompt RUX intervention for patients with SI-GVHD in clinical practice. Consistent with expectations, preemptive strategy was associated with significant better outcomes and rapid improvement in this patient populations. Further prospective trials will be important to confirm the preemptive impact.

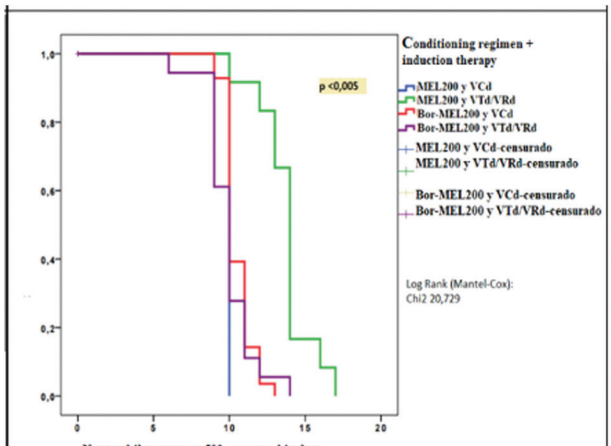
PB1787 BORTEZOMIB + HIGH-DOSE MELPHALAN (BORMEL200) VERSUS MEL200 AS A CONDITIONING REGIMEN FOR AUTOLOGOUS HEMATOPOIETIC PROGENITORS TRANSPLANTATION (TAPH) IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM).

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Background: Therapeutic strategy for transplant-eligible NDMM patients (pts) is triplet-based induction scheme, with novel therapeutic agents (immunomodulators (IMIDs), proteasome inhibitors (IP) and even monoclonal antibodies as Daratumumab), to obtain better responses prior to conditioning regimen and TAPH. The standard of conditioning is MEL200. BORMEL200 vs MEL200 conditioning has been proposed, with better responses, similar toxicity, and prolonged progression-free survival (PFS) and overall survival (OS).

Aims: To analyse efficacy and toxicity depending on the administered conditioning: BORMEL200 vs MEL200 and VCd induction vs VTd / VRd.
Methods: Unicentric, descriptive and retrospective study carried out at Guadalajara University Hospital, from February 2010 to June 2020, using clinical and analytical NDMM pts data with ≥ partial response in the 1st line of treatment (tt). From February 2010 to July 2019, pts received BORMEL200: Bor sc (1mg/m2) days -6, -3, +1, +4 + MEL200 iv (200mg/m2) day -2, with G -CSF from day +7. From July 2019 to present, MEL200 iv, without G-CSF. In each conditioning, induction subgroups were analyzed: VCd vs VTd / VRd.
Results: We identified 61 pts whose clinical characteristics and treatment (tt) data are listed in Table 1. 48 (78,7%) received BORMEL200 and 13 (21,3%) MEL200. In general, pts received bortezomib (V) - based induction, of them 51% (n=31) were treated with alkylating agents and 49% (n=30) received immunomodulatory drugs.
In the group of BORMEL200, after a median follow-up of 9,7 years, the PFS and OS median for VCd and for VTd/VRd was 4,2 years and 9,7 years vs 4,7 years and not reached, respectively. In a PFS multivariable analysis, were included as independent variables: sex, age >65 years old, use of IMIDs (VTd/VRd), ISS, preTAPH response, high risk cytogenetic and infused CD34/kg quantity. It was associated independently to relapse: IMID use (HR 0.119; p = 0.003), age> 65 years (HR 0.832; p <0.001), ISS-2 vs ISS-1 (HR 62.2; p <0.001), ISS-3 vs ISS-1 (HR 36.3; p = 0.004).
In the MEL200 group, statistical data is not offered due to the few pts treated in both arms and short follow-up period.
Regarding toxicity, the median of platelet recovery >20,000 was similar in both conditioning regimens. It was only found a significant association in the time till recovery neutrophils >500/ul, being superior in pts who received G-CSF during TAPH (Figure 1).



Neutrophils recovery >500, measured in days

Conditioning regimen + induction therapy	Median CI 95%		Median	
	Lower limit	Upper limit	Estimate	Error típico
MEL200 y VCd	.	.	10,000	.
MEL200 y VTd/VRd	13,578	14,422	14,000	,215
Bor-MEL200 y VCd	9,662	10,338	10,000	,172
Bor-MEL200 y VTd/VRd	9,379	10,621	10,000	,317
Global	9,545	10,455	10,000	,232

Figure 1. Toxicity results. Comparison of both condicioning regimens and its subgroups, Neutrophils >500/uL and platelets >20,000/uL recovery.

Summary/Conclusion: Among the patients with BORMEL200, the use of IMIDs does not provide better SLP in our series. BORMEL200 with VTd/VRd gets better postTAPH responses. An early recovery of neutrophils in conditioning with G-CSF is observed, with the clinical and socioeconomic implications associated. More patients need to be included in both treatment branches and a better follow-up and monitoring so that data may be confirmed.

PB1788 RESULTS OF SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH HEMATOLOGICAL DISEASES: RETROSPECTIVE ANALYSIS OF OUR HOSPITAL

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Background: Performing a 2nd Hematopoietic Stem Cell Transplantation (HSCT) after the relapse of the underlying disease is one of the therapeutic strategies in patients who achieve a response after relapse.
Aims: The aim of our study is to analyze the results and prognostic factors in patients who underwent a 2nd allogeneic HSCT.
Methods: We studied 126 patients who received a 2nd allogeneic HSCT in our center between 1995-2019, the 1st HSCT being autologous or allogeneic. Two groups were established: 1st: 1st autologous-2nd allogeneic / 2nd: 1st allogeneic-2nd allogeneic. Patient's characteristics are shown in Table1.
Results: With a median follow-up of 96 months (range: 21-300), the probabilities of overall survival (OS), progression-free survival (PFS), and probability of relapse (RP) at 5 and 10 years are 44.5 ± 5% (5 years); 31±5% (10 years), 38.9± 5% (5 years); 29.2± 5% (10 years) and 38 ± 6% (5 years); 46.2±7% (10 years) in the 1st group and 35.1±9% (5 years); 30±9% (10 years), 38.9± 9% (5 and 10 years) and 53.7±10% (5 and 10 years) in the 2nd group, respectively.
Transplant-related mortality in the first 100 days (TRM100) and global TRM are 23.4% and 39.4% in the 1st group and 12.5% and 18.8% in the 2nd group, respectively. There are no differences in the TRM100 or global TRM according to the intensity of the 2nd HSCT conditioning.
PFS is higher in patients transplanted in complete response: 43±7% vs 23.5±6% (p= 0.17). This advantage in PFS reached statistical significance in the 1st group: 45 ± 7.8% vs 16 ± 6%, p = 0.05. (Figure 1)
The presence of acute GVHD did not influence significantly OS, PFS or PR in any of the groups. The presence of chronic GVHD decreases PR and increases PFS and OS, but without being statistically significant.
We did not observe differences in OS, PFS or PR depending on whether the same or different donor was used in the 2nd HSTC, or whether the relapse was early or late.
Summary/Conclusion: Carrying out a 2nd HSCT in patients who relapse after a 1st HSCT is a feasible treatment option that offers a survival of 53 ± 4.4% at 5 years and 34.6 ± 4.6% at 10 years, being the main influencing factor the disease status at the 2nd HSCT.

PB1789 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR CHRONIC GRANULOMATOUS DISEASE: A SINGLE-CENTER 10-YEAR RETROSPECTIVE SERIES

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Background: Chronic Granulomatous Disease (CGD) is an inherited congenital disorder characterized by severe recurrent infections and inflammatory complications due to defects in phagocyte oxidative function. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is currently the only established curative treatment, but it remains a challenge to decide which patients (and when) should proceed to transplant. Historically, alloHSCT in these patients was associated with greater risk of graft failure, low donor chimerism, and mortality due to previous organ dysfunction, compared to other primary immunodeficiency disorders.
Aims: To describe baseline characteristics and outcomes of patients with CGD treated with alloHSCT in our Institution.
Methods: Retrospective descriptive analysis of patients with CGD who received an alloHSCT in our Institution between 2009 and 2018.
Results: In the 10-year period considered in this study, 5 patients (4 boys and one girl) were referred to our Institution and received an alloHSCT for CGD. All had severe and recurrent infections and most (n=4) had also inflammatory conditions (most frequently granulomatous colitis) leading to diagnosis, which was confirmed at a median age of 8 months (5 months-13 years). Most (n=3) had an X-linked genotype (CYBB gene mutation) and 2 had an autosomal recessive genotype (CYBA and NCF1 gene mutations).
Median age at transplant was 7 years (1-15 years). Two patients received a matched sibling transplant from peripheral blood progenitors, and the remainder received a matched unrelated donor transplant from bone marrow (n=2) and cord blood (n=1) progenitors. There was no documented active infection at time of transplant. Most patients (n=4) received a myeloablative conditioning regimen with busulfan+cyclophosphamide,

and additional anti-thymocyte globulin in 2 cases. Median time of in-patient care during peri-transplant period was 29 days (25-74 days). All patients had febrile neutropenia during the pre-engraftment period controlled with large spectrum antimicrobials.
Median time to engraftment was 17 days (13-55 days). Acute graft-versus-host disease (GVHD) was documented in 2 patients (grades 1 and 2). Full donor chimerism was attained in 3 patients at a median time of 41 days (32-54 days). Mixed and falling donor chimerism was observed in the other 2 patients, who had received bone marrow reduced-intensity conditioning and cord blood HSCT. They had secondary graft failure and proceeded to a second alloHSCT, at 8 and 17 months after the first transplant (from different matched unrelated donors, graft source was peripheral blood in both cases).
With a median follow-up time from first alloHSCT of approximately 8 years (1.7-10.7 years), 4 patients are alive and without manifestations of CGD. Three patients have developed chronic GVHD, mostly cutaneous and mild. CMV reactivation was documented in 4 patients and one had post-transplant EBV-related lymphoproliferative disease successfully treated with rituximab. One patient died at 3 months after second alloHSCT from associated complications.
Summary/Conclusion: CGD patients remain a challenge in the alloHSCT setting due to susceptibility to infectious and inflammatory complications. However, improvement of conditioning regimens and peri-transplant supportive care have contributed to better outcomes in this population.

PB1790 EXTRACORPOREAL PHOTOPHERESIS IN THE TREATMENT OF ACUTE OR CHRONIC GRAFT VERSUS HOST DISEASE (GVHD) IN PEDIATRIC PATIENTS: MONOCENTRIC EXPERIENCE

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Background: Steroid refractory (SR) and dependent (SD) acute or chronic Graft versus Host Disease (aGvHD/cGvHD) are severe complications of allogenic Hematopoietic Stem Cell Transplantation (HSCT) with high morbidity and mortality rates.
Extracorporeal Photopheresis (ECP) is a therapeutic option with T-cell immunoregulatory activity but without ImmunoSuppressive (IS) effects.
Aims: We retrospectively evaluated efficacy and safety of ECP in our pediatric population.
Methods: We reviewed data from 23 children with SR or SD GvHD followed at our Institution since 2010.
ECP was performed by COBE Spectra™and Therakos CELLEX™ systems; the schedule consisted of 2 consecutive days each week for 4-12 weeks with tapering to biweekly/monthly regimens, adjusted by patient response.
Complete and partial responses (CR and PR) were defined by resolution of all signs and symptoms of GvHD in every organ and by 1 grade improvement in 1 organ without any progression, respectively.
Results: Patients, HSCT, GvHD and treatment characteristics are summarized in Table.
Twenty-two (96%) and 14 (61%) children were diagnosed with aGvHD and cGvHD, respectively. Acute GvHD involved skin, gut and liver in 22 (96%), 8 (35%) and 5 (22%) cases; 4 (17%), 4 (17%) and 1 (4%) patients had a simultaneous involvement of skin+liver+gut, skin+liver and skin+gut, respectively. Grade I-II and III-IV aGvHD was observed in 13 (57%) and 9 (39%) children, respectively.
Among patients with cGvHD, involvement of skin, gut, liver, lung, mouth and eyes was detected in 11 (79%), 3 (21%), 8 (57%), 1(7%), 2 (14%) and 4 (29%) cases, respectively. Chronic GvHD was classified as mild, moderate and severe in 1 (7%), 10 (72%) and 3 (21%) patients.
ECP therapy was started in 10 (43%) patients for aGvHD and 13 (57%) for cGvHD.
Median ECP treatment duration was 3 months (1-29), with a median number of 16 ECP (2-74). ECP was associated with a new IS (MMF-Tacrolimus-Sirolimus), Jak2 inhibitor (Ruxolitinib), monoclonal antibodies (Rituximab or Basiliximab) and anti-TNFα in 11 (48%), 1 (4%), 5 (22%), in 5 (22%) patients, respectively. Overall response rates (ORR) evaluated at 1, 3 and 6 months were 78%, 83%, 74% and 67%,88%,100% for aGvHD and cGvHD respectively.
Infectious complications consisted of viral reactivations bacterial, fungal infections in 4 (17%)(1 CMV, 2 ADV, 1 ADV+EBV), 10 (43%) and 1 (4%) patients, respectively. No relapse of underlying disease occurred and only 1 (4%) child with positive minimal measurable disease (MRD) responded to tyrosine kinase inhibitor.
Median overall survival (mOS) was not correlated with grade for aGvHD [grade I-II vs III-IV; not reached (NR) vs 24 months;HR:2.6;p=0.14) or cGvHD (mild+moderate vs severe; NR vs 24 months; HR.4.6;p=0.09) while for involvement of gut in aGvHD [18 months vs NR;HR:3.26;p=0.06] and liver in cGvHD [50 months vs NR;HR:61.3;p=0.056] there was a trend with shorter mOS.
There were 12 (52%) and 11 (48%) patients with absolute lymphocyte count (ALC)<0.5 and ≥0.5 x10^3/μL, respectively; ALC ≥0.5 x10^3/μL was significantly correlated with higher 1-month ORR [100%vs64%;p=0.04] and longer mOS (NR vs 24 months; HR:0.2; p=0.02) while 3 and 6 month-ORR were not influenced (100% vs 80%; p=0.31; 100% vs 89%; p=0.44).

	n (%)
Patients,	23
Median age years (range)	8 (1-18)
Sex, male,	15 (65)
Diagnosis	
Malignancy	16 (70)
Non-malignancy	7 (30)
Donor type, n (%)	
Sibling	7 (30)
MUD	13 (57)
Haplo-identical	3 (13)
Stem cell source,	
Bone marrow	8 (35)
Peripheral blood	11 (48)
Cord blood	4 (17)
GvHD	
Acute GvHD	22 (96)
Chronic GvHD	14 (61)
GvHD prophylaxis	
CSA	22 (96)
Methotrexate	9 (39)
ATG	17 (74)
None (B-Alfa/beta depletion)	1 (4)
Cyclophosphamide	4 (29)
Acute GvHD site	
Skin	22 (96)
Liver	8 (35)
Gut	5 (22)
Acute GvHD grade,	
I-II	13 (57)
III-IV	9 (39)
Chronic GvHD sites,	
Skin	11 (79)
Liver	8 (57)
Gastro-intestinal tract	3 (21)
Lung	1 (7)
Eyes	4 (29)
Mouth	2 (14)
Chronic GvHD type	
De novo	1 (7)
Quiescent	10 (72)
Progressive	3 (21)
Chronic GvHD grade	
Mild	1 (7)
Moderate	10 (72)
Severe	3 (21)
GvHD treatment response	
1 month OR(CR/PR)	18 (78) [6 (26)/12 (52)]
3 months OR (CR/PR)	19 (83) [10 (44)/9 (39)]
6 months OR (CR/PR)	17 (74) [10 (44)/7 (30)]
GvHD treatment response (ALC stratified)	
<0.5x10^3/μL:1-3-6 months ORR	7/11 (63) 8/10 (80) 8/9 (88)
≥0.5 x10^3/μL:1-3-6 months ORR	11/11(100)-11/11(100)-10/10(100)
Median OS, months (range)	62 (1-169)

Summary/Conclusion: ECP treatment is a safe and effective treatment for aGvHD and cGVHD in our pediatric population with superior ORR, decreased infection complications, and disease relapse compared to IS combination treatment for clinical practice as reported in the literature. Prospective trials are needed to validate our observation and further investigate the correlation of ALC with outcomes

PB1791 BENDAMUSTINE IMMEDIATELY BEFORE MOBILIZATION MAY DIFFICULT THE COLLECTION OF HEMATOPOIETIC STEM CELLS IN LYMPHOMA.

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Background: Bendamustine is one of the chemotherapy agents widely used today in patients with lymphoma. Its impact on the yield of peripheral blood stem cells is not well known.
Aims: The aim of this study was to evaluate the influence of bendamustine as the last previous regimen used before hematopoietic stem cell (HSC) mobilization on HSC collected in patients with lymphoma, and to compare them with a group that has not received bendamustine.
Methods: This is a retrospective, multicenter study, which includes patients from 6 different centers in Spain. Nineteen patients who received bendamustine followed immediately by stem cell mobilization (SCM) were included. A single-center control group of consecutive patients was included, matched by histology, age and number of previous lines.
Results: Table 1 shows the characteristics of the included patients and the control group. Both groups are adequately balanced. No patients received previous lenalidomide, and none patient had previous transplant. The median number of bendamustine cycles was 3.6 (range 2-6). In most of the patients, the mobilization scheme was G-CSF 10 mg/Kg every 24 hours, although 7 patients in the bendamustine group received G-CSF 10 mg/Kg erery 12 hours, and 3 patients in each group were mobilized with G-CS plus chemotherapy. Median days of apheresis with the first attempt was 1.7 in the bendamustine group vs 1,4 in the control group, however in bendamustine group 3 patients didn't go to apheresis due to a low CD34 cell count in peripheral blood. Plerixafor was needed in 3 cases in the bendamustine group on the first attempt of mobilization, and in other 3 in the second attempt, but in any patient in the control group. In the bendamustine group, 7 patients required a second mobilization attempt (p= 0.003), 3 collected with the 2nd attempt and 1 with the 3rd, and 3 patients were unable to mobilize, none in the control group (p= 0.008). The median number of mobilized CD34 cells obtained with the first apheresis was 3.64x10^6/kg (range 0-9.6 64x10^6/kg) in the bendamustine group and 5.5x10^6/kg (range 1.1-10.4 64x10^6/kg) in the control (p = 0.003). No relationship was found between lymphoma histology, stage, doses, or number of cycles of bendamustine administered with the need of a second attempt or mobilization failure.

Patient characteristics	Benda. (n=19)	No Benda. (n=19)	p
Median age, years	53 (24-70)	50 (30-72)	*0.29*
Sex (male)	57%	68%	*0.45*
Diagnosis	FL 7	9	*0.11*
	MCL 4	2	
	HL 4	3	
	Others 4	5	
Stage at diagnosis	Localized 4	4	*0.6*
	Advanced 15	15	
BM involvement at diagnosis	47%	57%	*0.19*
Previous chemo lines, median (range)	2 (1-3)	2 (1-3)	*0.91*
Pre-apheresis leucocytes, x10^9/L	5.3 (1.6-12.3)	8.3 (1.5-20)	*0.31*
Pre-apheresis hemoglobin, g/dl	11.8 (9-12.3)	11.3 (8.9-13.1)	*0.26*

Benda. bendamustine. FL follicular lymphoma. MCL mantle cell lymphoma. HL Hodgkin lymphoma

Summary/Conclusion: Based on our results, we can conclude that bendamustine used immediately prior to mobilization could negatively affect the collection of HSC in lymphoma patients. We are expanding our series to confirm these results.

PB1792 COMPARISON OF VIABILITY AND HEMATOLOGIC RECOVERY AFTER ALLOGENEIC TRANSPLANTATIONS WITH FRESH OR FROZEN IN 5% DIMETHYLSULPHOXIDE (DMSO) HEMATOPOIETIC STEM CELLS (HSC)

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Background: In allogeneic transplantation the usual approach is to synchronize the conditioning of the patient with stem cell harvesting in order to infuse fresh cell products. The EBMT COVID-19 guidelines recommend cryopreservation of the graft to be considered if there is a concern that the donor is at risk of infection after the patient's conditioning is initiated.
Aims: We analyzed if cell viability or hematological recovery is affected in case stem cells are previously frozen.
Methods: Results from two groups of patients, each comprising of 16 males and 8 females, were analyzed. HSC from the first group were non-programmed frozen and stored at –80°C in a cryoprotective solution with a final 5% DMSO, 3.6% hydroxyethyl amylopectin (HES, Mw 450 000 Da) and 3% human serum albumin (HSA) concentrations. Platelets and plasma were removed from stem cell harvest prior to the addition of the cryoprotectant. The HSCs from the second group were transplanted without freezing. Fresh cell viability or viability after thawing (trypan blue exclusion test) and hematological recovery (neutrophils and platelets) of patients receiving cryopreserved cells or fresh cells were analyzed.
Results: The average viability was 98,67 % (SD ±1,633) for fresh HSCs and 91,63% (SD ±8,021) for cryopreserved cells. The average time for hematological recovery for the neutrophils, was 17,96(SD ±4,601) for fresh cells and 16,46 (SD ± 4,530) for frozen cells. The average time for hematological recovery for the platelets, was 15,25 (SD ± 4,590) for fresh cells and 16,26 (SD ± 6,032) for frozen cells. There was no statistically significant difference between the two groups for hematological recovery.
Summary/Conclusion: Use of fresh HSCs is the first choice for allogeneic stem cell transplantation. In cases of pandemics, such as the Covid-19 one, use of cells harvested and frozen prior to initiation of the condioning regimen is preferred. Cryopreservation of HSCs with a cryoprotective solution with low (5%) DMSO concentration and extracellular agents (hydroxyethyl amylopectin and HSA) is safe and well tolerated and gives excellent post thaw viability and post-transplant hematological recovery results.

PB1793 ESTABLISHING A TRANSPLANT SHARING PROGRAM

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Background: Autologous stem-cell transplantation (ASCT) is a prevalent therapy with firmly established efficacy and safety indices. However, to perform this procedure is necessary to transfer patients to referral centers with obvious implications for patients and their relatives. Besides, the increasing demand of autologous and allogeneic transplants may cause transplant delays.
Aims: Based on previous studies carried out in Canadian centers (Crump. Bone Marrow Transplant. 1992), an autologous transplant sharing program has been set between 3 centers in Spain to increase the availability of ASCT, avoid transplant delays and improve patient and family comfort.
Methods: Retrospective, observational and analytical study of the ASCT enrolled in this program between July 2017 and October 2019. Selected ASCT candidates for multiple myeloma (MM), lymphoma and acute myeloid leukemia (AML) from Infanta Leonor (ILH) and Nuestra Señora del Prado Hospitals (NSPH) were included after signing the informed consent. Uniform clinical protocols were used between the 3 hospitals. A clinical transplant update program for nurses and physicians was set up before the program started. The program is divided into 2 stages: First stage: Pre-transplant patient evaluation, stem-cell apheresis collection and cryopreservation as well as administration of high-dose therapy and hematopoietic stem-cell infusion were performed at 12 de Octubre hospital (H12O). Second stage: in absence of significant clinical events patients were transferred to the referring center (NSPH and ILH) on day +1 for supportive care.
Results:
Population: 12 patients (4 female, 8 male). Median age: 58 years (23-71). Diagnosis: multiple myeloma (MM): 9, acute promyelocytic leukemia (APL): 1, follicular lymphoma: 2. Conditioning regimens: Melfalan 200 (75%), CyBU (8%), BEAM (17%) All patients received standard prophylaxis with acyclovir, fluconazole and cotrimoxazole. G-CSF was allowed from day +5.

- **HSCT and engraftment:** no patient needed an additional bridge therapy because of transplant delay. All 12 patients were transferred on day +1. Median time to neutrophil (> 0.5x10^9/l) and platelets (> 20x10^9/l) engraftment was 11 days (10-14) and 12 days (11-20) respectively. Secondary graft failure: 1/12 patients.
- **Adverse events:** Febrile neutropenia was observed in all patients with microbiological documentation in 42%. Documented pathogens: bloodstream infections due to *Pseudomonas Aeruginosa*, *Enterobacter cloacae* and *Streptococcus gallolyticus*. Urinary tract infection: *Klebsiella pneumoniae*. 1 infectious colitis caused by *Campylobacter jejuni*. Engraftment syndrome was observed in 2 patients (17%) and grade ≥ 3 mucositis in 6 patients (50%). 7 patients (58%) required parenteral nutrition.
- **Results:** 11 patients were successfully discharged. 1 patient died due to secondary graft failure. Follow up was provided as needed in the referring center. Patients were reviewed in H12O on day +100 and annually therafter.

Summary/Conclusion: The sharing transplant program is a feasible and safe network that eases the access of patients to this therapy avoiding delays and prolonged stays in reference centers, with the consequent psychological and social benefit for patients and their families. Outcome and adverse events were according to literature. This is a pilot study that aims to extend to other centers within the PETHEMA group.

PB1794 ECULIZUMAB FOR TREATMENT OF TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY IN OUR CENTRE

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Background: TA-TMA is a rare complication of HSCT that remains difficult to address due its significant morbimortality, lack of standard diagnostic criteria and limited therapeutic options. It is caused by endothelial injury and complement activation. It is further more common after allo-HSCT. Higher risk is in those patients with calcineurin inhibitors (CI), high dose chemotherapy or radiation, infections,GvHD, HLA mismatch or mutations in the complement system. Gold standard for diagnosis is the biopsy of the affected organ, but in the last years laboratory and clinical criteria were also developed. Kidneys, lungs and gastrointestinal tract are the most common affected organs. First-line management includes withdrawal of the CI, treatment of co-existing infections and GvHD and hypertension control. There are no clear recommendations about optimal specific treatment. Eculizumab, though off-label, is one of the most used drugs due to the promising results reported by various studies.
Aims: To evaluate the characteristics and results of the patients diagnosed of TA-TMA and treated with eculizumab in our centre.
Methods: Case reports of patients diagnosed of TA-TMA and treated with eculizumab in our centre between 2018 and 2019.
Results: Case reports of 7 patients. Most of them women (4). Age 51.9±11.7 years old. All caucasic. Indications for transplant: lymphoma (3), MDS (2) and leukemia (2). All of them allo-HSCT with MTX and TCR as GvHD prophylaxis. 5 donors were unrelated (4 10/10, 1 9/10) and 2 were related with HLAid. Day at diagnosis: 162.8±154.4. Most common affected organs: kidneys (4) and CNS (3). All had trombocytopenia, high LDH and anemia at diagnosis; >1% squistocytes (9), proteinuria (6) and hypertension (6). Biopsy was not performed. Mutations and C5b-C9 levels were not studied. Anti-factor H antibodies and ADAMTS13 levels were normal. Almost all the patients (6) had concomitant GvHD or infection (8). First-line treatment was withdrawal of TCR and control of the co-existing conditions; 1 patient received TPE and 2 rituximab prior eculizumab. Eculizumab was initiated 9.9±9.3 days after TA-TMA diagnosis. Almost half of the patients (3) reached CR after induction therapy (6 doses), but only 2 are still alive. Most common cause of exitus was septic shock.
Summary/Conclusion: As previously reported cases, all of our patients treated with eculizumab underwent allogeneic HSCT and received a calcineurin inhibitor as prophylaxis for GVHD. Affected organs and laboratory findings also correlated with previous literature. None of them responded to withdrawal of tacrolimus and most of them had concomitant infection or GvHD, which are known adverse risk factors. Begin of the disorder in our patients was later than common and less than a half happened before day 100 after the transplant. Following protocols in our centre we used TPE or rituximab while waiting for eculizumab approval in our centre. Similar to previous reports, 71% of patients reached complete response after its initiation and those who did not often died because of infection complications. However, given the small amount of patients, further studies with alleatory design are required to recommend eculizumab as an effective therapy of TA-TMA that not respond to supportive treatment and to evaluate the associated risks and prognostic factors.

PB1795 A SINGLE SUBCUTANEOUS INJECTION OF PLERIXAFOR IN COMBINATION WITH G-CSF INCREASE THE MOBILIZATION EFFICIENCY AND FACILITATE THE CELLULAR PHENOTYPING AND FUNCTION OF HEMATOPOIETIC STEM CELLS

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Background: Plerixafor, a selective inhibitor of CXCR4, can effectively mobilize the hematopoietic stem cells (HSC) depending on the dose and the study. It demonstrated also the alteration of the cellular phenotype and function of HSC compared to that with G-CSF in the animal experiments, while rare in clinical studies.
Aims: To investigate the potential influence of Plerixafor in combination with G-CSF and G-CSF alone on the mobilization efficiency, and also the phenotype and function of mobilized stem cells.
Methods: 12 patients diagnosed with NHL and MM were prospectively analyzed. Patients were randomly divided into two groups (6 in G-CSF only (G) group and 6 in G-CSF plus Plerixafor (G+P) group). Patients in G group were receiving 10 μg/Kg of G-CSF for 5 days consecutively while in combine with a single dose of 240 μg/kg Plerixafor at day 5 in the G+P group. The end point of apheresis was to collect at least 2x10^6 CD34+ cells/kg. The cellular phenotype of mobilized peripheral blood stem cells (PBSCs) and harvest stem cells was analyzed by Flow cytometry. The gene expression profiling of CD34+ cells were analyzed by Illumina High-throughput sequencing.
Results: Plerixafor reduced the number of apheresis sessions. The mean numbers leukapheresis per person was 1.50 in G+P group and 2.17 in the G group. The median CD34+ cell counts in peripheral blood increased 7.88 times after the administration of Plerixafor in G+P group as compared prior-Plerixafor, While 1.69 times increase in G group at the time of apheresis. Compared with G-CSF alone, there was a trend towards higher level of monocytes ($p = 0.031$) and lymphocytes ($p = 0.095$) and lower level of granulocytes ($p = 0.076$) in the mobilized PBSCs in G+P group, particularly a significantly higher percentage of B cells ($p = 0.045$) and Treg cells ($p = 0.079$). The gene expression profiling involved in cell proliferation ($p<0.0001$) and hematopoiesis($p<0.0001$) were significantly increased in G+P group, which associated with better engraftment.
Summary/Conclusion: A single dose of Plerixafor in combination with G-CSF increase the mobilization efficiency and facilitate the cellular phenotyping and function of hematopoietic stem cells compared to that with G-CSF alone, which may promote a superior and long-term engraftment.

PB1796 OUTCOME OF HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH A DONOR AND RECIPIENT WITH SARS-COV2 INFECTION.

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Background: COVID-19 disease is an infectious disease caused by the most recently discovered SARS Coronavirus 2 (SARS- CoV-2). This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. The WHO classified COVID-19 a pandemic on March 11.[3] Although elderly and people with comorbidities patients are the most affected by the severe manifestations of the disease, patients undergoing hematopoietic stem cell transplantation (HCT) are a group of patients with special immunocompromised situation and could have potentially devastating outcome if they infected with SARS-CoV-2. Although the majority of infected patients have mild disease, critical illness occurs in about 6.1% of affected patients.[4] People at risk of severe outcome and death include those older than 60 years and those with comorbid disease states such as hypertension (HTN), chronic respiratory disease, chronic kidney disease

(CKD), cardiovascular disease, diabetes mellitus (DM), cancer and immunosuppressed patients [5]. Data emerging about cancer patients show that these patients have an increased risk of complications and intensive care unit (ICU) admissions.[6] Hematopoietic cell transplant (HCT) patients are severely immune-compromised and their course with COVID-19 disease is expected to be complicated. The patient that is reported here developed SARS-CoV-2 post HCT who received stem cells from donor diagnosed with SARS-CoV2 by Nasopharyngeal swab on the day of the HCT. It is possible that this might be one of the rarest cases during the pandemic.
Aims: case report
Methods: case report
Results: case report
Summary/Conclusion: During this COVID-19 pandemic era, any patient for whom an allogeneic transplant is planned should be tested with nasopharyngeal swab for SARS-CoV-2 infection especially prior to hospital admission.If the result for SARS-CoV-2 infection proves negative, the transplant procedure should be pursued as planned. Donors with SARS-CoV-2 detected in a respiratory sample are considered ineligible to donate. However, an ineligible donor may be collected in certain situations where delay is not possible or unavoidable.
Post-transplant care in HCT recipients with COVID-19 infection is feasible in regular transplant units, provided the patient does not present with respiratory symptoms or failure. Early and repeated testing for SARS-CoV-2 in post-transplant patients with concomitant infection mitigation strategies should be considered in patients who develop fever, respiratory symptoms and/or gastrointestinal symptoms to control the spread of COVID-19 both in patients and healthcare workers in hospital environments.
Clinical decision making and team work is crucial for patient survival in the COVID-19 pandemic era.
This case of an asymptomatic SARS-CoV-2 positive recipient, stem cell transplantation was pursued as planned from an asymptomatic SARS-CoV-2 positive stem cell donor with no significant adverse CRS or infection-related outcome in the recipient.

PB1797 LOW-DOSE PTCY PLUS HAPLO-INDENTICAL TRANSPLANTATION A FEASIBLE AND SAFE CONSOLIDATION STRATEGY FOR CAR T-CELL SALVAGED REFRACTORY/ RELAPSED B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA------ THREE CASE REPORT

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Background: Although chimeric antigen receptor (CAR) T-cell is highly-effective in remission induction for relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL), a substantial proportion of responded patients will eventually relapse. Haplo-identical allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered one of subsequent consolidation options post CAR T-cell salvage, especially for those without marched related or unrelated donors. However, haplo-identical HSCT is usually associated with higher rate of graft-versus-host-disease (GVHD), so how to reduce the rates and degree of GVHD which maintain graft-versus-leukemia capacity, is an active field of exploration in this setting. Post-transplant cyclophosphomide (PTCY) was showed to be promising GVHD prophylaxis for allo-HSCT, and recently there were several reports showed low-dose PTCT could achieve similar outcome.
Aims: CAR T-cell has been approved for the salvage for refractory/ relapsed (R/R) acute lymphoblastic leukemia, and a proportion of salvaged ALL patients can further consolidated by allo-HSCT. Here we reported three cases of CD19-targeted CAR T-cell salvaged R/R-ALL patients who intended for haplo-identical allo-HSCT.
Methods: There are three cases of R/R B-ALL in our institute, in whom two of them are Philadelphia chromosome-positive (ph-positive) B-ALL patients. All of them have already identified related haplo-identical donors prior to CAR-T salvage. Once patient achieved complete remission post CAR-T salvage, then proceeded to haplo-HSCT as soon as possible. Unmanipulated mobilized peripheral blood stem cell (MPBSC) from related haplo-identical donor was employed as a stem cell source, and GIAC protocol plus low-dose PTCY was employed for haplo-identical allo-HSCT.
Results: All of three cases achieved CR post CAR T-cell salvage. During the preparation of HSCT, one case ph-positive ALL relapsed and did not proceed to allo-HSCT, and the other two cases successfully proceeded to haplo-identical allo-HSCT by GIAC protocol plus low-dose PTCY. Both patients had a rapid graft engraftment and achieved complete chimerism (CC) after MPBSC infusion, one case had grade II aGVHD which resolved rapidly with mono-steroid treatment. Both of them are leukemia-free and GVHD-free at the last follow-up.
Summary/Conclusion: Low-dose PTCY plus GIAC protocol with MPBSC is a feasible consolidation for CAR T-cell salvaged B-ALL patients, however, for patients with rapid relapse post CAR T-cell salvage, it is still an unmet clinical need.

PB1798 DONOR LYMPHOCYTE INFUSION (DLI). A STRATEGY TO PREVENT OR TREAT RELAPSE FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION. ONE SINGLE CENTER EXPERIENCE.

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Background: Despite improvements in stem cell transplantation of patients with acute leukemia, relapse is still one of the main causes of mortality. DLI is one of the strategies used in high risk patients, allowing us to rescue 30-55% of the patients. It also reduces risk 2.3 times when it is used as a preemptive strategy.
Aims: Analyse our experience in the use of DLI as a prophylaxis, preemptive or treatment strategy.
Methods: A retrospective cohort study was performed among adult recipients of allogeneic HSCT between 2016 and 2019 who subsequently underwent DLI as a prophylaxis, preemptive or treatment strategy.
Results: A total of 10 patients were included. The median age was 52 (24-69), 70% were women (7) and 30% men (3). Underlying diseases: 7 Acute Myeloid Leukemia (70%), 2 Acute Lymphoid Leukemia (20%) and 1 Myelodysplastic Syndrome (10%). Patients received ASCT from related HLA-identical (10%), haploidentical (80%) and unrelated donors (10%). Disease status prior HSCT: 2 persistent disease (20%), 7 complete response (CR), 4 of them presented negative minimal residual disease (MRD) and the other 3 had positive MRD (molecular, cytogenetics or immunophenotypic markers). 1 patient with MDS had not received any previous treatment. At day +30: 90% presented CR, 4 of them complete chimerism (CC) and the other 6 mixed chimerism (MC). The patient with MDS presented persistent disease. One of the patients underwent a 2nd alloHSCT and received DLI after both transplants.
The median time for immunesuppressive treatment's interruption was 91 days (45-147). The median time to DLI indication was 137 days (114-475). The indications for DLI were: 4 (36.4%) as treatment (3 relapse diseases and 1 refractory), 4 (34.4%) prophylaxis because of high risk disease and 3 (27.2%) preemptive because of positive MRD or CC. The median DLI dose was 3 (1-4).
In the treatment group, 75% received DLI in combination with Azacitidine (1 of them in combination with Sorafenib) and 1 in monotherapy. In the prophylaxis group, 50% received it in combination with azacitidine and sorafenib or sorafenib only and the other 50% in monotherapy. In the preemptive group, 67% in combination with Azacitidine and 33% in monotherapy.
Related to response after DLI, in the treatment group: 75% refractory, 25% CR with positive MRD and MC. In prophylaxis group: 75% CR, negative MDR and CC, 25% CR and MC. In preemptive group: 67% CR, negative MRD and CC, 33% negative MRD and MC.
Therefore, 45.4% of all patients achieved CR, negative MRD and CC and the other 27.3% presented refractoriness.
GVHD rate was 50%. After a median time of follow-up of 4 years (1-4), 40% are still in remission. 4 patients died, 2 of them due to relapse (20%) and the other two because of infections
Summary/Conclusion: DLI represents an useful and safe preemptive and prophylactic strategy in patients with high risk of relapse. We achieved remission in 30-40% of patients. On the other hand, there was a limited response in patients with treatment indication, being necessary to individualize and to associate targeted therapies. In most of these cases,

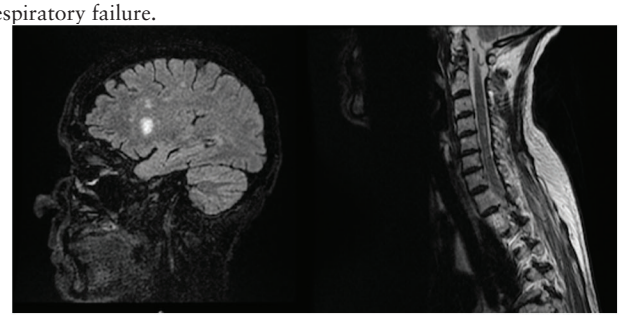
it has been necessary the use of intensive therapies with a decrease in survival.

PB1799 CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT OF GRAFT VERSUS HOST DISEASE (GVHD) AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Background: CNS-GvHD remains a very uncommon entity after allo-HSCT and should be considered in absence of other diseases that justify neurological symptoms. CNS-GvHD criteria were described at Consensus Conference on Clinical Practice in chronic GvHD in 2010.
Aims: To describe a case of CNS-GvHD, a very rare entity still under-reported. We believe all cases should be reported to properly detect and treat this entity.
Methods: A 61-year-old woman diagnosed of mixed phenotype acute myeloid leukemia (AML) in June-20. After chemotherapy, on first remission MRD+, she underwent haploidentical HSCT, after fludarabine and busulfan conditioning; GvHD prophylaxis with cyclophosphamide, cyclosporine A (CsA) and mycophenolate mofetil (MMF). Acute skin GvHD grade IV on day +17, treated with systemic steroids with complete response. On day +59 she was admitted to emergency room with progressive inferior limbs motor deficit and hyperalgesia, followed by confusion, somnolence and visual hallucinations. No fever; adequate adherence to acyclovir, posaconazole and cotrimoxazole prophylaxis. Physical examination: decreased strength in lower limbs, dysesthetic alterations and vivid myotatic reflexes.
Laboratory findings: no toxic-metabolic abnormalities, normal B12, folic acid and CK levels. Autoimmunity: negative. No schistocytes in blood smear. Nevertheless, CsA was discontinued and MMF started. Cerebrospinal fluid (CSF): no pleocytosis, erythrocytes, nor oligoclonal bands; slight protein elevation (62.1 mg/dL). Microbiological analysis: CMV reactivation in blood sample and positive microarray for HHV-7 in CSF (negative in blood sample). Clinical relevance of HHV-7 was evaluated by neurologists, discarding it as the cause of the picture. Both viruses were covered with foscarnet since admittance, completing 4 weeks treatment. No evidence of EBV, HSV, VZV, HHV-6, HHV-8, polyomavirus, enterovirus, coxackie, toxoplasma, bacterial or fungal infection in CSF. Broad spectrum antibiotics and amphotericin B were also started. AML relapse was ruled out with marrow full donor chimerism and normal immunophenotype in CSF. Electromyography: motor polyneuropathy without demyelination. Cervical spine MRI: hyperintense lesion in T2 at C4-C5 affecting posterior cords; brain MRI: multiple hyperintense lesions in T2 affecting both hemispheres.
During hospitalization she developed gastrointestinal GvHD grade II, so we started methylprednisolone, with partial response. Simultaneously, neurological picture deteriorated with progressively impaired motor function, bradypsychia and dysphagia. New brain MRI showed lesions exacerbation.
Results: Methylprednisolone was substituted for dexamethasone, adding immunoglobulins, with improvement of consciousness, language and dysphagia within 48h; more discreet improvement of motor impairment. Dexamethasone was tapered with sustained neurological effect. A month later, under posaconazole prophylaxis, she developed fungal pneumonia without response to amphotericin B and isavuconazole and died due to respiratory failure.



Summary/Conclusion: Neurological complications after allo-HSCT present a wide variety of symptoms, associating high morbi-mortality. Our case exhibits CNS and peripheral nervous symptoms, not classifiable in any entity, with infectious, toxic or vascular etiologies as well as AML relapse discarded. Our patient met mandatory criteria for CNS-GvHD, with neurological worsening concurring in time with exacerbation of intestinal GvHD, and 3 facultative criteria, showing a rapid symptoms improvement after starting dexamethasone, so we assumed it as a neurological manifestation of GvHD.

Stem cell transplantation - Experimental

PB1800 EFFECT OF THE DURATION OF CRYOPRESERVATION ON THE VIABILITY AND PROLIFERATIVE POTENTIAL OF HSCS DURING AUTOGRAFT HARVESTING IN PATIENTS WITH MM

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Background: Autotransplantation of hematopoietic stem cells (HSC) (AutoHSCT) is the standard of therapy for young and middle-aged patients with multiple myeloma (MM) and is performed in order to restore hematopoiesis. Mandatory step AutoHSCT is the cryopreservation of HSC on the time required for high-dose chemotherapy or to re-AutoHSCT. The quality of the autograft depends on the speed of solving postsimulation aplasia of the bone marrow. Markers of autograft quality are the number of CD34+cells and the proliferative potential of HSCs, which can be judged by their colony-forming ability (CFA). When evaluating CFA, three indicators are taken into account separately: the number of granulocyte-macrophage colony-forming units (CFU-GM), erythroid burst-forming units (BFU-E), and total colony-forming units (CFU-total).
Aims: To evaluate the viability and proliferative potential of HSCs prepared for AutoHSCT in MM patients by the number of CD34+cells and CFA HSCs, depending on the timing of their cryopreservation.
Methods: CFA HSCs were evaluated based on the results of 12-14 days of cell culture in MethoCult H4435. CD34+cells were determined on a Cytomics FC500 flow laser cytofluorometer using a set of Stem Kit Reagents.
A retrospective analysis of autograft parameters during harvesting and subsequent transplantation, depending on the timing of cell cryopreservation, was performed in MM patients aged 32 to 68 years. The duration of cryopreservation ranged from 2 weeks to 1.5 years, with a median of 6 months. Depending on the shelf life, patients were divided into 3 groups: group 1 - shelf life from 1 to 5.9 months (n=83); group 2 - from 6 to 10 months (n=34); and group 3 - ≥ 10 months (n=10). The data of 91 MM patients were analyzed, the total number of analyzed cases was 127.
Results: The number of total CFU in group 1 is reduced to 66% of the original, in the second group to 60%, in group 3 to 44%. In groups 1 and 2, there was a proportional decrease in both CFU-GM and BFU-E. However, in group 3, with cryopreservation periods of more than 10 months, a statistically significant decrease in the number of BFU-E was shown; p=0.01. In the same group, patients with longer platelet recovery periods were noted.
The number of CD34+cells after cryopreservation is reduced to 77 % in group 1, 39% in group 2 and 49% in group 3. No statistically significant correlations with the shelf life were found, probably due to the wide range of values in all groups, but a significant decrease in the number of CD34+cells was shown. Even in group 1 with a minimum shelf life, the number of cells decreased by almost a third. The CFA results obtained are comparable to the reduced number of CD34+cells in the samples.
Summary/Conclusion: The data obtained by us indicate a reduction in the number of CD34+cells and a decrease in their proliferative potential according to the CFA data already in the group with a minimum shelf life. The lowest values were found in the group with a shelf life of more than 10 months. The results of the study show the expediency of earlier preparation of the autograft, eliminating the possibility of a negative impact of previous induction therapy, in order to obtain a cell suspension with the maximum content of HSC, especially when planning tandem or repeated AutoHSCT in patients with newly diagnosed MM.

PB1801 CYCLOSPORINE CAN INHIBIT INTESTINAL AGVHD BY REGULATING MITOCHONDRIAL APOPTOSIS

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Background: Acute graft-versus-host disease (aGVHD) limits the success rate of allogeneic hematopoietic stem cell transplantation (allo HSCT),which is a major complication and remains a significant cause of morbidity and mortality.Cyclosporine can inhibit the induction of MPTP by Ca2 + and ROS, protect the integrity of mitochondrial cristae junction and intima, and reduce the level of ROS and the formation of autophagy.It can regulate the expression of Bax and Bcl-2, reduce the oxidative damage and apoptosis induced by oxidative stress (OS).Low plasma CsA concentrations early following allo-HSCT is associated with an increased risk of developing aGVHD.Conversely, Higher therapeutic CsA levels early post transplantation reduce risk of aGVHD and improves survival.In the absence of specific drugs, the correct understanding and optimization of cyclosporine treatment has important clinical significance for the prevention and treatment of aGVHD.
Aims: To investigate the therapeutic effects of cyclosporine on gastrointestinal aGVHD and the regulatory mechanisms at the level of abnormal mitochondrial apoptosis in the intestine.
Methods: After were irradiated by 60co X rays,CB6F1 mice were transplated by using the mononuclear cells suspension (bone marrow + spleen) of Balb/c mice infused into the tail vein.The model group was administrated with 0.9% sodium chloride intragastrically,and the treatment group was administrated with intragastrically 5mg/kg cyclosporine. After 28 days, the clinical score of aGVHD and the pathological inflammation score of small intestinal mucosal were evaluated,respectively.The small intestinal mucosal mitochondria were observed by using transmission electron microscopy (TEM). Western blotting and immunofluorescence were used to detect the expression of apoptosis related proteins (bcl2 and bax)in two groups.
Results: 1. The differences of clinical aGVHD scores between the two groups are significant(P<0.01)(Fig 1 C).
2. The treatment effect of cyclosporine on intestinal aGVHD. The observation of HE staining showed that, compared with blank group, intestine tissue of the mice in treated group were improved (Fig 1 A and B), which indicated the treatment effect of cyclosporine in improving intestinal aGVHD is obvious. In addition, the pathological inflammation score between the two groups differed statistically significantly.(P<0.1)(Fig 1 G).
3. The expression levels of mitochondrial apoptosis related proteins tested by immunofluorescence. Found that compared with the blank group, cyclosporine not only can increase the intestinal Bcl2 expression level, but also decrease the Bax expression level.(Fig 1 D).
5. Bcl2 and Bax level tested by western blotting. Cyclosporine corrected the aberrant levels of apoptotic proteins, increased Bcl2 expression and decreased Bax expression levels after transplantation (Fig 1 K), all of which were statistically significant(P<0.01) (Fig 1 H and I).There was a significant difference in the relative expression levels, i.e., BCL2 / Bax of the two groups. (P<0.01)(Fig 1 J).
4. Mitochondrial structure was observation by TEM. After transplantation, mitochondrial structure swelling, broken membrane structure. However, in the treated group,mitochondria structure was relatively intact.(Fig 1 E and F).

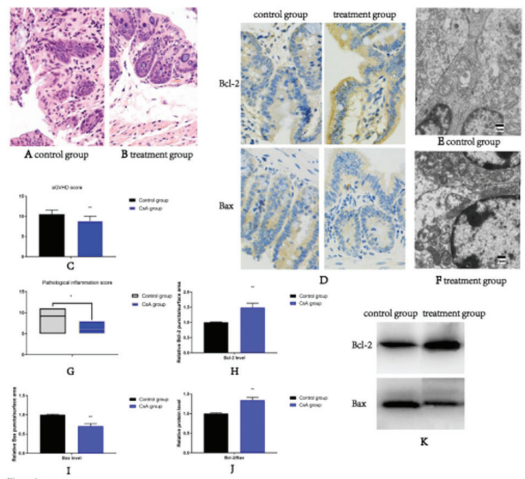


Figure 1
A,B:Small bowel pathological observation of mice in each group (×200).
C:The expression of apoptosis related proteins in small intestinal mitochondria was detected by immunofluorescence(×400).
E,F:Cell structure was observed by transmission electron microscope (×1650).

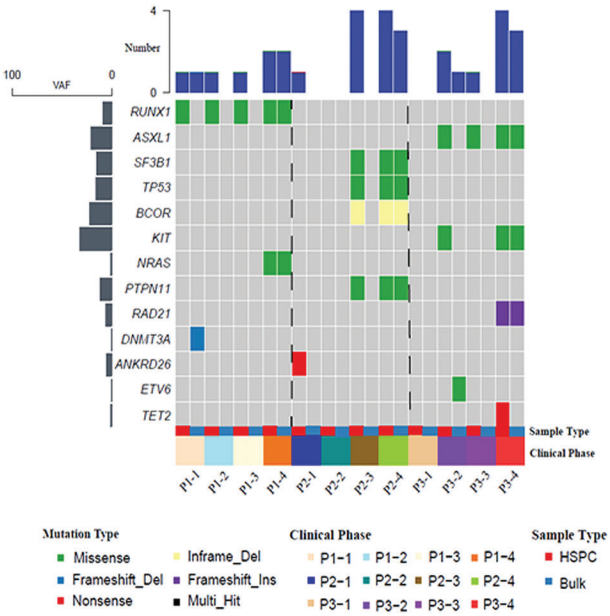
Summary/Conclusion: Cyclosporine can reduce apoptosis and protect intestinal mucosal barrier by inhibiting the activity of T lymphocytes, protecting the structure and function of the mitochondrial membrane, thereby reducing the incidence of intestinal aGVHD after transplantation.

PB1802 NEXT-GENERATION SEQUENCING-DEFINED MINIMAL RESIDUAL DISEASE AT THE STEM/PROGENITOR CELL LEVEL PREDICT POST-TRANSPLANTATION RELAPSE IN ACUTE MYELOID LEUKEMIA

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Background: Allogeneic hematopoietic cell transplantation (allo-HSCT) is the most effective curative therapy in patients with acute myeloid leukemia (AML). However, relapse from the original disease is still one of the main causes of treatment failure. Thus high-sensitivity methods to detect minimal residual disease (MRD) in AML after transplantation are crucial. Single cell sequencing indicated that higher clonal diversity at the stem/progenitor cell level (HSPC) in AML, but the significance of MRD monitoring at the HSPC level is unclear.
Aims: To evaluate the value of MRD monitoring based on the stem cell level in predicting post-transplantation relapse.
Methods: DNA was extracted from cells collected from bone marrow (BM) samples. Genetic profiling included the targeted sequencing of 37 genes, which had been selected based on their known or potential involvement in the pathogenesis of acute myelogenous leukemia. Multiplexed libraries were sequenced with Illumina NovaSeq6000 and average raw sequencing depth on target per sample ≥10000×. The mutation variant allele frequency (VAF) ≥1% was considered as MRD positive criterion.
Results: We performed next-generation sequencing (NGS) to profile the mutation status in three AML patients (P1-P3) with relapse after transplantation. For each patient, two BM samples including bulk BM and CD34+ HSPC were collected at post-HSCT at day30 day60 day90 and relapse, respectively. Compared to bulk BM and multidimensional flow cytometry (MFC), MRD monitoring based on the HSPC level is likely more sensitive to predict relapse after transplantation (Figure 1). One of the patients was detectable as MRD positive at post-HSCT day30. Moreover, we observed that some hotspot mutations might be detected only in the HSPC sample.



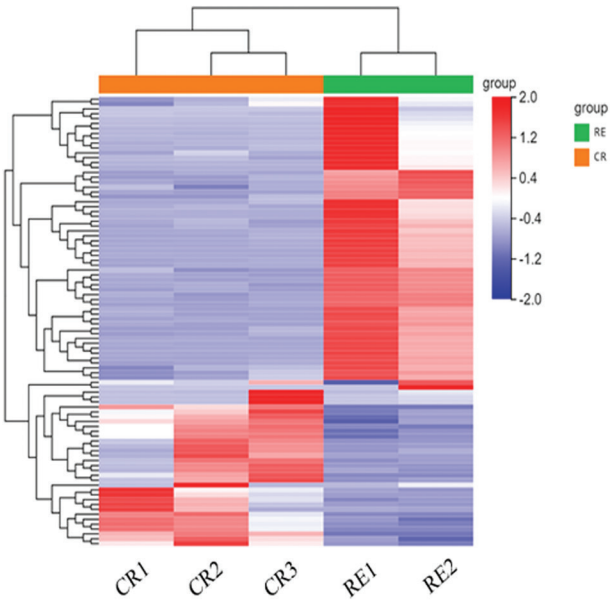
Summary/Conclusion: Our study unveiled that phenotypically normal CD34+ HSPC possess some genetic abnormalities in cases with negative MCF MRD. NGS-defined MRD at the HSPC level in AML patients is feasible and can predict post-transplantation relapse much earlier.

PB1803 THE STUDY OF MICRORNAS IN CD34+ HSPCS FROM AML PATIENTS WITH RELAPSE AFTER ALLOGENEIC TRANSPLANTATION

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Background: Relapse of the original disease is a major cause of death after allogeneic hematopoietic cell transplantation for acute myeloid leukemia (AML). It has been established that AML is driven by a subpopulation of rare cells with intrinsically defined stem cell properties. However, the mechanism of post-transplantation relapses at the stem cell level is not clear.
Aims: To describe role of microRNA (miRNA) in CD34+ hematopoietic stem/progenitor cells (HSPCs) from AML patients with relapse after allogeneic transplantation.
Methods: Bone marrow samples from 5 AML patients who received allogeneic hematopoietic cell transplantation, of which 2 patients relapsed after transplantation (RE) and 3 patients remained complete remission (CR). CD34+ HSPCs were sorted by CD34+ microbeads and analyzed by RNA-sequencing on an Illumina Hiseq 2500 platform to characterized all of miRNAs. Gene expression levels between groups of CD34+ HSPCs were compared with degeR to find out differential miRNAs. We performed the GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analysis for the target gene candidates of differential miRNAs to predict the potential function of relapsed specific microRNAs. A value of P<0.05 (2-sided) was considered to be statistically significant.
Results: Compared with CR patients, we found that 61 miRNA were upregulated and 31 are significantly downregulated. The analysis showed the total of 92 miRNAs to be signifcantly altered as shown in the heatmap in Figure 1. The target gene candidates of differential miRNAs were enriched in numerous Go biological process including: immune system process, cell cycle, apoptotic process, protein transport, intracellular signal transduction, protein phosphorylation and so on. The top 10 signifcantly (P< 0.05) affected pathways identified by GO analysis.



Summary/Conclusion: The present study proved that miRNAs play an important role in AML patients with relapse after transplantation. The result may improved understanding of the special molecular alterations in relapse after transplantation and may provide potential targets for future clinical applications.

Thalassemias

PB1804 HEMOGLOBINOPATHIES AND COVID-19: THE EXPERIENCE OF A CENTER IN NORTHERN GREECE

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Background: Healthcare systems around the globe are still facing the evolving threat of the corovavirus-19 (COVID-19) pandemic. Hemoglobinopathies include a group of genetic disorders, with the two main pillars being thalassemias and sickle cell disease (SCD). Due to their immunocompromised status, such patients (pts) have been protected as extremely vulnerable to COVID-19 infection. Despite limited data in literature, recent reports present conflicting results
Aims: We prospectively investigated the incidence and outcomes of COVID-19 in pts with hemoglobinopathies and correlated them to their coexistent comorbidities.
Methods: We studied pts with different hemoglobinopathies, consecutively monitored at our Center, who were infected with SARS-COV 2 during the first and second "waves" of the pandemic in Greece (March - December 2020). The following factors were studied: age, employment, blood type, liver and heart hemosiderosis, splenectomy, concomitant endocrine disorders and transfusion dependency.
Results: Among 250 pts regularly followed-up at our Center (7 with HbH hemoglobinopathy 150 with Thalassemia major, 53 with SCD and 41 with non transfusion dependent thalassemia), 9 (3.4%) were infected with COVID-19 (5 male: 4 female). COVID-19 pts' age range was 20-46 (median 35.1). During the same time period the prevalence of COVID-19 infection in Greece's general population, regarding the same age groups, was 1.89%. Two pts had HbH hemoglobinopathy, 1 Sickle Cell Disease (SCD), and 6 transfusion dependent β-thalassemia (TDT). In total, 7/9 pts were transfusion dependent (TD). Blood type was A+ in 55.5%, B+ in 11.1%, AB+ in 11.1% and O+ in 22.2% of pts. The range of ferritin levels at the time of infection was 180-992 ng/ml (median 434). Seven out of 9 pts had median MRI T2* liver iron concentration (LIC) of 1.696 g/dw and median MRIT2* of the heart 33.7 tms. However, their ejection fracture (EF) was >50% at all cases. Two pts were splenectomized and 1 had functional asplenia. Only 2 pts had concomitant endocrine disorders (hypothyroidism and hypogonadism). These pts were on hormone replacement therapy. All TD pts were on iron chelation therapy (5 on deferasirox and 1 on both deroxamine and deferiprone). Three pts were healthcare employees.Six out of 9 pts required hospitalization for a median time of 5.8 days (1 with HbH, 1 with SCD during crisis and 4 with TDT), but no one required Intensive Care Unit (ICU) monitoring, intubation or intensive ventilation support. All pts presented with fever (3 with febrile neutropenia), while 2 TDT pts had ground-glass opacities. All hospitalized pts received wide-range antibiotics plus azithromycin (as did 1 TDT pt who stayed at home). Heparin was administered in the SCD pt and in 1 of the TDT pts. One pt with HbH also received hydroxychloroquine and 1 with TDT dexamethasone. At the end of follow-up (median of 3.5 months, range 1.2-4.2), all pts are alive. On the contrary, mortality of the general Greek population in the same age group and time period was 1%.
Summary/Conclusion: Our real-world data suggest that the prevalence of COVID-19 in pts with hemoglobinopathies is slightly increased compared to the general population. Considering that these pts are more strictly monitored, we could hypothesize that self-applied precautions are effective. No death or severe pulmonary disease requiring intubation was observed. In compliance with recent data, our findings do not indicate increased mortality and morbidity of COVID-19 in pts with hemoglobinopathies, followed in a Specialized Center. However, more data are needed for a safe conclusion to be extracted.

PB1805 ENERGIZE AND ENERGIZE-T: TWO PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES OF MITAPIVAT IN ADULTS WITH NON–TRANSFUSION-DEPENDENT OR TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

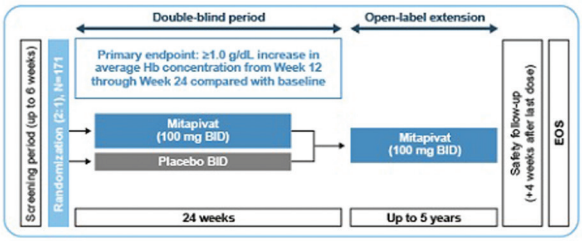
K. H. Kuo [1,*], D. M. Layton [2], H. Al-Samkari [3], A. Kattamis [4], S. Sheth [5], A. Taher [6], V. Viprakasit [7], C. X. Chamberlain [8], L. Czapla [8], S. Gheuens [8], L. Jiang [8], M. Lynch [8], B. Tong [8], K. Uhlig [8], M. D. Cappellini [9]

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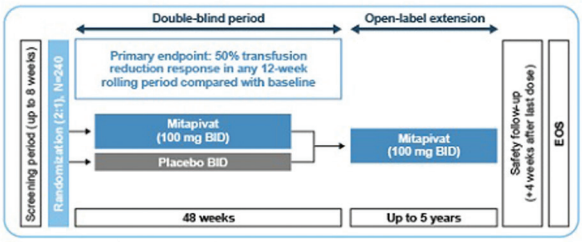
States, [4]First Department of Pediatrics, National and Kapodistrian University of Athens BR, Athens, Greece, [5]Weill Cornell Medical College, New York, NY, United States, [6]American University of Beirut, Beirut, Lebanon, [7]Siriraj Hospital, Mahidol University, Bangkok, Thailand, [8]Agios Pharmaceuticals, Inc., Cambridge, MA, United States, [9]University of Milan, Milan, Italy

Background: Thalassemias are characterized by imbalanced globin-chain production resulting in excess α- or β-globin precipitation, hemolytic anemia, and ineffective erythropoiesis. Adenosine triphosphate (ATP) levels are reduced in thalassemic red blood cells (RBCs), despite increased energy demands. Mitapivat (AG-348) is an oral activator of RBC pyruvate kinase (PKR), a glycolytic enzyme that regulates ATP production. In a phase 2 study of patients (pts) with α- or β-non–transfusion-dependent thalassemia (NTDT), twice-daily (BID) dosing with mitapivat increased hemoglobin (Hb) levels by ≥1.0 g/dL in 80% of pts, supporting the broadening of mitapivat's development in thalassemia.
Aims: To report the study designs of ENERGIZE (EudraCT: 2021-000211-23) and ENERGIZE-T (EudraCT: 2021-000212-34), two phase 3 trials to assess the efficacy and safety of mitapivat in adults with α- or β-NTDT or transfusion-dependent thalassemia (TDT), respectively.
Methods: Both studies are phase 3, multicenter, randomized, double-blind, placebo-controlled trials. In ENERGIZE, approximately 171 eligible adults with NTDT will be randomized (2:1) to receive 100 mg mitapivat BID or placebo for 24 weeks (wks). Upon completion, eligible pts can transition to a 5-year, open-label extension. Key inclusion criteria: documented diagnosis of thalassemia (β-thalassemia ± α-globin mutations, Hb E β-thalassemia, or α-thalassemia [Hb H disease]), Hb concentration ≤10.0 g/dL, and NTDT defined as ≤5 RBC units during the 24-wk period before randomization and no RBC transfusion ≤8 wks prior. The primary endpoint is an Hb response defined as a ≥1.0 g/dL increase in average Hb concentration from Wk 12 through 24 compared with baseline (BL). Secondary endpoints include pt-reported outcomes, changes in Hb, markers of hemolysis and erythropoiesis, and safety. In ENERGIZE-T, approximately 240 eligible adults with TDT will be randomized (2:1) to receive 100 mg mitapivat BID or placebo for 48 wks. Upon completion, eligible pts can transition to a 5-year, open-label extension. Key inclusion criteria: documented diagnosis of thalassemia (same genotypes as detailed for the ENERGIZE study), and TDT defined as 6–20 RBC units transfused and no transfusion-free period ≥6 wks during the 24 wks before randomization. The primary endpoint is a transfusion reduction response, defined as a ≥50% reduction in transfused RBC units with a reduction of ≥2 units of transfused RBCs in any consecutive 12-wk period through Wk 48 compared with BL. Secondary endpoints include additional measures of transfusion burden, changes in iron markers, and safety.
Results: Not yet available.

ENERGIZE: Phase 3 randomized clinical trial for adults with α- or β-non–transfusion-dependent thalassemia



ENERGIZE-T: Phase 3 randomized clinical trial for adults with α- or β-transfusion-dependent thalassemia



BID=twice daily; EOS=end of study; Hb=hemoglobin.

Summary/Conclusion: ENERGIZE and ENERGIZE-T are the first pivotal studies to assess a potential treatment across a broad spectrum of pts with thalassemia (ie, pts with TDT and NTDT; α- and β-thalassemias). This phase 3 program will evaluate the efficacy and safety of mitapivat, a novel, first-in-class oral activator of PKR. Both studies will start enrollment in 2021.

PB1806 DESIGN AND DEVELOPMENT OF A MACHINE LEARNING-BASED PREDICTIVE MODELLING TOOL TO ACCURATELY PREDICT THALASSEMIA CARRIER STATE USING FULL BLOOD COUNT INDICES AND HAEMOGLOBIN VARIANTS

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Background: An effective screening programme to detect Thalassemia carriers is a vital part of Thalassemia prevention. There are many challenges to an effective screening programme, especially in low-resource settings. Machine learning (ML) has been instrumentalized in a range of prognostic and diagnostic medical tasks to overcome domain-specific and technical challenges. This study attempted to apply an ML-based tool to Thalassemia screening to accurately predict the Alpha thalassemia carrier state from a simple blood test. An effective screening programme to detect Thalassemia carriers is a vital part of Thalassemia prevention. There are many challenges to an effective screening programme,especially in low-resource settings. Considering alpha-thalassemia, genetic testing is needed for a confirmatory diagnosis of a carrier, which is expensive and not widely available. In this era of big data and exponentially increasing computing power, machine learning (ML) is being increasingly used in a range of prognostic and diagnostic medical tasks to overcome domain-specific challenges.
Aims: This study attempted to apply modern machine learning algorithms to alpha-thalassemia screening data, and develop a cost-effective and time-saving ML tool which can accurately predict the alpha thalassemia carrier state using simple blood tests. This tool can then be used in circumstances where there are constraints to genetic testing, and can act as a complimentary diagnostic tool which can identify high risk individuals who need to undergo confirmatory genetic testing.
Methods: Ethical clearance was obtained from the Ethics Review Committee of Postgraduate Institute of Medicine, University of Colombo. A database of 288 cases from the Human Genetics Unit (HGU) of the Faculty of Medicine, Colombo was used to train and test the ML tool. Three different models were formulated and tested on a validation set. Random Forest Algorithm, and an Artificial Neural Network (ANN) with four hidden layers were used to train each of the models. The relative performances of the algorithms on each model were compared in terms of overall accuracy and F1 score, which is a measure of sensitivity and positive predictive value.
Results: Dataset included predominantly alpha-thalassemia carriers (n = 149), but also individuals with normal red cell indices (n = 55), iron deficiency anaemia (n = 21) and beta-thalassemia carriers (n = 17). Model 1 was trained to differentiate between alpha-thalassemia carriers and normal individuals, and the Random Forest outperformed the ANN with an Accuracy of 93.5% and an F1 score of 87.5%. Model 2 differentiated between alpha-thalassemia silent carriers and alpha-thalassemia traits, and the Random Forest again showed a superior performance with an accuracy of 88.8% and an F1 score of 86.3%. Both models showed a satisfactory performance in all categories in the confusion matrix which plotted the true labels against predicted labels. Model 3 was developed to differentiate between thalassemia carriers, iron deficiency and normal individuals. Although ANN showed a superior performance with an overall accuracy and F1 score of 83.3% on model 3, the model only correctly classified one of the three iron deficiency cases in the validation set.

Summary of the Results obtained in the three predictive models

Model	Input Variables (Predictors)	Output (Target) Categories	Performance of the best model on test set	Most Important Feature (via Decision Tree visualisation)
Differentiating alpha thalassemia carriers from 'normal' individuals (Model 1)	Full Blood Count MCV, MCH, MCHC, Hb, PCV Haemoglobin Variants HbA	• Alpha thalassemia carrier • 'Normal' Individuals	*Random Forest :* Accuracy – 93.5% F1 score – 87.5%	MCV ≤ 80fL
Differentiating between two types of alpha thalassemia carriers (Model 2)	Full Blood Count MCV, MCH Hb, PCV, RDW, RBC Haemoglobin Variants HbA, HbA2	• Alpha trait • Alpha Silent carrier • 'Normal' Individuals	*Random Forest :* Accuracy – 88.88% F1 score – 86.36%	MCH ≤ 21pg
Differentiating between thalassemia, iron deficiency and 'normal' individuals(Model 3)	Full Blood Count MCV, MCH, MCHC, Hb, PCV Haemoglobin Variants HbA	• Thalassemia • Iron Deficiency • 'Normal' Individuals	*Neural Network:* Accuracy – 83.33% F1 score – 83.3%	MCV ≤ 80fL

Summary/Conclusion: Model 1 and 2 showed satisfactory performance, while model 3 did not. Model 1 and 2 can be combined to a diagnostic tool to identify alpha-thalassemia carrier states. The tool could be used in situations where there are constraints to genetic testing after being validated prospectively with a larger dataset.

PB1807 RETROSPECTIVE ANALYSIS OF OGTT IN PATIENTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA DURING THEIR SECOND DECADE OF LIFE

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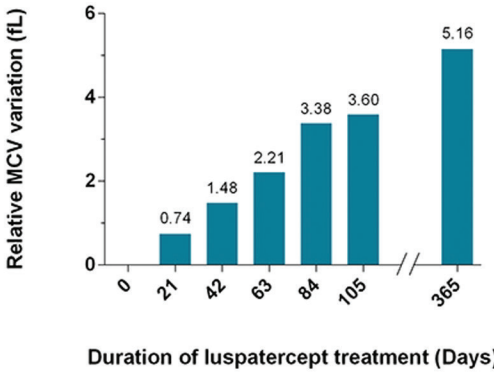
Background: Current guidelines recommend yearly evaluation of glucose metabolism with Oral Glucose Tolerance Test (OGTT) in patients with transfusion-dependent thalassemia from their 10th year of age onwards.
Aims: To retrospectively analyse all the OGTT tests performed in a single pediatric center during the last decade and evaluate the necessity of yearly performed OGTT in patients with transfusion-dependent b-thalassemia during the second decade of life.
Methods: One hundred and seventy tests performed in 39 patients (24 boys) were included in the analysis. Mean age at the time of each OGTT was 14.15 ± 2.79 years.
Results: Seventeen tests (10%) in 8 patients (5 boys) were characterized as Impaired Glucose Tolerance (IGT) with a 2-hour glucose value above 140 mg/dl but below 200 mg/dl. In 20 tests (87.06%) fasting glucose values were between 100-125 mg/dl (Impaired Fasting Glucose, IFG), whereas in 2 tests (1.18%) fasting glucose values were above 200 mg/dl (Diabetes Mellitus, DM). These 22 abnormal fasting glucose values were belonged to 12 patients (8 boys). Acknowledging the fact that there could be sporadic technical errors, especially in fasting glucose abnormal values, we selectively separated patients with either IGT and abnormal HOMA, MATSUDA or QUICKI indices or persistent IFG or IGT. With these criteria, 7 patients (4 boys) were identified. When compared with the rest 32 patients, these 7 patients with a definite abnormal glucose metabolism did not significantly differ regarding their age, anthropometric parameters or ferritin levels. In order to address selection criteria for performing OGTT but without missing a single patient with a definite glucose intolerance, these criteria should include: i) a first OGTT test at the initiation of puberty, ii) OGTT in any patient with a fasting glucose above 100 mg/dl and iii) OGTT in any patient with a HOMA-IR index above 1.85 and yearly onwards. By adopting these criteria in our cohort of patients, not a single patient with consistent abnormal glucose metabolism would have been missed, while, on the other hand, total OGTT tests performed could have been reduced from 170 to only 91, translating to a significant reduction of 46.47%.
Summary/Conclusion: Only a small percentage of young patients with transfusion-dependent b-thalassemia exhibit abnormal glucose metabolism during their second decade of life. By adopting specific selection criteria, one may avoid the performing of this time- and money-consuming test in a significant proportion of patients, albeit, without sacrificing timely detection and intervention.

PB1808 MCV VARIATION AS AN EARLY PREDICTOR OF RESPONSE TO LUSPATERCEPT IN NTDT PATIENTS: PRELIMINARY DATA

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Background: Beta-thalassemia is characterized by ineffective erythropoiesis, leading to a decreased number of mature and functional RBC, resulting in mild to severe anemia. Luspatercept is the first approved disease-modifying drug, currently indicated for Transfusion-Dependent Thalassemia (TDT) and in advanced trials for Non Transfusion-Dependent Thalassemia (NTDT). The response to luspatercept is quantified by the increase in total hemoglobin (Hb) in NTDT and by the decrease in transfusional need for TDT, but both changes require a long time to be consistently assessed.
Aims: To explore the hypothesis that early modifications in red blood cell indices could have a predictive value of response to luspatercept.
Methods: As reference Centre for Hemoglobinopathies of University of Torino we took part of luspatercept phase II/III clinical trials (NCT01749540, NCT02268409, NCT02604433, NCT03342404, NCT04064060). In this analysis we considered only local blood tests for all our patients that received luspatercept; patients or time frames on placebo were excluded. Responders and non responders were defined according to published clinical trial protocols: specifically, an increase in Hb ≥ 1.5 g/dL (NTDT) or a reduction in RBC transfusion need ≥ 33% (TDT) from baseline in weeks 13 to 24.
A generalized least-square regression model was used to ascertain whether the interaction between groups and time with respect to Hb, MCV, MCH, MCHC, RDW and Reticulocytes count was significant. A correlation structure was specified to account for repeated measures over time on the same patient with a continuous-time autoregressive of order 1 correlation structure. A recursive partitioning tree model was further developed to identify biomarkers time-dependent thresholds associated with heterogeneous treatment effects.
Results: The overall time of luspatercept treatment has been 32.0 years. The median duration for NTDT was 2.4 years (range 0.2-6.0) and for TDT 1.7 years (range 0.3-6.0) for each patient. We reviewed 1024 blood tests of 14 NTDT patients (9 responders, 5 non-responders) and 1968 blood tests of 14 TDT patients (10 responders and 4 non-responders).
No predictor of response was identified in blood test indices of TDT patients.
In NTDT patients, beyond the hemoglobin that defines the response, the index with better discriminative power was the MCV. A statistically significant trend difference in MCV was observed between responders and non-responders (p=0.03). Although the difference between groups is significant from 27 weeks after treatment start, responders show a relative increase in MCV compared to non-responders from the first weeks of treatment, reaching a mean variation of +5.16 fL at one year (see figure). The change remains long term. At baseline responders and non responders did not differ for age, genotype and total Hb, whereas mean baseline MCV was lower in responders (66.1 vs 72.3 fL), but this difference was not significant.



Relative MCV variation during treatment with luspatercept for the responders group, calculated as difference from MCV values of non-responders and normalized for baseline. Reported values represent the mean prediction of the statistical model based on clinical data. N(patient)=14, N(observations)=1024. P=0.03.

Summary/Conclusion: NTDT patients who respond to luspatercept treatment show an early increase in MCV; this change keeps up to 6 years. In part, this could be due to the rise in reticulocytes. In our data, a variation of reticulocytes alone is not sufficient to predict the response, but this could be due to the small sample size. More likely the MCV improvement could be the result of the not fully understood effects of luspatercept in regulating the late-stage RBC maturation.
These data need verification on a large set. If confirmed, the early MCV change may be easily applied in the clinical setting to predict long-term response to luspatercept among NTDT patients.

PB1809 THE PATIENTS WITH THALASSEMIA MAJOR MAY STILL DISPLAY GROWTH HORMONE DEFICIENCY DESPITE OPTIMUM TRANSFUSION AND IRON CHELATION THERAPY.

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Background: Growth retardation (GR) and pubertal disorders are the earliest consequences of iron toxicity resulting from the pituitary iron deposition in children and adolescents with thalassemia major (TM). It is suggested that appropriate transfusion and iron chelation therapy (ICT) support proper growth and development.
Aims: The purpose of this study was to evaluate if the current treatment protocols may support a normal growth progression and sexual development in patients (pts) with TM.
Methods: We recruited male (M) and female (F) TM pts born after 2000. The pts with an acute or chronic illness that may interfere with growth and development or stem cell transplantation recipients were excluded. The Ethical Committee of Clinical Investigation (19.02.2020, 20-2.1T/2) approved this study. Transfused packed red cell units (pRBC) and average pre-transfusion hemoglobin (Hb) per year were recorded. Serum ferritin (SF) was monitored monthly (m). Myocardial (T2*) and liver (R2) iron were assessed by magnetic resonance imaging (MRI) after 8-years (y) of age. Annual median SF, prescribed chelator(s), mean chelator doses were recorded. Transfusional iron intake (TII) was estimated and expressed as mg/ kg b.w./days. Height (H) and weight (W) assessments were performed using the Harpenden stadiometer, and puberty was evaluated by Tanner staging at 3 monthly. H-standard deviation scores (h-SDS) were calculated. All pts were assessed annually for bone mineral density (BMD) after 8 y. The mean SDS of the lumbar spine (L1-4) BMD between -1 and -2.5 was defined as osteopenia and <-2.5 as osteoporosis. Growth hormone (GH) secretion was assessed by L-dopa and insulin tests in those with standing-H below the –2 SD. Pts whose GH response to both stimulation tests (STs) was less than 5 ng/ml with the monoclonal assay was defined as GH deficiency (GHD).
Results: We evaluated 30 TM (28 β/β, 1 β/δβ, 1 HbH) pts (13 F and 17 M) with the mean age of 12,5 ± 4,5 y. All pts have received pRBC for 11,1 ± 4,4 y and maintained pre-transfusion Hb> 9 g/dl. The patients started ICT by the SF of 1430 ± 795 ug/L and maintained ≤1500 ug/L at all times during 9 ± 4.2 y. Twenty-four pts received only Deferasirox (DFX) chelation while 6 were initiated ICT by Deferoxamine (DFO) and continued with DFX. Liver iron concentration (LIC) and myocardial T2* (mT2*) in 22 pts were between 0.9-5.4 (2.1 ± 1.3 SD) mg Fe/g d.w. and 19.4-43.5 (28 ± 6.7 SD) ms, respectively, in all assessments. The puberty initiated at 12.8 ± 1.1 y in M (n=12) & 11.2 ± 1.3 y in F (n=12) and progressed without hormone replacement in all. Overall, growth velocity reduced compared to the non-thalassemic population after 8 y with clear evidence of growth catch-up by the onset of puberty. Five pts (16.5%) developed h-SDS< -2 at 10-12 y-old when all but one had S1/2 puberty and displayed GHD. All pts received GH therapy. The pt no 4 was entirely unresponsive to GH-STs, developed GR at 1 y-old, and has remained unresponsive to GH therapy (Table). The 14 (%58) and 5 (21%) of 24 pts demonstrated osteopenia and osteoporosis, respectively. The BMD-SDS improved following pubertal spurt.

Table. The growth progression by GH treatment in thalassemia major patients with GR and GH deficiency

Pts no	Iron chelator		Max SF (ug/L)	Target h-SDS	Prior GH therapy			1st y of GH		Final G & D		
	I	FU			P	B-/C-age (y)	h-SDS	P	GV (cm)	P	C-age (y)	h-SDS
1	DFO	DFX	*4725	-1,41	S1	11,5/13	-2,46	S2	7,1	S5	18	-1,68
2	DFO	DFX	*2465	0,24	S1	10/13,2	-3,10	S2	8,9	S5	18	-0,19
3	DFX	DFX	1528	0,66	S2	11/12,7	-3,16	S3	9,2	S5	16	-1,64
4	DFX	DFX	1580	0,21	S1	6/10,7	-3,41	S1	3,2	S3	16	-4,30
5	DFX	DFX	1183	-0,54	S1	7,5/11,5	-2,31	S1	6,8	S1	13	-1,90

I: Initial, FU: Follow-up, B-age: Bone-age, C-age; Chronological-age, GV; Growth velocity, GH; Growth hormone,GR; Growth retardation, DFO; Deferoxamine, DFX; Deferasirox, G&D; Growth and Development
*The max. SF reached during 1st years on DFO then SF normalized around 1000 ug/L

Summary/Conclusion: The high prevalence of GHD in TM patients receiving an optimum transfusion and ICT throughout their life was disappointed. The most probable explanation is, growth patterns and bone-maturation in TM pts might differ from the non-thalassemic population, and the GH-STs may lead to overdiagnosis of GH deficiency in this distinct population.

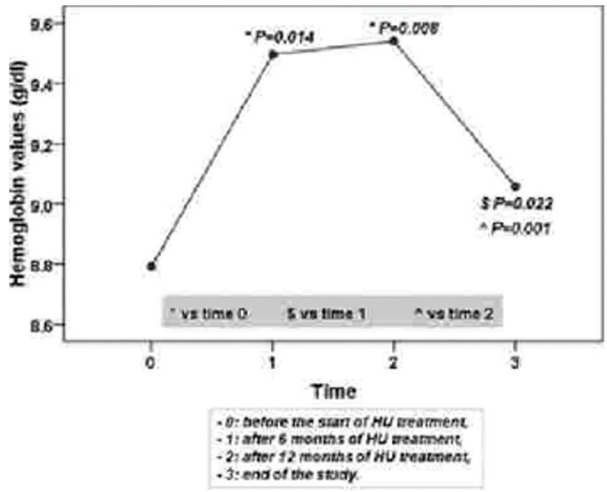
PB1810 THE USE OF HYDROXYUREA IN THE REAL LIFE OF MIOT NETWORK: AN OBSERVATIONAL STUDY

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Background: Hydroxyurea (HU) has been widely used in clinical practice to manage patients with non-transfusion dependent thalassaemia (NTDT). Few data are available about the effects of its administration in Italian patients.
Aims: This multicenter study aimed to assess haematological and non-haematological outcomes following short- and long-term exposure to HU.
Methods: Among the 79 NTDT patients (<4 transfusions per year) consecutively enrolled in the Myocardial Iron Overload in Thalassaemia (MIOT) network, we considered 71 patients (30 females) treated for >12 months with HU. Patients were followed prospectively until September 2019.
Results: Patients started the treatment with HU at a mean age of 37.0±12.1 years and anemia was the indication in the 88.6% of the cases. The mean duration of HU treatment was 8.2±5.8 years.
After 12 months of therapy a significant increase in hemoglobin and mean corpuscular volume values and a significant decrease in the number of white blood cells, indirect bilirubin, nucleated red blood cells, and platelets, in uric acid levels, and in soluble transferrin receptor values were detected. We defined responders the 28 patients who achieved a ≥1.0 g/dl increase in haemoglobin levels after 12 months. Responders received a significantly higher dose of HU and showed significantly lower pre-treatment haemoglobin values. At receiving operating curve analysis, a dosage greater than 16.6 mg/dl discriminated the responders with acceptable sensitivity and good specificity (59.3% and 85.7%, respectively) and with an area under the curve of 0.75 (P<0.0001). The responders experienced a significantly higher decrease in white blood cells after 12 months of treatment.
The hematological response dropped in long-term treatment (see Figure).

During the HU treatment we did not detect significant changes in the frequency of dyspnea, asthenia, atrial dilatations, cardiovascular complications (pulmonary hypertension, arrhythmias, ulcers, and deep vein thrombosis), extramedullary hematopotesis (EMH), and fibroadipose involution of the EMH masses.



Summary/Conclusion: This study seems to suggest that not only for the hematological responder patients, but also for those affected by specific complications, HU could be still a valid option to limit the advance of the overall clinical burden disease without carrying significant adverse events and increase in mortality.

PB1811 MICRO-RNA 451 EXPRESSION AS A HEMOLYTIC MARKER IN EGYPTIAN CHILDREN WITH BETA-THALASSEMIA

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Background: Beta-thalassemia (BT) is a genetic hematological disorder due to defect in beta globin gene, with extravascular hemolysis being a major feature of the disease. BT is the most common genetically inherited hemoglobin disorder in Egypt with a carrier rate reaching 10%. miRNA-451, an erythroid cell-specific miRNA, is upregulated during erythroid maturation, and could serve as a useful non-invasive biomarker for various diseases.
Aims: To investigate whether plasma miRNA-451can be considered as a hemolytic marker.
Methods: This cross-sectional study was conducted on 29 patients with BT attending the Alexandria University Children's Hospital Hematology outpatient clinic, Alexandria, Egypt. Patients were approached during their routine visits at the clinic and consecutively recruited if they accepted to participate and matched inclusion criteria, which were having BT (major or intermedia phenotype), being aged between 1 and 18 years, and having no known organ dysfunction (as renal or liver impairment). Ten age and sex-matched healthy chidlren were included as a control group provided they had a normal hemoglobin and RBCs indices for age. The BT patients were categorized as transfusion-dependent (TDT) if they had been receiving at least 8 packed red blood cells (PRBCs) transfusions per year, while patients receiving no or occasional transfusions were classified as non-transfusion dependent (NTDT). Complete blood counts, aspartate aminotransferase, total bilirubin, and lactate dehydrogenase where measured. Real-time quantitative PCR for miRNA was performed to detect the expression levels of miRNA-451. miRNA 134-2p was used as internal control. We compared the expression of miRNA-451 in the patients' plasma of patients to that of healthy controls.
Results: Among the 29 included patients, 16 had NTDT (age ranged from 3.2 to 17.6 years) and 13 had TDT (age from 4.5 to 14.8 years) and ten controls aged 3 to 14 years old. Plasma miRNA 451 expression was higher among β-thalassemia patients (median=0.7) when compared to controls (median=0.53) but not statistically significant, (p = 0.272). Similarly, there was an increased expression levels among TDT subgroup when compared to NTDT subgroup, (p = 0.288). The level of miRNA-451 was higher among severe cases than mild and moderate cases, (p = 0.301). There was also a higher miRNA-451 expression among splenectomized patients, (p = 0.10). In order to evaluate the diagnostic value of plasma miR-451, the $2^{-\Delta\Delta Ct}$ values of miRNA-451 from the patients' group were used to construct a ROC curve. Plasma miR-451 did not confidently discriminate between normal controls and patients (AUC = 0.621; p = 0.26). In controls, the Hb, RBCs and platelet count were all significantly correlating with the plasma miR-451 (p = 0.03, 0.008, 0.008, respectively). While in the patients' group, among the hemolytic markers only the ALP was significantly correlating with the plasma miR-451 (p = 0.007), as well as the BMI Z score among clinical parameters (p <0.001).
Summary/Conclusion: In order to investigate whether plasma miRNA-451can be considered as a hemolytic marker, we measured the expression of miRNA-451 in the plasma of Egyptian children with BT patients and compared it to healthy controls. miRNA-451 was more expressed in TDT patients compared to NTDT patients and controls, but this was not statistically significant. Plasma miR-451 failed to discriminate between normal controls and patients.

PB1812 CHELATION THERAPY WITH THE TWO DEFERASIROX FORMULATIONS IN TRANSFUSION-DEPENDENT THALASSEMIA CHILDREN OVER THE PAST TWO DECADES: A SINGLE CENTER EXPERIENCE

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Background: Deferasirox (DFX) is once-daily oral iron chelator that was developed out of need for a long-acting chelator for patients with chronic iron overload. The first marketed formulation was a dispersible tablet (DT) thathad to be mixed inalarge amount of liquid and to be taken on an empty stomach. In addition to being unpalatable, it was commonly related to gastrointestinal symptoms. In that context, a new formulationin in the form of film coated tablet (FCT) was developed. FCT is still given once-daily, but can be taken with a light meal and differs with regards to excipients, offering improved palatability and tolerance.
Aims: To retrospectively report on the long-term experience of DFX use in transfusion-dependent thalassemia (TDT) children followed at a single Unit and to present a comparison between its two formulations.
Methods: Medical records of patients who received DFX were retrospectively evaluated. Data regarding demographics, duration and dose of chelation, renal and liver function, ferritin levels, and clinical adverse events were recorded. Statistical analysis was performed using the Wilcoxon test.
Results: A total of 44 patients treated with DFX DT were identified, between 2003 and 2016. Mean age at time of DFX DT exposure was 7.6(2– 15.3) years. Mean duration of exposure was 58.3 (3-141) months and mean daily dose 23.4(10-40)mg/kg. Prior to initiation, mean ferritin levels were 1094.7 (114–2760) ng/ml and at end of study 1149.1 (216-3184) ng/ml(P=0.6). At study entry mean creatinine levels were 0.49 (0.34-0.84) mg/dl and at end of study 0.7 (0.37-1.06) mg/dl (P<0.0001). During follow up 26/44 patients (59%) temporarily interrupted treatment, at one or more time points, on account of the following: 7/26 patients(26.9%) due to increased liver enzyme levels, 4/26(15,4%) due to renal dysfunction including increased creatinine levels and/or increased protein or calcium output, 4/26(15.4%) due to abnormal liver enzyme levels and concurrent renal dysfunction,, 2/26(7.7%) due to epigastralgia, and 1/26 (3.8%) due to either rash, epigastralgia or pregnancy. In 17/44 patients (38.6%) a switch to another chelator was decided due to recurrent adverse events after drug re-initiation.
A total of 27 children received DFX FCT after it was marketed in September 2017 until February 2021. Mean age at initiation was 12.9 (2 –18) years. Mean exposure time was 27.15 (8-40) months and mean daily dose was 16.4 (10-27.5) mg/kg. Prior to DFX FCT mean ferritin levels were 1197.2 (438–2094) ng/ml and mean creatinine levels 0.66 (0.4-0.98) mg/dl. At end of study mean ferritin and creatinine levels were 1300 (515-2829) ng/ml (P=0.75) and 0.7 (0.38-0.96) mg/dl (P=0.15), respectively.
During follow up 5/27 patients (18.5%) temporarily interrupted treatment due to increased liver enzyme levels (4/5,80%) or increased creatinine levels (1/5,20%). In total, 6/27 patients (22.2%) switched to other chelationregimens.
Summary/Conclusion: DFX demonstrated an adequately efficacious and safe profile in a pediatric thalassemia cohort over almost 2 decades. Although experience with DFX FCT is comparably limited, results are encouraging, especially in terms of number of related renal adverse

events. The new formulation's favorable safety profile along with its improved palatability may offer, in the long run, better adherence and optimal control of iron overload-related complications.

PB1813 ROLE OF TELEMEDICINE IN MANAGEMENT OF ADULT EGYPTIAN THALASSAEMIA PATIENTS DURING COVID-19 PANDEMIC; PATIENTS SURVEY

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Background: COVID-19 caused a massive damage to the whole world. Telemedicine (TM) is an excellent, safe,effective method to follow Adult B-thalassemia patients which are experiencing a chronic morbidity.
Aims: Evaluating medical service administrated to Adult B-thalassemia patients after 3 months of online follow up.
Methods: Since April 2020, follow up of our patients done via audio visual calls & whats app group which was created during the pandemic to follow thalassemia patients.Our clinic serves patients in an area range of about 1000 Km^2, and out of 100 adult B-thalassemia (major and intermedia) who are regularly following in haematology clinic only 30 patients were able to connect through whats app group with the physician.
After Three months (in July 2020) a simple Arabic questionnaire was given to our patients. Questionnaire asked about gender, degree of education, and whether the patient from urban or rural area.
The patients were asked if the application was easy to use & time saving, and was the online consultations were effective.They were asked about the new labs they performed and if their treatment was modified accordingly, & how often this happened. Whether their condition required attendance to casuality & for what reason.
Regarding COVID-19, patients were asked if the pandemic affected their routine medical service and receiving their treatment. In addition there were inquiries about any suspicious symptoms they suffered from since the start of the pandemic, if they notified the physician once they have these symptoms, if they performed COVID-19 swab,and what is the treatment they were prescribed.
Finally, we have asked about attendance to the hospital despite of TM service and for what reason.
Results: Thirty patients included in this study, 24(80%) females & 6(20%) males with median age of 29.5(17-50) years. Twenty-five (83%) patients were educated to higher school or more while 5 of patients were not educated. Twenty (67%) patients lived in urban areas &10 (33%) patients lived in rural areas.
Twenty-eight (93.3%) patients found the application easy while 2(6.7%) patients found it difficult. The application was time saving & consultations were efficient for 29 (97%) patients while it was not in only 1(3%) patient. Twenty-four (80%) patients didn't attend the casuality department while 6(20%) patients attended for blood transfusion.
Nineteen (63.3%) patients were asked to do new labs. Five (16.6%) patients needed to change their treatment, 2 of them changed it one time and 3 patients changed it more than one time. Twenty-five (83.4%) patients contacted consultant more than one time.TM consultations increased since the start of whats app group for 25 (83.4%)patients with no change in 4(13.3%) patients while it decreased in one (3.3%) patient only.
As regard to COVID-19, Ten(33.3%) patients had suspicious symptoms as fever or sore throat, 8 of them notified their consultant with description of Azithromycin to all of them. Despite TM, 21(70%) patients attended to the hospital, 14 of them to get monthly treatment, 6 patients for examination & treatment, and one patient for examination only.
About 70 consultations had been sent through whats app group before the survey and about 115 laboratory results sent during the 3 months of online follow up.
Summary/Conclusion: Current evidence supports that telemedicine can be a fast, safe, and effective tool to increase care for adult thalassemia patients during pandemic time.

PB1814 DISTINCTION BETWEEN IRON DEFICIENCY ANEMIA AND MINOR B-THALASSEMIA: DETERMINATION OF CUT-OFF OPTIMAL VALUES OF TEN HEMATOLOGICAL FORMULAS

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Background: Anemia is a public health problem. Two etiologies of microcytic anemia are relatively common in our country: iron deficiency anemia (IDA) and minor β-thalassemia (βTM). To guide the clinician in discriminating IDA from βTM, several studies have developed indices and formulas based on cells blood count parameters determined by hematology analyzers.
Aims: The aim of our study was to study the performance of these formulas to discriminate βTM and IDA and to identify the cut-off values adapted to our population for each formula.
Methods: After reviewing the records of adult patients with IDA and βTM, two groups were formed (IDA (n=172) and βTM group (n=69)). Demographic and cells blood count data were recorded. Performances of ten formulas and indices reported in the literature in the discrimination between IDA and βTM were studied. Statistical analysis was performed using SPSS 19.0. Sensitivity, specificity, Likelihood ratios, predictive values and analysis of ROC curves were carried out. Optimal cut-off values were determined according to calculation of Youden Index (J).
Results: Among CBC parameters, the hemoglobin rate, the erythrocyte count and the IDR-SD parameter showed an excellent discriminating power (respectively; AUC= 0.913, 0.971 and 0.968). Performance assessment of the various original cut-off indices, three of them were reliable: Green King index (Se= 71.01%, Sp= 97.67%; AUC=0.96), RDWI (Se= 78.26%, Sp=97.67%; AUC=0.95), and Sirdah index (Se=76.81%, Sp=97.67%; AUC=0.965). At the new cut-off, the England and Fraser index, the Green King index, the Sirdah index and the RDWI were the most effective in diagnosing βTM. At these new thresholds, only England and Fraser index and Sirdah index showed a gain in sensitivity and accuracy.
Summary/Conclusion: The use of formulas and indices to distinguish βTM from IDA is a considerable decision support tool for the clinician, however the adoption of population-specific cut-offs helps to improve the performance of these formulas and indices. The technology deployed by hematology analyzers and some clinical data would be necessary for optimal diagnostic guidance.

PB1815 USE OF RED BLOOD CELL AND RETICULOCYTE PARAMETERS FOR THE SCREENING OF MICROCYTIC ANAEMIA

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Background: Anaemia is a global public health problem that affects almost one-third of the world population. Thalassaemia and iron deficiency anaemia are the most common causes of microcytic anaemia, with similar clinical and laboratory features, making their diagnostic often complicated. During the last decade, cell counter-based formulae and algorithms have been proposed in the differential diagnosis of microcytic anaemias. Unfortunately, only a few studies take into account certain not so rare clinical situations where microcytic anaemia may occur.
Aims: The aim of this study was to develop an algorithm as first tier screening tool in the differential diagnosis of microcytic anaemias.
Methods: We retrospectively analyzed results of complete red blood cells (RBCs) and reticulocyte (RET) counts obtained on the Sysmex XN-9000 of 280 adults, divided into 5 different groups: iron deficiency anaemia (n=56), β-thalassaemia minor (n=68), heterozygous haemoglobinopathies (n=24), hereditary spherocytosis (n=14) and other patients (n=118). A Classification and Regression Tree (CART) analysis was performed to obtain an algorithm in order to predict these groups.
Results: Four parameters were selected by the CART analysis: the percentage of microcytic RBCs (%MicroR), the %MicroR to percentage of hypochormic RBCs ratio (%MicroR/%Hypo-He), the reticulocyte haemoglobin content (RET-He) and the reticulocyte count to immature reticulocyte fraction ratio (RET/IRF). When applying the algorithm, 93/106 of the hereditary RBC disorder patients and 41/56 iron deficiency anaemia patients were corectly screened. The correct overall classification rate reached 83.6%. The best sensitivity and specificity were obtain for the screening of β-thalassaemia minor, with 92.6% and 94.8% respectively.
Summary/Conclusion: We proposed a costless, affordable, easy to use and effective algorithm that can be used routinely for the differential diagnosis of microcytic anaemias. The latter is based on erythrocyte and reticulocyte parameters offered by the most recent generation of the Sysmex analyzers, the XN-9000.

PB1816 IMMUNE PROFILE EVALUATION IN PEDIATRIC PATIENTS WITH TRANSFUSION DEPENDENT THALASSEMIA

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Background: Transfusions, oxidative stress splenectomy, as well as iron overload have been correlated to immune defects in transfusion dependent thalassemia patients. However, literature reports on immunoglobulin levels in this patient population remain contradictory. On the other hand, hyper reaction to constant immune challenges has also been a topic of controversy.
Aims: To evaluate the immune profile of pediatric multi - transfused patients with beta thalassemia.
Methods: The study group consisted of pediatric transfusion dependent thalassemia patients followed at a single Pediatric Hematology Department. Patients with a history of splenectomy, active autoimmune disease, active severe infection or any systemic condition that could affect the immune profile were excluded. Blood samples were collected from all subjects for evaluation of immunoglobin levels, C3 and C4 complement factors, red cell auto-antibodies, as well as antinuclear (ANA), and anti-double stranded DNA (anti-sdDNA), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies. Clinical and laboratory data were obtained from chart reviews, including demographics, presence of severe infections, duration of transfusion, history of allo-immunization, chelation therapy, heart T2* MRI and Liver Iron Concentration (LIC), as well as mean annual hemoglobin and ferritin levels.
Results: In total, 24 patients enrolled in the study. Mean patient age was 13.3 (2–19) years and 18/24 (75%) were males. No record of severe infection was noted. Mean annual pre-transfusion hemoglobin level was 9.5±0.48 (8.5-10.3) g/dl and mean annual ferritin level 1,228±538 (409-2,627) ng/ml. Mean duration of transfusion therapy was 9.6±5 (1.5–18) years. All except one patient were on chelation therapy. In specific, 12/23 patients (52.1%) were on deferasirox, 4/23 (17.3%) on deferiprone, 2/23 (8.6%) on deferoxamine 4/23 (17.3%) on deferoxamine / deferiprone combination and 1/23 (4.3%) on deferasirox / deferiprone combination. In 21/24 patients an annual MRI evaluation was available, with a mean heart T2* value of 32.01±6.19 (22.3-49) ms and a mean LIC of 8.05± 9.3 (1.28-32.9) mg/gdw.
With respect to immunoglobulin levels, mean IgG levels were 9.94±2.7 (6.3–15.1) gr/l with 7/24 (29.1%) patients presenting with lower than normal values, mean IgM levels were 1.1±0.6 (0.47 – 2.2) gr/l with 5/24 (20.8%) patients presenting with lower than normal values and mean IgA levels were 1.56±0.7 (0.6-3.38)gr/l with 2/24 (8.3%) patients presenting with lower and 2/24 patients (8.3%) with higher than normal levels. In total 10/24 patients (41.6%) and 1/24 (4.1%) had lower C3 and C4, respectively, with mean values of 0.77±0.14 (0.53 – 1.06) gr/l and 0.17±0.05 (0.09 – 0.28) gr/l. Positive ANA titres of ≥ 1:80 were found in 7/24 patients (29.1%) whereas no patient presented with positive anti-ds DNA, anti – TPO, anti- TG or red cell auto-antibodies. In total, 4/24 (16.6%) patients presented with a positive indirect Coombs test. No significant correlation was found between immunoglobulin levels, complement factors levels or autoantibody presence with age, duration of transfusion, allo-immunization, chelation therapy or iron overload.
Summary/Conclusion: The present study revealed an abnormal immune profile in a number of transfusion dependent pediatric patients, although no correlation to parameters studied was made. Larger prospective studies are needed in order to identify clinical relevance of the reported findings.

PB1817 KNOWLEDGE ON THALASSAEMIA AMONG STUDENTS AGED BETWEEN 14-17YRS IN KURUNEGALA DISTRICT, SRI LANKA

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Background: Prevention and control of thalassemia in a country needs public education to prevent marriages between carriers. Correct message has to be delivered to the community so that the public will understand the importance of prevention. Kurunegala is one of the districts in Sri Lanka where thalassaemia is highly prevalent.
Aims: The aim of this study was to assess the knowledge on thalassemia of school children aged 14-17 years in Kurunegala district, Sri Lanka.
Methods: Descriptive cross-sectional study. Using probability proportional to size sampling technique, 55 clusters of 30 students in the age range 14-17 years each, were selected from all the schools in Kurunegala district. Within each selected school, the required number of children was selected randomly.
Results: Out of the participants (n=1821), majority (92.6%) had heard of thalassaemia before. Majority (83.4%) of participants showed high knowledge score regarding thalassaemia. Age, gender, ethnicity and the type of school correlated with knowledge score.
Summary/Conclusion: Based on study findings, students of Kurunegla district, showed satisfactory level of knowledge regarding thalassaemia. Good knowledge in young generation regarding the disease, diagnosis and prevention will reduce the incidence of thalassaemia in Kurunegala district in the future.

PB1818 GENETIC VARIATIONS OF IRON REGULATORY PROTEINS: FERROPORTIN-1(-8CG), TMPRSS6 (RS855791) AND HEMOJUVELIN (I222N AND G320V) WITHIN B-THALASSEMIA MAJOR PATIENTS

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Background: β-thalassemia represents one of the most common human genetic disorders. The standard line of therapy is to combine regular blood transfusion with effective iron chelation, however iron overload remains a major cause of morbidity and mortality. Iron regulatory proteins and their genetic variants together with changes in hepcidin levels in thalassemic patients could affect the disease manifestations.
Aims: The aim of this work was to study genetic variations of ferroportin-1(-8CG), TMPRSS6 (rs855791) and hemojuvelin (HJV I222N and G320V) within β-thalassemia major patients.
Methods: tial
Polymerase chain reaction Restriction Fragment Length Polymorphism (PCR RFLP) analysis was used to study the four mentioned polymorphisms in comparison to fifty normal control subjects, to assess their poten
Results: Liver Iron Concentration (LIC) was significantly higher in patients harboring the homomutant FPN1 (GG) genotype compared to those with the wild genotype, Pulmonary artery pressure (PAP) was significantly higher in patients harboring the mutant FPN1 genotypes. MRI cardiac T2* was significantly lower among patients with the homomutant HJV I222N (AA) genotype.
Summary/Conclusion: Our results suggest that genetic variants in iron regulatory proteins could alter the manifestations of iron overload thus resulting in different clinical phenotypes of thalassemic patients.

PB1819 HB MARUCHI [ALPHA165 (E14) ALA> PRO; HBA1: C.196G> C]: A NEW THALASSEMIA HEMOGLOBINOPATHY RELATED TO THE ALPHA1 GLOBIN GENE

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Background: In thalassemias there are structural variants that, however, present a phenotype of α-thalassemia called thalassemic hemoglobinopathies, they are included in the so-called α-thalassemia no deletion. Non-deletion thalassemia represents 12% of all α-thalassemia in our country and 36% is due to thalassemic hemoglobinopathies
Aims: We present a new mutation in CD65 of the HBA1 gene, where the change AAG>TAG (Ala>Pro) generates a thalassemic hemoglobinopathy.
Methods: The propositus, a 37-year-old man from Madrid, was studied because he presented sustained microcytosis without iron deficiency. Hb A2 and Hb F levels were measured by ion exchange HPLC (VARIANT II). Hemoglobin was studied by capillary zone electrophoresis and ion exchange HPLC. The most frequent α-thalassemia mutations were ruled

out by multiplex PCR (Alpha-Globin StripAssay kit) and molecular characterization was performed by automatic sequencing of the α globin genes.
Results: The propositus presented microcytosis (MCV 78.3 fL) with hypochromia (HCM 26.3 pg), without anemia (Hb 14.1 g /dL) and normal reticulocytes (1.01%). No abnormal hemoglobins were detected and Hb A2 and Hb F levels were within normality (2.6% and 0.8% respectively). Molecular characterization of the globin α1 gene, by automatic sequencing, identified a new HBA1: c.196G>C transversion mutation, which resulted in an amino acid change from Ala>Pro at codon 65 of exon 2 in the heterozygous state [α165(E14)Ala>Pro;HBA1:c.196G>C] which we have named Hb Maruchi.
Summary/Conclusion: The binding of heme to globin involves a very specific stereochemical adjustment that helps stabilize the tertiary conformation of the subunit. The heme group inserts into a cleft between the E and F helices. While the vinyl groups are asymmetrically located in the hydrophobic interior of the cleft, the propionic acids of porphyrin are oriented toward the hydrophilic surface, interacting with certain nonpolar amino acids in the CD, E, F and FG regions of the α and β globin chains. Most of these nonpolar amino acids are invariant residues. Therefore, it is not surprising that substitutions of any of the residues located in these regions can result in a decrease in the stability of the heme-globin bond and, subsequently, of the globin chain. The CD65 of the HBA1 gene encodes an Ala corresponding to position E14 of the α1 globin chain, located inside the pocket of the heme group. In Hb Maruchi this Ala is replaced by a Pro, which causes instability of the α1 globin chain, this instability is enhanced by the fact that Pro is an amino acid that cannot participate in the configuration of the alpha helix of the secondary structure deforming said structure. This new variant causes thalassemia instead of hemolysis because its α chains are unstable, catabolizing very rapidly before the formation of αβ dimers. The α1Maruchi gene does not produce functional α chains, hence the thalassemia phenotype. This variant is so unstable and catabolizes so rapidly that its detection by electrophoretic and chromatographic methods is impossible. The diagnosis of this type of mutations is important because the association with α0-thalassemia can lead to more severe forms such as Hb H disease or hydrops fetalis.

PB1820 EVALUATION OF IMMUNE FUNCTIONS IN TRANSFUSION-DEPENDENT THALASSEMIA PATIENTS WITH ALLOIMMUNIZATION

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Background: It is suggested that alloimmunization develops due to erythrocyte antigen differences between the blood donor and the recipient, the immune status of the recipient and the immune modulatory effects of repeated allogeneic blood transfusions on the immune system of the recipient. Understanding the immune regulators responsible for alloantibody development in transfusion dependent thalassemia patients will provide appropriate data for the reduction and / or prevention of alloimmunization rate.
Aims: We aimed to evaluate the association of alloimmunization and basic immune functions in transfusion-dependent thalassemia patients.
Methods: Fifty-four patients with a diagnosis of transfusion-dependent thalassemia between the ages of 1-24 who were regularly monitored in the Thalassemia Unit were retrospectively evaluated. In these patients, the frequency and types of alloantibodies and the basic immune functions tests and demographic characteristics that affect their formation were examined.
Results: The rate of alloantibody detection was 29.6%, and clinical alloimmunization was detected in 24% of the patients. The most common type of alloantibody is against the Rhesus system (70%) and secondly against the Kell system (23%) and Lutherian system (7%).
When the relationship between regular transfusion initiation age and development of alloantibody was examined; it is found out that while in 38 patients without alloantibody development the median age was 11.5 months (4-32 months), in 16 patients with alloantibody development the median age was 15 months (6-54 months). The age of initiation of regular transfusion was statistically significantly late in patients with alloantibody development (p=0.03). The frequency of transfusion between the groups was compared, and it was found that due to development of alloantibody, the need for transfusion, and therefore, more frequent transfusions increased significantly (p<0.001). Direct coombs positivity was detected in 8 (50%) of 16 patients with alloantibody development. Direct coombs was found positive in 5 (13.2%) of 38 patients without alloantibody development, and a statistically significant relationship was found between alloantibody development and direct coombs positivity (p=0.01). The 5 patients without alloantibody development but with direct coombs positivity mentioned here are patients with splenectomy.
No significant difference was found between the groups in terms of IgG, IgA, and IgM values (p=0.403, p=0.747, p=0.272). Similarly, there is no statistical significance between C3 level and development of alloantibody (p=1.00). Serum C4 levels were found to be low in 8 (14.8%) of 54 patients, 6 of these 8 patients were found to be alloantibody positive. There was no significant difference between the total lymphocyte count, $CD3^+$, $CD4^+$, $CD8^+$, and NK cells in the two groups whose lymphocyte panel results were evaluated (p=0.270, p=0.291, p=0.05, p=1.00, p=0.483). However, $CD19^+$ B cells were lower in the alloantibody present group (p=0.02). In addition, serum C4 level was found to be statistically significantly lower in patients with alloantibody development (p=0.006).
Summary/Conclusion: In this study, we found a strong relationship between alloantibody development and D. coombs positivity, low C4 and low $CD19^+$ B cell numbers.We believe that studies at molecular level should be increased and studies should be conducted with a larger number of patients in order to elucidate the immune pathogenesis of alloimmunization and determine the markers that will enable early recognition.

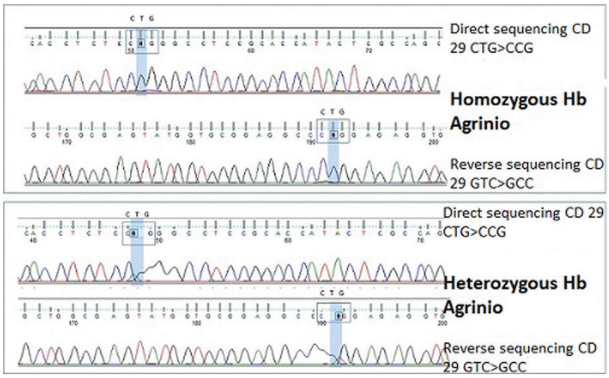
PB1821 A RARE CASE OF SEVERE ANAEMIA SINCE BIRTH: HAEMOGLOBIN AGRINIO.

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Background: Alpha thalassemia is characterized by the reduced or absence synthesis of alpha globin chains, most commonly due to delectional mutations. Hemoglobin Agrinio [α29(B10) Leu→Pro, CTG>CCG (α2)], is an infrequent nondelectional alfa thalasemia (α-Thal).
Aims: To describe an unusual case of neonatal anaemia and its diagnostical and therapeutical approach.
Methods: A systematic research of PubMed's Medline was done, using de words Agrinio, neonatal and Thalassemia. Then, we analysed the case using electronic health records of our centre (previous parents informed consent), for history taking and laboratory data collection.
Results: Case description: A newborn girl was admitted to the neonatal intensive care unit because of respiratory distress showing severe microcytic anemia (haemoglobin 67 g/L, MCV 70.5 fl) and increased lactate dehydrogenase (6630 U/L, reference range 225-660 U/L). Rest of hemolysis parameters were normal. All the obstetric control had been passed with no incident, except for the finding of mild pericardial effusion and cardiomegaly in the third trimester ultrasound. Delivery proceed without incidence.
During her admission, moderate pulmonary hypertension (corrected at first 48 hours), and patent foramen ovale were found. Toxic, infectious diseases and RH/ABO incompatibility were ruled out. Peripheral blood smear only showed significant anisopoikilocytosis with the presence of microcytosis, hypochromic red blood cells, target cells, helmet red blood cells, and reticulocytes. Capillary electrophoresis of haemoglobin was normal.
At sixteen days of life, she was discharged with supportive oral iron. In the next two months, she needed to be admitted twice, due to hyporexia, rejection of feeds and general decline in general appearance, with severe anemia and moderate transfusion dependence.
Given the consanguinity of the parents, both of gypsy ethnicity, and the suspicion of possible congenital haemolytic anaemia, thalassemia genetic study was requested to our reference centre, Hospital San Carlos, Madrid. After analysis, they concluded that the patient was a homozygous carrier of the CTG> CCG mutation in codon 29 of the first exon of the alpha 2 gene, which determines the change from leucine to proline

at position 10 of the B helix of the alpha chain (haemoglobin Agrinio). Both parents were studied with diagnosis of heterozygous carriers of this mutation. None of her older siblings presented this mutation, so an HLA compatibility study has been carried out to consider the possibility of hematopoietic progenitors transplant in the future.



Summary/Conclusion: Discussion: Cases like the one presented, even today, pose a diagnostic and therapeutic challenge. Clinical suspicion (more in cases of the severity of ours), should guide us towards carrying out complementary tests quickly in order to be able to provide adequate treatment in time.
Agrinio haemoglobin is an unknown hemoglobinopathy, but molecular characterization of entities like this and the communication of results could help us make these patients increasingly less challenging in clinical practice.
Conclusion: In cases like the one presented, clinical suspicion is vital, and guided by this suspicion, genetic techniques and molecular diagnosis will be key to the definitive diagnostic orientation and the subsequent therapeutic approach.

Thrombosis and vascular biology - Biology & Translational Research

PB1822 DIAGNOSIS OF THROMBOPHILIA IN YOUNG PATIENTS AND THE EFFICIENCY OF SECONDARY PREVENTION OF THROMBOSIS WITH DIRECT ORAL ANTICOAGULANTS

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Background: The term "thrombophilia" means a tendency to thrombosis with an early age onset, family history, severity of thrombosis, disproportionate to the known causative factor and episodes of recurrent thrombosis.
Aims: To examine young patients who had a registered fact of thrombosis of various localization, in the absence of an obvious causative agent, for markers of hematogenous thrombophilia, to assess the possibilities of direct oral anticoagulants for the secondary prevention of thrombus formation.
Methods: Examination of 81 patients (men - 50, women - 31) between the ages of 17 and 45 was carried out. Somatic diseases in which the secondary thrombophilia, complicated by thrombosis may occur were excluded. The age structure of the examined: 5 patients aged 17 - 20 years, 28: 21 - 30, 38: 31 - 40, 10: 41 - 50 years. In 32 patients (38%), the disease debuted with pulmonary embolism; in 11 cases (14%) - ischemic stroke; in 3 (5%) - myocardial infarction; in 35 (43%) - pathology of the veins of the lower extremities. Relapses of vascular complications were already registered in 30 patients at the time of diagnosis.
Results: The following thrombophilia markers were found in 72 patients (men - 43, women - 29): F5 Leiden mutations - in 30 patients, prothrombin F2 G20210A - in 15, MTHFR - in 25, antithrombin III deficiency - in 6 and protein C - in 13, hyperhomocysteinemia - in 30, primary antiphospholipid syndrome (APS) - in 20 patients. In six patients, only one gene mutation took place, in other cases a combined form of thrombophilia was diagnosed. In 55 cases, there was heredity due to pathological thrombus formation.
Acute thrombosis was treated in accordance with national and international guidelines. For the purpose of the secondary prevention of thrombus formation, the drug Dabigatrana etexilate was prescribed to 37 patients; duration of drug administration was from 12 months to 9 years; the dose of the drug was selected individually from 150 to 300 mg per day. The drug Rivaroxaban was prescribed to 25 patients, the duration of drug administration was from 12 months to 6 years; the dose of the drug is 10 - 20 mg per day. The drug Apixaban was prescribed to 10 patients (30 - 50 years old), the duration of drug administration was from 6 months up to 2 years, the dosage - 5-10 mg per day. Only one patient after the administration of Dabigatrana etexilate had a relapse of PE due to low adherence to treatment. The rest had no recurrence of thrombotic complications. No hemorrhagic complications were diagnosed with the use of dabigatran and apixaban. In 5 patients receiving rivaroxaban, there were minor nosebleeds; in three cases they stopped when the dose was reduced from 20 to 15-10 mg, two patients were transferred to dabigatran. No life-threatening bleeding has been reported. Angiovitis was prescribed in case of hyperhomocysteinemia. Replacement therapy was used in the congenital deficiencies of protein C and antithrombin III.
Summary/Conclusion: Timely diagnosis of the variant of hematogenous thrombophilia in young patients with thrombosis and the appointment of adequate therapy contribute to the relapse-free course of the disease.

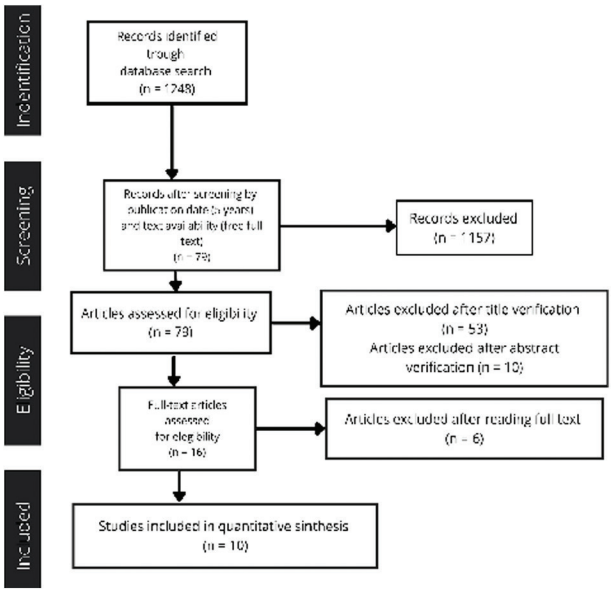
PB1823 EFFECTS OF DIABETES MELLITUS ON HEMOSTATIC CHANGES, A SYSTEMATIC REVEW

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Background: Diabetes is a metabolic syndrome that generates an increase in glucose levels, so diabetic patients have been associated with the development of hemostatic complications, such as endothelial and platelet dysfunctions, coagulation factors, natural anticoagulants and the fibrinolytic system. They are also more prone to hypercoagulability cases.
Aims: This systematic review aims on how diabetes mellitus affects hemostatic changes.
Methods: Three electronic databases (SciELO, LILACS, PubMed) were consulted in search for articles, published in the last five years, using the following keywords searched in DeCs/MeSH: diabetes mellitus, hemostasis, blood disease.
The initial online search led to the retrieval of 1.248 references and reviewers extracted data independently. A total of 10 articles were used in the review. The checklist of 27 items and 4-step flow chart (Table 1) indicated by the PRISMA methodology were used.
Results: The study by Wieczór, R. et al. (2019) evaluated patients with symptomatic peripheral arterial disease and demonstrated that the concomitance of this disease with DM2 contributes to an increase in the concentration of fibrinogen in the blood. Pretorius, Thomson et al (2018) also reported that the presence of amyloid fibrin, the increase in circulating inflammatory biomarkers and a hyperglycemic state contributes to blood hypercoagulability. Greenhalgh, KA, et al. (2017) shows a brief connection between a variant of fibrinogen present in diabetics and significant changes in the structure of the clot and fibrinolysis, resulting in dense fibrin networks, difficult to lyse.
It is observed in the study by Sumaya, W et al. (2020) that individuals with diabetes may have changes in their lipid profile, converging to cases of lipotoxicity and changes in fibrinolysis. According to IS Sobzkak and Stewart, A (2019) 80% of patients with diabetes die from cardiovascular events. The randomized test conducted by Bratsheth, V et al. (2017) shows that physical exercise in one year was not able to bring greater control over pro-coagulant disorders and more serious diseases, such as albuminuria and acute myocardial infarction. However, research by Patti, G., Cavallari, I., Andreotti, F. et al. (2019) shows that more aggressive antithrombotic strategies can be indicated for diabetics with cardiovascular diseases.
The study by Gajos, G., Siniarski, A., et al. (2018) analyzed patients with DM2 and concluded that inadequate glycemic control, with increased platelet activation and oxidative stress, causes an increase in the formation of polyhedrocytes in contracted blood clots.
Newman, JD et al. (2017) evidenced that the glucose concentrations in the patient with DM potentiate the activation of the platelet-megakaryocyte hemostatic axis allowing the inorganic arsenic to cause atherothrombotic risk in diabetic patients.

The study by Bryk, AH, et al. (2019) showed that the markers of extracellular neutrophil traps in circulating plasma are related to glycemic control, so that the detectable increase refers to a prothrombotic state, especially hypofibrinolysis in patients with DM2.



Summary/Conclusion: The analyzed articles call attention to the changes in the coagulation patterns and in the lipid profile of the diabetic, situations that may imply the occurrence of cardiovascular and atherothrombotic events, responsible for increasing the population's morbidity and mortality.

PB1824 EVALUATION OF D-DIMERS CONCENTRATIONS IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS SURGERY

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Background: Cardiac surgery under cardiopulmonary bypass (CBP) still involve major bleeding of which platelet injury is generally believed to be its primary nonsurgical cause. However, in some patients, excessive fibrinolysis may be the primary etiology of blood loss in postoperative period. The D-dimer assay, a measure of cross-linked fibrin degradation product, constitutes a specific test for fibrinolysis.
Aims: In this present study, we sought to assess the changes of D-dimers concentrations in cardiac patients before and after CBP and whether the D-dimers formation correlates with postoperative bleeding.
Methods: A total of 30 patients undergoing cardiac surgery under CBP were included in a prospective observational study. Patients' variables, postoperative bleeding volume, transfusions during the operation and 24 hours after, laboratory variables in preoperative, intraoperative and postoperative period (hemoglobin, hematocrit, platelet count, prothrombin rate, activated partial thromboplastin time, fibrinogen level) were registered. D-dimers concentration was measured using an enzyme-linked immunosorbent assay (ELISA) technique VIDAS before CBP and 5 minutes after heparin neutralization.
Results: There were 30 patients with an average age of 54.4 years old (18-79 years old).Based on the surgery indication, Patients were split up into three groups: coronary insufficiency (P)(N=12), valvulopathy (V)(N=14) and other reasons (C) (N=4). The mean preoperative D-dimers concentration was 509ng/ml ranging from 150ng/ml to 2200ng/ml. Among groups, the mean D-dimers levels were estimated as follows: 438ng/ml in group P, 625ng/ml in group V and 314ng/ml in group C. In postoperative time, D-dimers levels were significantly increased (p=0.01).In fact, the mean D-dimers concentration were 889ng/ml ranging from 270ng/ml to 3940ng/ml. Regarding groups, the D-dimers levels were respectively 527ng/ml, 1320ng/ml and 468ng/ml in group P, group V and group C with a statistically significant difference (p=0.05).Therefore, group V showed the highest increase of D-dimers level after CBP. This latter group consisted predominantly of female patients (H/F=4/10), showed the longest aortic cross clamp time (65.5min), had the highest mean number of red blood cell units transfused within and after surgery (1±0.96 and 1±1.24 units respectively) and the highest mean number of fresh frozen plasma transfused (2±2.9 units). On the other side, based on the median value of the rate of fall of hemoglobin between preoperative and postoperative time which was estimated at 2.5 g/dl, we defined two groups (N=15).There was no statistically significant difference in the mean D-dimers levels in the two groups (P=0.08) contrary to preoperative hemoglobin level and postoperative bleeding volume 24 hours after surgery. Furthermore, our study didn't demonstrate a correlation between D-dimers concentration and postoperative bleeding loss.
Summary/Conclusion: In summary, our results indicate, in small number, that there is an activation of fibrinolysis in patients undergoing CBP surgery as shown by the elevation of D-dimers level in the early postoperative period. A large study is desirable to study fibrinolysis in patients undergoing CBP, its pathophysiological implications and its correlation with hemorrhage complications

PB1825 A RARE CASE OF BI-ATRIAL THROMBI IN A STAGE IV PANCREATIC CANCER PATIENT WITH ATRIAL FIBRILLATION ON WARFARIN

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Background: Atrial fibrillation (AF) is the most common arrhythmia and can result in adverse consequences of reduced cardiac output or formation of atrial thrombus. AF-related systemic thromboembolic events are the leading cause of mortality and morbidity in AF patients. Thus patients are placed on anticoagulants after risk stratification.
Aims: We present an unusual case of a 78-year old male with Stage IV pancreatic cancer and underlying AF who was found to have bi-atrial thrombi while on warfarin therapy.
Methods: Case report with information extracted from patient chart per CARE (CAse REport) guidelines
Results: CT abdomen and pelvis for routine surveillance revealed small thrombi within the right atrium and left atrial appendage, which was new compared to his most recent CT imaging performed 3 months prior. At the time of imaging, the patient was noted to have supra-therapeutic prothrombin time-international normalized ratio(PT-INR) of 3.3. The patient was admitted and initiated on unfractionated heparin infusion. He declined transitioning to low molecular weight heparin therapy as this regimen required daily subcutaneous injections. He was instead discharged home on apixaban.
Summary/Conclusion: Pancreatic cancer is associated with a hypercoagulable state; the development of thrombi despite being on anticoagulation highlights the significance of clinical awareness of thromboembolism in patients with cancer regardless of therapeutic warfarin anticoagulation. The choice of an ideal anticoagulant in patients with concomitant AF and cancer remains a controversy. Traditionally, warfarin has been the mainstay of anticoagulation therapy for stroke and systemic thromboembolism prevention in patients with AF. However, our case of failed anticoagulation with warfarin suggests that this agent may be a less ideal choice in patients with underlying malignancy, particularly in the setting of hepatic dysfunction. Recent clinical evidence suggests that a number of direct oral anticoagulants (DOACs) can effectively prevent thrombotic events with comparable safety index in cancer patients to conventional therapy. Prudent consideration of multidisciplinary factors (thrombotic and bleeding risk, drug-drug interactions, patient's renal and hepatic function, nutritional status, patient preferences) is required in order to deliver individualised, safe, and effective anticoagulation therapy.

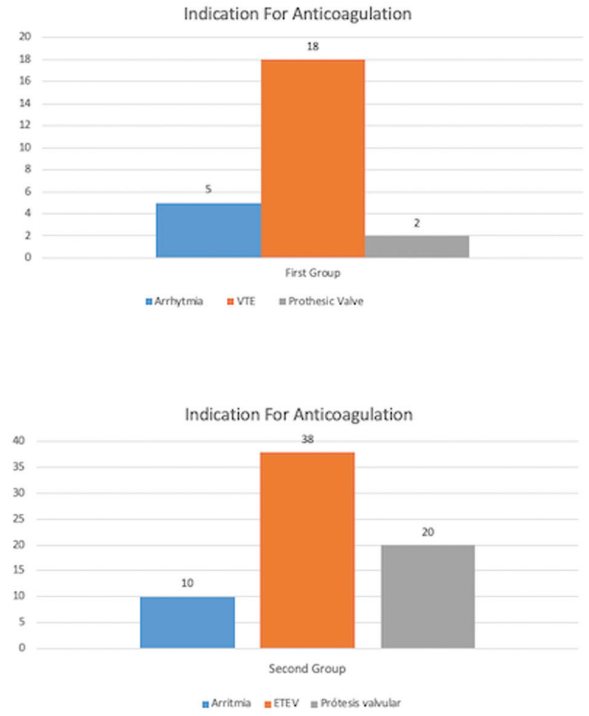
PB1826 EXPERIENCE IN THE USE OF BIOSIMILAR ENOXAPARIN SODIUM FOR PROPHYLAXIS AND TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE IN OUR HOSPITAL

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Background: A biosimilar is a medicine of biotechnological origin, produced according to specific requirements established by the European Medicines Agency (EMA) regarding quality, efficacy and safety.
Aims: The main objective is to evaluate the efficacy and safety of using enoxaparin sodium biosimilar (Inhixa ®) available in our center, for the

prophylaxis of venous thromboembolic disease and the treatment of deep vein thrombosis, as well as hemorrhagic or thrombotic complications.
Methods: We evaluated two groups of patients with enoxaparin sodium biosimilar:
First group: Patients continuously anticoagulated at full doses, who were suspended oral anticoagulation due to recurrent hemorrhagic diathesis, active cancer under chemotherapy treatment and / or thrombosis.
- 25 patients treated with heparin at weight adapted doses once a day, as a starting dose, and then subsequently, according to anti-Xa levels.
- Ages between 50 and 88 years old.
- Indication of main anticoagulation: 5 arrhythmia, 18 VTE and 2 prosthetic valves.
- Most of the cases presented several associated diagnoses, and 75% of them comorbidities.
Second group: Anticoagulated patients with VKA with high thromboembolic risk, who have required bridging therapy at full doses.
- 98 patients. Bridging therapy consisted of suspending VKA from 4 (acenocoumarol) to 6 days (warfarin) before the procedure and substitution with biosimilar enoxaparin sodium: 1.5 mg / kg / 24 h, and administration of a prophylactic dose 4,000 IU, 12 hours before of the procedure, and another dose 6-12 hours after it, depending on the risk of bleeding from the intervention and the thrombotic risk of the patient's underlying disease.
- The ages ranged from 21 to 87 years.
- Indication for main anticoagulation: 10 arrhythmias, 58 VTE (with or without thrombophilia) and 30 prosthetic valves.
Results: In patients who had secondary bleeding to VKA, it totally disappeared with heparin. As side effects, only 3 patients had complications, being allergic reaction to heparin. There were no bleeding or thrombotic phenomena. There were 6 cases of hematomas at the heparin puncture sites.



Summary/Conclusion: Although these are few cases, the results obtained confirm the efficacy, safety and cost-effectiveness of the continuous use of enoxaparin sodium biosimilar in the prevention of VTE in patients requiring anticoagulation, when VKA are contraindicated and and DOACs cannot be managed. Anti-Xa levels are very useful for dose adjustment when necessary. Biosimilar enoxaparin sodium administered at therapeutic doses in the perioperative period, according to the scheme described, is associated with a low incidence of VTE recurrence and bleeding. Treatment should be personalized according to each patient and factors related to the surgical intervention. Further studies will provide more confirmatory data. Biosimilar drugs have the potential to offer the National Health System cost savings and expand access to therapeutic innovations.

PB1827 STUDIES OF GEOGRAPHIC VARIATIONS IN RISK FACTORS ASSOCIATED WITH THROMBOPHILIA AND ITS POSSIBLE IMPACT ON DISEASE MANAGEMENT PLANNING

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Background: Thrombophilia is a hypercoagulability disease that gives rise to clot formation in the blood leading to stroke, deep vein thrombosis, or pulmonary embolism. The prevalence of different risk factors associated with thrombophilia varies in different regions of the world that may impact its clinical management. However, no studies have been conducted in Al Ahsa concerning thrombophilia. Therefore, the aim of this study is to find out the risk factors associated with thrombophilia in Al-Ahsa.
Aims: Therefore, the aim of this study is to find out the risk factors associated with thrombophilia in Al-Ahsa and its comparison with other regions of the world.
Methods: This was retrospective cross-sectional study. It included 329 thrombophilia patients attending King Abdulaziz Hospital (KAH) from 2015-20. Patient data was retrieved from BestCare and was analyzed using SPSS version 20.
Results: Thrombophilia was significantly more prevalent in females than males. It was most common in the age group 44-54 years (44.7%). The main risk factors associated with thrombophilia were anti-phospholipid syndrome (52.3%), Protein S deficiency (17.9%), Protein C deficiency (13.4%), anti-thrombin deficiency (7.6%), familial predisposition (4.3%) and lupus anticoagulant (0.3%). Frequencies of thrombophilia-associated risk factors in Al-Ahsa region was significantly different from Korean population ($p<0.05$) (Figure 5).

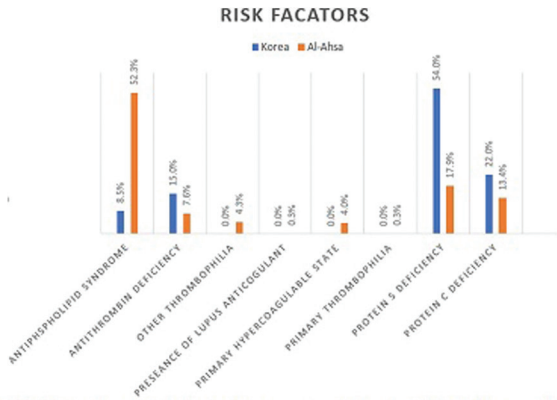


Figure 5: Multiple Bar chart displaying the percentage of thrombophilia risk factors in Al Ahsa and in Korea [12].

Summary/Conclusion: In our studies, female gender, anti-phospholipid syndrome, Protein S deficiency, Protein C deficiency, anti-thrombin deficiency and familial predisposition were found to be major risk factors associated with thrombophilia, respectively, that showed significant difference from other populations. These geographic variations in frequencies of different risk factors associated with thrombophilia may be attributed to different lifestyle, nutritional habits, genetic make-up and other ethnic differences in various geographical regions of the world. Strategies related to clinically manage thrombophilia in any clinical settings should consider prevalence of different genetic and non-genetic risk factors in that region.
References:

PB1828 THE USEFUL OF TESTING DIRECT ORAL ANTICOAGULANTS

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Background: Direct oral anticoagulants (DOAC) do not require routine laboratory monitoring, but it is useful to know the impact on coagulation

assays in order to interpret the results specially in emergency situations as bleeding or urgent perioperative management.
Aims: The objective of our study is to determnine de DOAC concentration with specific test in control patients under different DOAC treatment and compare the results with routine coagulation assays in different moments, plasma concentration at peak (3 hours after drug intake) and through (just before intake).
Methods: Samples from volunteers patients with non-valvular atrial fibrillation (NVAF) under DOAC treatmente were collected at peak and through plasma concentrations. For all samples prothrombine time (PT) with Tromborel and activated partial thromboplastin time (APTT) with Actin-FS were measured. For anti-Xa DOAC also anti-Xa activity (heparin calibrated) with Innovance Heparine and plasma concentration with STA-Liquid anti-Xa (Stago) was quantified anf for Dabigatran thrombin time (TT) with Thromboclotin and the specific test STA-ECAII (Stago) were used.
Results: 30 patients were included (59% males, median age 71 [IQR 41-88] years. 3 Dabigatran 150 mg/12 hours, 2 Dabigatran 110 mg/12 hours, 8 Rivaroxaban 20 mg/24 hours, 2 Rivaroxaban 15 mg/hours, 14 Apixaban 5 mg/12 hours and 1 Apixaban 2,5 mg/12 hours. The results for different test at peak and through are seen in Table 1. Under Dabigatran TT was uncoagulable for all samples, and all PT and APTT results were pathological. The most statistical correlation test with DOAC level (Apixaban and Rivaroxaban) was anti-Xa (heparin calibrated) specially at throug moment with a P<0.0001

Table 1 Results of coagulaion test at throuh and peak moments under DOAC treatment

	APIXABAN n:15 Median (25th-75th percentile)		RIVAROXABAN n:10 Median (25th-75th percentile)		DABIGATRAN n:5 Median (25th-75th percentile)	
	Through	Peak	Through	Peak	Through	Peak
PT sec (normal range 10-14)	13.1 (12.5-13.5)	14.3 (13.5-14.8)	12.8 (11.7-16.5)	16.1 (15.5-24.2)	15.6 (15.1-15.7)	16.6 (16.3-17.8)
APTT ratio (normal range 0.8-1.2)	1.15 (1.1-1.3)	1.2 (1.1-1.2)	1.1 (1.0-1.4)	1.4 (1.3-1.7)	1.7 (1.6-1.9)	2.1 (1.8-2.2)
Anti-Xa IU/mL (heparin calibrated)	0.56 (0.36-0.78)	1.79 (1.25-2.01)	0.25 (0.05-0.73)	1.70 (1.63-1.75)		
Concentration ng/mL	82 (66-106)	223 (157-303)	31 (11-73)	228 (170-338)	190 (158-205)	300 (245-335)

Summary/Conclusion: The results of DOAC concentration at peak and through are similar to literature except for Dabigatran that in our study are higher perhaps because there are few samples. Similar to other studies Dabigatran is the DOAC that most modifies coagulation assays specially APTT also at through moments and Apixaban is the DOAC that nearly no prolongs PT neither APTT on-therapy concentrations. For these reasons PT and APTT are not recommended to know coagulation state under DOAC treatment. The quatification of DOAC levels in plasma is more informative and useful tan other coagulation parameter so in case to measure low plasma concentrations in special circumstances specific test calibrated are required but if these are not available for direct FXa inhibitors a heparin-calibrated chromogenic assay can be indicative of clinically relevant levels of a ditrect FXa inhibitor.

PB1829 DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM IN AN ADOLESCENT WITH SARS-COV-2 INFECTION

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Background: Pulmonary embolism (PE) is reported in around 2.6–8.9% of COVID-19 hospitalized adult patients, but it is very rare in children and adolescents with symptomatic infection from SARS-CoV-2.
Aims: This is the case of a 15-year-old male patient with COVID-19 complicated by deep vein thrombosis (DVT) who developed PE.
Methods: The patient presented with fever and a four-day history of pain and swelling of the right lower limb, without any history of injury. It is notable that 15 days before admission, he experienced diarrhea, vomiting and low-grade fever for 48 hours. The adolescent boy had short stature and was rather overweighted for his age and gender (body mass index: 25.2 kg/m^2), while over the last two years he was receiving anastrozole (aromatase inhibitor), for height increase.
Results: On admission, due to pain, limited mobility of the right limb and edema of the ipsilateral knee, a triplex ultrasound was performed that revealed DVT extended from the right iliac to the popliteal vein. RT-PCR for SARS-CoV-2 was positive, while the rest of the laboratory results showed a prolongation in prothrombin time (16.3 seconds, normal values: 10-14 sec), elevated d-dimers (10 mg/dl, n.v.: < 0.5 mg/dl), high levels of factor VIII (214 IU/dl, n.v: 50-150 IU/dl), low levels of antithrombin (36 IU/ml, n.v.: 80-120 IU/ml) and increased ferritin (346 µg/L, n.v.: 10-150 µg/L). Initial management consisted of antibiotic therapy plus anticoagulation with subcutaneous low molecular weight heparin (LMWH) i.e. tinzaparin in therapeutic dose. Soon after admission the patient developed severe hypotension with low diastolic blood pressure, refractive to IV normal saline boluses while his oxygen saturation dropped to 94% few hours later. A CT pulmonary angiogram (CTPA) was performed revealing a big thrombus with longitudinal diameter of 3 cm, in the left pulmonary artery, establishing the diagnosis of PE on the ground of DVT. After PE diagnosis, the patient was transferred to the intensive care unit (ICU) for 48 hours, and subsequently at the special SARS-CoV-2 ward for 4 weeks. He completed a ten-day course of intravenous dexamethasone and anticoagulation treatment was switched to oral warfarin, after completion of three weeks of LWMH. Apart from COVID-19 whose hypercoagulable physis is already well-established the patient had additional risk factors predisposing to thromboembolic episodes. More precisely, he was overweight and under aromatase inhibitor therapy (which can be procoagulant by increasing testosterone levels). Moreover, the preexisting symptoms from the gastrointestinal system, could have predisposed him to DVT in view of dehydration and increased viscosity. On top of it, it is noteworthy that the patient had excessive screen time for his tele-education the last three weeks prior to the onset of VTE, meaning there were long periods of immobilization. Additionally, during the course of COVID-19 infection he had low levels of antithrombin, a serious prothrombotic condition attributed to the disease.
Summary/Conclusion: This case underlines the fact that pediatric patients with COVID-19, are predisposed to the development of thromboembolic events, especially in the presence of preexisting prothrombotic risk factors. Larger studies in pediatric population with SARS-CoV-2 infection are needed, for the establishment of recommendations regarding risk evaluation, hemostatic monitoring and application of anticoagulation in outpatient, as well as hospitalized patients.

PB1830 COVID-19 ASSOCIATED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP); A CASE SERIES AND MINI-REVIEW

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Background: Thrombotic microangiopathies are a group of disorders that are mainly related to endothelial dysfunction. This category of endothelial dysfunction results of several imbalances between platelets, endothelium and immune system, also cytokine production
Aims: To report cases with thrombotic thrombocytopenic purpura (TTP) and COVID-19 and review COVID-19 endothelial dysfunction literature.
Methods: Primary laboratory data, peripheral blood smear, ADAMTS13 antigen activity level, and antibody ordered for each of these four patients. Treatments for COVID-19 administered for all patients. Traditional treatments for TTP also were administered.

Results: There were numerous schistocytes (more than 5%) in peripheral blood smears for each patient. ADAMTS13 antigen activity level was below 10%, and ADAMTS13 antibody was elevated for each patient. COVID-19 PCR was positive for all patients, and CT-Scans were indicative of the involvement of COVID-19.
Summary/Conclusion: Conclusion: In this case series, we reported four COVID-19 patients who presented with signs and symptoms of anemia and thrombocytopenia, resulting in thrombotic thrombocytopenic purpura.

PB1832 A YOUNG WOMEN WITH LIGNEOUS MEMBRANES WHO WANTS TO BE PREGNANT

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Background: Plasminogen deficiency is a rare condition with autosomal recessive inheritance. Severe hypoplasminogenemia is associated with 'ligneous' lesions on each mucous membranes especialy eye, ear, mouth, pharynx, respiratory and female genital tract; cervix and endometrium. Furthermore, plasminogen deficient women complained from infertility. These kind of patient's diagnosis remained elusive for years.
Aims: We want to share this young women in order to take attention and form a greater familiarity with the clinical and histopathologic features of this condition among gynecologists.
Methods: Data from the files of a 32 year -old nulliparous young woman with intractable gingivitis and dental problems and a history of persistent conjuctivitis is documented.
Results: She was refered to a gynaecologist due to infertility and cervicitis. Colposcopic and ultrasound examination of the uterus revealed, woody membraneous lesion which cover the inner site of the uterine cavity. We decided to give fresh frozen plasma (FFP) infusions both IV and locally to the uterine cavity after diagnosis of plasminogen deficiency. Heparine added FFP (50ml) also 5mg recombinant plazminogen activator (rt-PA, Actilyse^{R})remained in the cavity for 2-4 hours. Although a regular cavity view was achieved after FFP replacement therapy and local application, freeze embrional transfer was performed without a proper pregnancy achievement.
Summary/Conclusion: Gynecologists and clinicians who are familiar with this bizarre disease's clinical and histopathologic features will diagnose timely and manage properly.

PB1833 AN AUDIT OF DIAGNOSIS AND MANAGEMENT OF PE IN DGH AND LITERATURE REVIEW.

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Background: Pulmonary embolism remains a worldwide major health problem.**1** It is among the most common causes of vascular death after myocardial infarction and stroke, and is the leading preventable cause of death in patients in hospital. Pulmonary embolism (PE) is a life-threatening condition resulting from dislodged thrombi occluding the pulmonary vasculature; right heart failure and cardiac arrest may ensue if not aggressively treated.
Common clinical features include dyspnoea, pleuritic chest pain, and hypoxaemia. There may also be evidence of a concurrent deep vein thrombosis. Hypotension, syncope, tachycardia, and signs of right heart failure are less common signs but are important to recognise as they suggest a high-risk PE with a larger clot burden and a higher mortality rate. Clinical probability, assessed by a validated prediction rule and clinical judgement, is the basis for all diagnostic strategies for PE. Computed tomographic pulmonary angiography is the definitive diagnostic investigation..Haemodynamically unstable patients require urgent primary reperfusion (usually thrombolysis), anticoagulation, and supportive care. Those at intermediate risk of a poor outcome require anticoagulation and ongoing monitoring; rescue reperfusion should be used if patients become haemodynamically unstable.
Aims: Objectives of this audit was to determine compliance rates with NICE CG 144 in diagnosing PE and Re-audited after 1 year to assess improvement in practice
Methods: - **First Loop –** Notes of 100 patients who were referred for CTPA to radiology department was taken and analysed for clinical features and documentation of wells score and results of CTPA during 2017. Subsequently results were presented in medical grand round and recommendations were dissipated to medial teams and published in hospital news bulletin. In first loop only in 3% patients Wells score was calculated. While incidence of PE was 14%
- **Second loop –** Notes of 50 patients who were referred for CTPA to radiology department was taken and analysed for clinical features and documentation of wells score and results of CTPA during 2018. Again results were presented in medical grand round and recommendations were dissipated to medial teams and published in hospital news bulletin. In 2nd loop wells score was calculated in only 18% of patients and incidence of PE was 22%.
Results: Clinical features of PE in descending order (as per NICE)
- Dyspnoea (70% of patients). 1st 67. 2nd 72. Tachypnoea (RR >20). Pleuritic Chest pain. 47% 50%
- Apprehension. Tachycardia (HR >100). 1% -8%. Cough. 1st 7% 2nd 16 %
- Haemoptysis.1st 2% 2nd 8%. Leg Pain. Clinical evidence of DVT (10% of patients). Dizziness 1%>2%
- Majority of patients presented with mix symptoms.

Good clinical history and examination are key factors to establish the diagnosis followed by an appropriate investigation depending on risk stratification
Summary/Conclusion: Difficult to know how many patients warranted CTPA. Can assume unnecessary CTPAs have been performed. Costly investigation. Radiation – one CTPA = 350 CXRs Slight increase in compliance with NICE guidelines (from 3% to 18%).

Transfusion medicine

PB1834 ERYTHROCYTE AND PLATELET TRANSFUSION PRACTISES IN PEDIATRIC HEMATOLOGY AND ONCOLOGY PATIENTS AND INVESTIGATION OF THEIR EFFECTS ON OUTCOME

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Background: Supportive treatments have vital importance in pediatric oncology patients, besides the treatment intended to cancer.
Aims: We aimed to define the frequency and thresholds of erythrocyte and platelet transfusions which are administered to pediatric hematology and oncology patients and to investigate the effects of transfusions on outcome.
Methods: Eighty leukemia (31.6%) and 173 lymphoma or solid tumor (68.4%) patients who were diagnosed and treated in Dokuz Eylül University Pediatric Hematology and Oncology Departments between the January 1, 2013 and January 1, 2018 and transfused with erythrocyte and/or platelet suspension at least for one time period in the course of their treatments are involved in this study. The data of the patients were scanned by clinical follow-up records and DEU Hospital Blood Bank records, retrospectively.
Results: A total of 1389 units of erythrocyte suspension (ES) and 1357 units of platelet suspension (PS) were administered to the leukemia group; 1604 units of erythrocyte suspension and 1243 units of platelet suspension were administered to the lymphoma and solid tumor group. A significant difference was detected between the leukemia and solid tumor groups in terms of ES and PS transfusion numbers; as the leukemia group had more transfusions ($p<0.001$). Pretransfusion mean hemoglobin and platelet values were 7.3±0.69 (6.2-11.7) g/dL and 22.8±6.95 (10.5-53.3)x10^9/L in leukemia patients and 8.2±1.21 (5-13.9) g/dL and 30±30.86 (4.3-260) x10^9/L in lymphoma and solid tumor patients, respectively. A positive correlation was detected between platelet values at initial diagnosis and total number of PS transfusion numbers of leukemia patients ($p<0.001$). There was no relation between Hb value at diagnosis and ES transfusion numbers. In lymphoma or solid tumor patients; negative correlation was found between Hb levels at diagnosis and ES transfusion numbers ($p=0.005$). When the patients were compared in terms of survival rates as classified according to pretransfusion mean Hb and platelet values, the overall survival rate was found to be shorter in leukemia patients whose pretransfusion mean hemoglobin and platelet values were above 7.5 gr/dL and 30 x10^9/L, respectively (Log rank $p=0.044$ and 0.046). Event free survival rates were also

negatively affected in leukemia patients whose pretransfusion hemoglobin was above 7.5 gr/dL (Log rank p=0.006). There was no significant association between pretransfusion values and survival rates in patients with lymphoma and solid tumors.
Summary/Conclusion: Total ES and PS transfusion numbers were higher in patients with leukemia in comparison with patients with lymphoma and solid tumors. On the other hand, pretransfusion Hb and platelet thresholds were found to be higher in the lymphoma and solid tumor patients in comparison with the leukemia group. Leukemia patients with higher pretransfusion Hb and platelet thresholds were found to have lower survival rates; however, studies including more homogeneous and extensive patient groups are needed to demonstrate this association more clearly.

PB1835 FREQUENCY OF DIFFERENT BLOOD GROUPS AND ITS ASSOCIATION WITH BODY MASS INDEX AND BLOOD PRESSURE AMONG TWO-THOUSAND-EIGHT-HUNDRED-EIGHTY-THREE BLOOD DONORS

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Background: The association of hypertension and obesity with blood group "B" was reported by many researchers. Recognition of a positive relation with blood group might reflect increased susceptibility to hypertension wich is still required to be explored by new researches.
Aims: to determine the frequency of different blood groups among blood transfusion post donors and find the association of blood groups and body mass index with blood pressure.
Methods: this cross-sectional study was performed at blood donors transfusion post, from january 2018 to December 2019, participants were divided into groups on the basis of their ABO blood groups, rhesus D and on body mass index criteria. Blood groups were determined by simple conventional slide method. Blood pressure was estimated by manual auscultatory technique with a mercury sphygmomanometer. Data was analysed using SPPS .16
Results: there were 2883 blood donors with an overall mean age of 37± 10,27 years (range: 17-66 years), 288 female and 2595 male, sex-ratio M/F = 9,01. Blood group O was the predominant group (1284→44,5%), besides, 2561 (89%) subject were rhesus positive. The overall mean values for weight, height and BMI were: 80±14.49 kg (50-150), 173.07 ± 7.50 (150-198) and 27,13 ± 4,42 kg/m^2 (16.01-54.09): according to the blood group and BMI, our donors are distributed as follows: blood group A (+): n= 891, the average BMI = 27,12 ± 4,46 kg/m^2 (17,28-50,78), A (-): n= 103, the average BMI is = 18,40 ± 5,02 kg/m^2 (18,3-54,69), blood group AB (-): n= 22, the average BMI = 26,78 ± 2,23 kg/m^2 (20,68- 34,66), blood group AB (+): n=116, the average BMI = 26,69± 4,26 kg/m^2 (17,99- 39,63), blood group B (-): n= 47, the average BMI = 26,90 ± 5,16 kg/m^2 (18,29- 39,27), blood group B (+): n= 420, the average BMI = 26,97 ± 4,34 kg/m^2 (17,36- 44,44), blood group O (-): n= 145, the average BMI = 27,01 ± 4,66 kg/m^2 (18,59- 44,18), blood group O (+): n= 1139, the average BMI = 27,14 ± 4,72 kg/m^2 (16,07- 46,30). Moreover 314 subjects (1%) were pre-hypertensive: blood group A: n= 184 (6%), blood group AB: n=26 (0,9%), blood group B: n=79 (2,7%), blood group O: n= 25 (0,9%). Relative risk of hypertension for obese was grater than non obese: AUC=0.459 (p=0.009), body mass index was associated with both systolic pressure (p=0.001), on the other hand, in our study, no significant differences were observed in the mean SBP (systolic blood pressure) and diastolic blood pressure (DBP) among the ABO study groups: AUC: 0,276, p=0.067 and AUC = 0, 429, p=0,156 for the two evaluations respectively
Summary/Conclusion: blood group O was the most common blood group, it is strongly correlated with the risk of obesity, but in contrast to some researches, regression analysis of the present data did not find any significant association of blood groups with DBP and SBP

PB1836 THE PREVALENCE OF MNS, KIDD, DUFFY BLOOD GROUP SYSTEMS PHENOTYPES IN BLOOD DONORS LIVING IN THE EUROPEAN PART OF RUSSIAN FEDERATION

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Background: Patients with hematological disorders are at high risk of developing post-transfusion complications. The possibility of alloimmunization to red blood cell antigens grows with an increase in the number of transfusions.The incidence of alloantibodies in patients ofour hematology clinic is 1.8%. A register of blood donors typed for a wide range of transfusion-dangerous antigens was created to select compatible red blood cells.
Aims: The aim was to study the prevalence of MNS, Kidd, Duffy blood group systems phenotypes in blood donors living inthe European part of Russian Federation and to compare with them in Caucasoids of Europe and America.
Methods: Immunohematological tests were carried out using equipment and reagents from BioRad (USA).
Results: The register currently includes 327 donors of blood components. The prevalence of phenotypes is shown in the table.

Table. The prevalence of red blood cells antigens

System	Phenotype	Prevalence (%)	
		Blood donors of European territory of Russia	Caucasoids of Europe and America (Shaz B.H., 2013)
MNS	M+N-S+s-	6,7	6
	M+N-S+s+	13,2	14
	M+N-S-s+	11,3	10
	M+N+S+s-	6,4	4
	M+N+S+s+	20,2	22
	M+N+S-s+	22,9	23
	M-N+S+s-	0,6	1
	M-N+S+s+	4,6	6
	M-N+S-s+	14,1	15
	M+N-S-s-	0	0
	M+N+S-s-	0	0
	M-N+S-s-	0	0
Kidd	Jk(a+b-)	22,2	26
	Jk(a-b+)	24,5	23
	Jk(a+b+)	53,3	50
Duffy	Fy(a+b-)	22,0	17
	Fy(a-b+)	27,5	34
	Fy(a+b+)	50,5	49

Summary/Conclusion: No significant difference was found in the prevalence of MNS, Kidd, Duffy phenotypes in blood donors living inthe European part of Russian Federation and with them in Caucasoids of Europe and America.

Index

Aabrams V., PB1725
Ababou M., PB1375, PB1551, PB1598
Abadi U., S255, EP503
Abáigar M., EP893
Abbadi R., PB1563
Abbas H., EP401
Abbas W. A., EP715
Abbasian M., EP788
Abbaszadeh Z., EP1203
Abboud C., EP480
Abboud M., S260, S314, PB1762, PB1763
Abd El Aziz M., PB1430
Abdalhadi A., PB1710
Abdallah A.-O., EP743
Abdallah G., EP715
Abdelaziz M., EP1118
Abdelhady A., S210, EP516
Abdellatif R., EP369
Abdelmonem E., EP715
Abdel-Wahab O. I., EP330, EP633
Abderrahim I., PB1629
Abderrahim K., EP714, EP817, EP831, PB1586
Abdo A., EP975
Abdul-Hay M., EP739
Abdulla F., PB1664
Abdullaev A., EP681, EP1071, EP1325
Abdullah K. A., PB1422
Abe M., EP942
Abe Y., S226
Abedi M., EP1235
Abella E., PB1649
Abeysekara A., PB1817
Abi Nehme S., PB1398
Abichou G., PB1452
Abildgaard N., EP851, PB1740
Abo El Ezz S., PB1367
Abonour R., EP985
Abou Dalle I., EP1228
Abou Mourad Y., EP365
Abouchahla W., EP343
Abraham A., EP519
Abraham J., S157
Abramenko I., EP615, EP623
Abramovich D., EP840
Abreu R. M., EP1039
Abrisqueta P., EP546, PB1444
Abruzzese E., S154, EP673, EP1079
Abu Zaid M., S235
Abuin Blanco A., PB1734
Accardi F., EP949
Accurso V., S154
Acebes-Huerta A., EP812
Acevedo L. M., S238
Acevedo García R., S293
Achebe M., EP1206
Achour M., PB1373, PB1423, PB1556, PB1585
Achouro B., EP714, EP817, EP831, PB1586
Acıpayam C., EP1216, EP1218, EP1316
Ackermann C., EP410
Ackermann J., EP547
Acosta Fleitas C., PB1561, PB1798
Acosta-Rivera M., EP1019
Acuña E., EP450
Acuña Butta P., EP1072
Acuña-Cruz E., EP352, EP546
Adachi N., S218
Adaklı Aksoy B., PB1372
Adam A.-S., PB1536, PB1815
Adam J., EP1200
Adam-Frey S., EP1059
Adamczyk E., S164
Adami F., EP1053
Adamidou D., PB1816
Adamis H., PB1440
Adamo F. M., EP620
Adamopoulos I., EP919
Adams G., EP1133
Adams H., EP608
Adams R., S133
Adamson P., S221
Addas Carvalho M., EP1213
Adebayo O., EP956
Ademokun C., EP1130, EP1133
Adès L., S126, S162, S166, EP906, EP928, PB1408
Adeyemi A., EP1145
Adhinaveni R., EP603
Adib D., PB1566
Adinolfi E., EP753
Adnani L., S305
Adorno E., EP1054
Adramerina A., PB1812, PB1816
Advani R., S205, EP506
Affinito S., S157
Afkhami M., EP351
Afonso C., EP1102, EP1114, EP1121, EP1274, EP1290, PB1630
Agarwal A., EP510
Agarwal A., EP1019, EP984
Agathangelidis A., EP609
Aggarwal S. K., EP1235
Agha M., S190, EP964, EP972
Aghajan M., S277
Agis H., EP971, EP1011
Agius R., EP602
Agodoa I., EP1201, PB1769
Agrawal-Singh S., S129
Agriello E., EP625, PB1380
Aguado B., PB1799
Aguiar E., S278, EP488
Aguiar M., PB1463
Aguilar C., EP1329
Aguilar Y., PB1821
Aguilar-Garrido P., EP374
Aguirre Ruiz P., EP411
Ahchouch S., PB1375
Ahlers C. M., PB1698
Ahlgren L., EP406
Ahmad A., PB1454
Ahmad A., EP835
Ahmad A.-S., PB1377
Ahmad H., EP835
Ahmad Asnawi A. W., PB1489
Ahmadi T., S180
Ahman J., S150
Ahmed M., EP830
Ahmed M., PB1395, PB1406
Ahmed N., EP743
Ahmed S., EP1276
Ahmed Z., EP1164
Ahmed Nacer R., EP1255, PB1629
Ahsan A., EP1062
Ai W., EP518
Ailawadhi S., PB1639
Ailinca-Luchian S., EP733
Ainley L., EP983
Aissaoui L., PB1423, PB1556, PB1585
Ait Ouali D., EP1255, PB1629
Aitken M., EP374
Aittokallio T., EP614
Aiuti A., S102, S258, S269, EP741, EP1298
Akashi K., EP914, EP1101, EP1105
Akbas H., EP1316
Akbayram S., EP1316, PB1755
Akçan M., EP1216, EP1218, EP1316
Akhmedov M., EP1260
Akhmerzaeva Z., EP360
Akhrouf S., PB1629
Akhtar O. S., PB1498
Akinci B., EP1316, PB1755
Akram M., S190, EP964, EP1003
Akrama A., PB1557
Akria L., PB1663
Al Aboudi K., PB1454
Al-Adhami M., S174, EP595, PB1471, PB1477
Al-Ali H. K., EP1092
Al-Ammari M., EP554
Al Anezi K., PB1664
Al Askar A., EP1322
Al Battah A., PB1454
Al-Darraji A., EP834, PB1589, PB1729
Al Enazi M., EP814
Al Essa W., EP603
Al-Hadad S., EP834, PB1589, PB1729
Al Hashmi H., EP814, PB1664
Al-Homsi A. S., EP739
Al-Jadiry M., EP834, PB1589, PB1729
Al Jijakli A., S156
Al-Kali A., S169, EP908
Al Malki M., EP345, EP351, EP740
Al Mulhem N., EP814
Al Musailem N., EP814
Al Nabhani I., EP362
Al Raizah A., EP1322
Al Saeed H., EP1220
Al-Saeed R., EP834, PB1589, PB1729
Al Saleh A. S., EP830
Al-Samkari H., S103, S267, S270, S271, EP692, EP696, EP1144, PB1805
Al-Sawaf O., S144, S146, EP632
Al Shami A., EP814
Al-Shemari S., EP631, PB1557
Al Sudairy R., EP369
Al Tabaa Y., EP511
Al Zahrani M., EP1322
AlAfifi A., PB1774
Alagappan D., EP635
Alahmari B., EP830
Alain D., EP652
Alanazi N., PB1827
Alanoglu G., EP1316
Alaoui M., PB1597
Alaskar A., EP830
Alba N., PB1696
Albayrak C., EP1316, PB1372, PB1482
Albayrak D., PB1482
Albertazzi E., EP741
Albi E., EP634
Albo Lopez C., PB1462, PB1464
Albo Lopez M. D. C., PB1604, PB1794
Alborov A., EP836
Albring J., S235
Albtoosh B., EP554
Alburquerque-Prieto C., EP492, EP574
Alcaide A. B., EP809
Alcantar L., EP1010
Alcantar-Orozco E., EP739
Alcazer V., S121
Alcoceba M., EP612, EP631
Aldapt M., PB1454
Alderuccio J. P., EP518
Aldin A., EP779
Aldosari K., EP1322
Aldoss I., EP345, EP351
Alegre A., EP973, EP1021
Alegre F., EP809
Aleinikova O., EP358
Alejo-Valle O., EP398
Aleku M., EP846
Aleman A., EP936
Alencar A. J., EP500, EP633
Aleshina O., EP361
Alessandria B., EP860
Alexander K., EP781
Alexander M., EP371
Alexander S., S221
Alexander W., EP1057
Alexandrou A., EP596
Alexe G., S126
Alexeeva Y., PB1402
Alfayate A., EP1346, PB1819
Alfayez M., EP401, PB1609
Alfia G., EP1112
Alfinito F., EP827
Alfonso A., EP479
Alfonso G., EP927
Alfonso Piérola A., EP907
Alford J. S., S176
Algarra J.-L., EP352
Algarra L., EP447
Algeri M., S116
Alghaithi I., EP1220
Alghamdi A., EP830
Alhejazi A., EP830
Alho A., PB1449
Ali G., PB1796
Ali H., EP345, EP351, EP1075, PB1713
Ali H. A., EP1159
Ali K., EP1135
Ali M., EP373
Ali S., PB1719

Ali S., PB1383
Ali S., EP784
Ali Khan M., EP631
Alignani D., EP809
Alinari L., EP861
Alison P., EP754
Alizadeh H., PB1641
Aljama M., EP1015
Aljurf M., EP1228, EP1276
Alkaiyat M., EP369
Alkhateeb H. B., S169
Alkhateeb M., PB1710
Alkhraisat S., EP830
Alkindi S., EP1220
Alkodsi A., EP856
Allain V., EP540
Allan J., S105
Allan J. N., S147
Allen C., PB1761
Allen I., EP743
Allen P., S218
Allò M., PB1810
Allocati E., PB1550
Allred A., EP964
Allsup D., EP644
AlMajed M., PB1827
Almáši M., EP954, PB1677
Almegren M., EP1322
Almeida A., S106
Almeida A., EP1054, PB1631
Almeida A., S152
Almeida D. R., EP1039
Almeida Arvizu A., EP1156
Almici C., EP449
AlMohammadi A., PB1422
Almudaiheem H., EP1220
AlMukhaylid S., PB1827
AlMutairi N., PB1827
Alnahdi M., EP1322
Alnajjar F., EP554, PB1609
Alnakhli A., PB1609
Alnoamani M., PB1609
Alonso J., EP479
Alonso N., EP352, EP546
Alonso R., EP721, PB1689
Alonso S., EP616
Alonso-Dominguez J. M., EP670
Alonso-Saladrigues A., EP734
Alonso Vence N., PB1734
Alotaibi A., EP1261
Alottaibi S., PB1557
Alquezar-Artieda N., EP320
Alraihan A., PB1557
Alrajhi A., EP554, PB1609
Alrayes E., EP1322
Alric C., EP482
Alrifai T., PB1825
Alsadi H., EP830
AlShehab B., PB1827
Alshehri A., PB1533
AlShehry N., PB1609
Alshuaibi T., EP1322
Alt C., EP1198
Altaf S., PB1609
Altamura S., S100, S275
Altareb M., EP1276, PB1796
Altman J. K., S135, EP437, EP443, EP448, EP462, PB1408
Altmüller J., S225
Altooq J., EP1220
Altuna D., EP665
Alun P., PB1383
Alvarado-Valero Y., S113, S167, EP367, EP430, EP440, EP463, EP466
Álvarez N., EP412
Alvarez Bollea M., EP997
Alvarez-Larrán A., S158, EP472, EP481, EP670, EP1084, EP1089
Alvarez Román M. T., EP1072
Álvarez Sánchez-Redondo N., EP408
Alvarez-Twose I., S201
Alves D., PB1449
Alves R., EP421, EP630, PB1350, PB1630
Alves R., EP809
Alwie Y., S128, S139
Aly N., EP1185
Alzahrani K., PB1609
Alzahrani M., EP830
Amaador K., EP796, EP804, EP873
Amador M.-L., EP352
Amal C., EP714
Amandi S., PB1526
Amandine C., EP1278
Amare P., EP958
Amato V., EP394
Ambarkhane S., EP553, PB1444
Amber V., EP1238
Amdiev A., EP1190
Amel L., EP1285
Amendola A., PB1460
Amer A., PB1377
Amer K., PB1753
Amiable C., EP383
Amigo M.-L., EP352
Amigo M., EP447
Amin A., S187
Amin H., EP1031
Amit O., S255, S284, S285
Ammatuna E., EP420, EP1284
Ammendola F., EP1310
Ammon A., EP887
Amnam I., EP351
Amorós C., EP563
Amoura Z., EP330
Amouri A., PB1420
Ampazoglou E.-D., EP1146, PB1351
Amstislavskiy V., S120
An G., EP1024, PB1670
An H., S251
An L., EP346
An Z.-Y., EP1142
Anagnostopoulos A., EP609, EP1153, EP1232, EP1254, EP1256, EP1299, PB1368, PB1583, PB1697, PB1721, PB1804
Anagnou N., EP939
Anand J., EP1175
Anand S., S238
Anastasia A., EP793
Andari V., PB1368
Andel J., EP971
Andemariam B., S263, S314, EP1206, PB1762
Andersch F., EP381
Andersen C., EP1107
Andersen L., S134
Andersen M. K., EP359
Andersen M., S159
Andersen N. S., EP359
Anderson A.R., EP1205, EP1209
Anderson K., S186
Anderson M., EP944
Anderson Jr L. D., EP984, EP988, EP1010, EP1173
Anderson Tvedt T. H., EP1296
Andersson A., EP718
Andersson B., EP1028
Andersson T. M.-L., EP1088
Ando M., EP443
Andolfo I., S276, EP688
Andorno A., EP603
Andrade-Campos M.-M., EP890, EP1089
André M., EP496, EP654, PB1444
Andreadis C., S210
Andreas M., EP1187
Andreasson B., S158
Andreatos E., EP1010
Andreeff M., EP379, EP401, EP430, EP464, EP471, EP1068
Andreescu M., EP828
Andres O., S270, EP692
Andresen V., EP383
Andrew G., EP432
Andrey K., EP781
Andrieux G., S199
Andrievskikh M., EP1190
Angeletti I., EP651
Angelopoulou M. K., EP551, EP631, EP773, EP774, EP777, EP808, EP939, EP1272, PB1560, PB1577
Angelosanto N., EP480
Angelov D., EP1292
Angelova S., PB1421
Anghileri E., S259
Angona A., EP670, EP1089
Anguille S., EP739
Anguita J., EP726, EP1168
Anguita Santos F., PB1599
Anguita Velasco J., PB1791
Angurukankanamge W. P., PB1817
Angus J., EP1258
Aniceto Silva J. P., PB1823
Anisimova E., EP1110
Anjos R., PB1767
Anna S., EP644
Annibali O., EP793, EP867, EP883, EP1184
Annunziata M. A., PB1550
Annunziata M., S112
Ansell S. M., S205
Antherieu G., EP451
Anthony C., PB1743
Antic D., S307, EP629, EP631, EP1043, EP1326
Antoine G., EP1278
Antonarelli G., S259
Antoniadou A., S287
António A., PB1727
Antonucci L., EP1203
Anttonen M., EP1192
Anwar F., EP1015
Anyanwu F., EP559
Anyfanti P., EP1232
Anz B. M., EP1019
Anzai T., EP507
Anžej Doma S., EP1109
Aparicio Pérez C., PB1788
Apel A., S285
Apodaca Chávez E. I., EP1156
Apolito V., S308, EP474
Apostolakou F., S280
Appelmann I., EP387
Apperley J., S153, PB1521
Appius A., PB1480
Aprile A., S249, S268
Aprile S. M., EP1152
Aquilina N., PB1595
Aquino S., S182
Aragona V., EP723
Arai S., S239, EP717, EP1224
Arakaev O., EP358
Arangio Febbo M., EP810
Arango J., S133
Arango-Hisijara I., EP782
Arapaki M., EP551, EP773, EP774, EP777, EP1272, PB1560
Aras B., PB1403
Arash-Kaps L., EP694
Araújo A. L., EP579, PB1693
Araújo E., PB1767
Arbelbide J., EP927, PB1380
Arbeteta Juanis J., PB1425, PB1450, PB1692, PB1787
Arboix-Calas F., PB1752
Arcaini L., EP1098
Arcas Vega M. R., PB1722
Arce Fernández O., PB1526
Arcese W., S240, EP420
Archetti S., EP449
Arcioni F., EP1307
Arcuri G., PB1765
Arcuri L., EP550
Ardekani G. S., EP1169
Ardeshna K., EP504, EP518, EP765, EP783, PB1570
Areias A., EP425
Arellano M. L., S117, EP452, EP909
Arellano-Rodrigo E., EP1084
Arena V., S114, EP624
Arends C. M., EP755
Arenillas L., EP606, EP890
Arens A. I., EP517
Arens R., S141
Arfeuille C., EP343
Argemi J., EP809
Argento C., PB1771
Argüello de Tomás M., EP1132
Argüello Marina M., EP1327
Argüello-Tomás M., PB1696
Argumanez M., PB1692, PB1787
Arias C., EP498
Arias-Arias A., EP621
Aribandi A., PB1469, PB1718
Aribi A., EP345, EP351
Ariceta B., EP411
Arikan F., PB1683, PB1705
Aristei C., EP1288
Arjomand A., EP855
Arlet J.-B., S314, EP1207, PB1762
Armari S., EP1313
Armengol L., EP606
Armour M., EP985
Armstrong M., PB1433
Armytage T., EP433
Arnan M., EP479, EP889, PB1407
Arnan Sangerman M., S138
Arnaudov G., PB1421
Arnold D., EP1154
Arnold L., EP592
Arnulf B., S180, EP1003
Arock M., EP1065, EP1066, EP1068, EP1070
Aronen P., EP580
Arora P., S299, PB1733
Arosio G., EP658
Arquero T., EP889
Arranz R., EP546
Arricibita Varea A., S123, EP378
Arrizabalaga B., EP712, EP889
Arruda A., EP1083, EP1093
Arruda M. D. G., EP1054, EP1286, PB1631
Arslan S., EP351, EP345
Artemyeva A., EP1264
Artola M. T., EP329, EP350, EP352, EP546
Arts R. J., EP1067
Artuso S., EP673
Artyukhina Z., PB1800
Artz A., EP345, EP351

Arya R., PB1596
Asada S., S300
Asari K., EP332
Asatiani E., PB1626, PB1713
Ascani S., S227
Asch A. S., S214
Aschan J., EP1028
Asemissen A. M., S183
Asghar N., EP1015
Ashaye A., PB1738
Asher S., EP1047
Ashraf B., PB1547
Ashraf K. K., PB1441
Ashykhmin A., EP776
Asimakopoulos J., EP551, EP808, EP1272, PB1560, PB1577
Asinari M., PB1380
Asiri M., PB1533
Askari E., S191
Aslam A., PB1354, PB1355, PB1356
Aslam M., EP989, EP1038, PB1643
Aslan N., EP1316, PB1755
Asma A., EP817, EP831, PB1586
Asma H., EP683, PB1558, PB1559
Asnafi V., EP790
Asou C., PB1455
Asou N., EP667, EP668, PB1455
Aspa J., PB1654, PB1694
Aspa Cilleruelo J. M., EP1327
Assad A., EP1075, PB1715, PB1716
Assanto G. M., S306, EP1319
Asset G., EP980, EP981, EP986
Assi S., S105, S122
Assimakopoulos I., EP773, EP774
Assimakopoulou T., EP551
Astermark J., S256
Astibia B., EP1338
Astori C., EP1098
Ataga K. I., EP1219, PB1764
Atallah E., EP438
Atenafu E. G., EP989, EP1038, PB1643
Atene C. G., EP617
Athanasiadis P., EP614
Athanasiadou A., PB1368, PB1378, PB1721
Athanasopoulos E., PB1468
Atieh T., EP743
Atkinson E., EP628
Atsuta Y., S244, EP507, EP667, EP668, EP1229
Attarbaschi A., S116, EP342
Attas R., EP814
Attie K., S263, EP1305
Attolico I., S154
Au T., PB1625
Auda K., PB1729
Audia S., S295, EP697, EP705, EP1125, EP1143, EP1147
Audisio E., S308, S114, EP474
Augsberger C., EP879
Augusto V., EP995, EP999
Augustson B., EP986
Aumann K., S199
Aumann S., S288
Auner H., EP974, EP976
Auperin A., S221
Aurer I., EP561, EP573, EP826, PB1494, PB1539, PB1605, PB1684
Auteri G., EP1079, EP1124, EP1129
Autore F., EP604, PB1506
Avanzi M. P., S213, EP791
Avci J., PB1657
Avci T., PB1403
Avendaño A., EP1234
Avendaño Pita A., EP1253
Avet-Loiseau H., S180, PB1653
Avenoso D., S283, EP1276, EP1279
Avetisyan G., EP329, EP413
Avgeris M., EP959
Avigdor A., S255, EP502, EP503, EP526, EP716
Avila Contreras L. G., PB1438
Aviv A., EP502
Avivar-Oyonarte C., EP1183, PB1607
Avivi I., S255, S284, S285, EP495, EP1023
Avramidou R., EP1254
Avtaeva Y., EP1328
Avvisati G., EP867
Awan F., S214
Awasthi S., EP1051
Ayad A., PB1479
Ayala R., EP408, EP412, EP708
Ayalon Dangur I., S309
Ayaz Ahmed M., PB1424
Ayçiçek A., EP1316, PB1372, PB1755
Aydın Köker S., EP1216, EP1218, PB1755
Aydınok Y., EP355, EP1216, EP1218, EP1304, EP1306, EP1316, EP1317, PB1523, PB1755, PB1809
Ayed W., PB1420
Ayedi A., PB1592
Aygun B., S261
Ayhan Y., EP704, PB1820
Ayinan D., EP1316, PB1755
Aytaç S., PB1365, PB1372
Azap A., EP1283
Azar Ahmad S., S134
Azerad M.-A., S156
Azevedo A., EP388
Azevedo J., PB1616
Azhdari Tehrani H., PB1830
Azibeiro R., EP1234
Azik M. F., EP1316, PB1755
Azık F., EP1216, EP1218
Aziz M., EP743
Azizy M., PB1683
Aznar-Moreno M. V., EP574
Azoury V., EP701
Azza E., PB1373, PB1423, PB1585
Azzaoui I., S295
Azzazi M., PB1774

Baazizi M., EP1255, PB1629
Babaeva F., EP564, PB1574
Babenko E., PB1612, PB1617
Babichenko I., EP1325
Babiker H., EP452
Babikyan D., PB1411
Babor F., EP326
Babu S., EP503, EP566
Babuin E., EP880
Babushkin V., EP1110
Bacal J., EP814, PB1664
Bacchiarri F., EP631
Baccouche H., PB1814
Bachelor A., PB1475
Bachier C., EP541, PB1415
Bachy E., S210, S212, S216, EP501, EP511, PB1546
Bacigalupo A., EP394, EP1233
Backhaus D., EP435
Backstrom J. T., S101
Backus T., EP839, EP840, EP842
Bacon C., EP1178
Bacon C. L., EP628, EP876
Bacon L., EP1292
Bacon T., EP972
Badaev R., PB1402
Badarau A., EP784
Badawy S., EP1312
Badea A., EP828
Badelita S. N., EP1192, PB1652
Bader P., S116
Badiola J., PB1696
Badmazhapova D., PB1785
Badoiu Niculae M. D., EP828
Badros A. Z., S187, EP1001, EP1026
Bae S. H., EP1029
Baer C. R., S128
Baer M. R., S117, EP913, EP917, EP926, EP1106
Bagal B., EP958
Baglione F., EP665
Bagnardi V., EP553
Bagnato S., EP1307, PB1770
Bagnoli F., EP744
Bagó J., EP724
Bagratuni T., S280, EP939
Bagul P., EP746
Bahlis N. J., S188, S192, EP963, EP1002, EP1008, EP1019
Bahmanyar S., EP1126
Bahrani A., EP814
Bahri M., PB1556
Bahri M., PB1423, PB1585
Bahri O., PB1585
Bai J.-F., EP513
Bai X., EP924
Baiges A., EP1084
Baile M., EP1234
Baile Gonzalez M., EP1253
Bailén R., EP726, EP1168
Bailey K., PB1654, PB1694
Bailey M., EP1207
Bailey N., PB1566
Bailey R., EP445
Bailey T., S314, EP1150, PB1762
Baillet C., EP511
Bailly C., EP511
Bain J., EP1210, EP1215
Baiocchi R., EP861
Bairey O., EP636, PB1505
Bak M., EP1107
Baker B. W., EP963
Baker J., S253
Baker R., S211, S299
Bakhtina V., EP647, EP1110
Bakin E., PB1612
Bakiri M., EP551
Bakkus M., EP343
Bal C., PB1403
Balabanian K., S162
Balabanov S., PB1517
Balachandran N., EP596
Balagué O., EP872
Balashova V., EP1040, PB1800
Balasubramanian S., EP869
Balatzenko G., PB1421, PB1503
Balbas M., EP524
Baldacci E., EP571, EP1152
Baldaque I., EP1281
Baldauf C., EP1059
Balderas C., EP363, EP1335
Baldini L., EP1031, EP1099
Baldini S., EP455
Baldoli C., S102
Baldoni S., EP620
Balducci E., EP898
Balduini A., S249
Baldus C. D., EP318, EP375, EP436
Balea M., EP828
Baliakas P., S143
Balık Aydın B., PB1458, PB1699
Baljevic M., S188, EP1002, EP1008
Balkan C., EP355, PB1523
Balkis M., PB1371, PB1374
Ball B., EP351
Ball M., S195
Balla A., EP572
Ballal R., S263
Ballanti S., S182
Ballardini F., PB1387
Ballestar N., EP481
Ballew N., EP366
Ballotta L., EP543, EP795
Ballourah W., EP369
Balocco M., EP1307
Balogh E., EP572
Balsat M., EP494, EP1262
Baltadakis I., PB1515
Baltasar P., PB1493
Baltazar Arrellano S., PB1438
Balti M., EP1055
Balzarotti M., S219, PB1448
Bamezai S., S124
Bamigbola O., EP1177
Banchs M. I., EP606
Bandini L., S125
Bandman O., S299, PB1733
Bando H., S226
Banella C., EP420
Banerjee A., S193, EP964, EP967, EP977, EP978, EP990, EP1049
Banerji V., S148, EP931
Banfi D., EP750
Bang S.-M., EP1024
Bangeas A., PB1376, PB1378
Bankar A., EP675, EP1093
Bankova A., EP1224
Bannerji R., S147
Banús-Mulet A., EP415
Bao L., EP1050, PB1646, PB1647, PB1685
Bao Perez L., PB1734
Baothman A., PB1422
Bar M., EP1019
Bar-On Y., S255, S284, S285
Bara C., EP757
Barabanshikova M., PB1612
Baraldo M., EP1273
Baran-Marszak F., S143, EP652
Baranes M., PB1663
Barankiewicz J., EP829
Baranova O., EP360
Barata J. T., S106, EP418
Baratiri F., EP810
Barba P., EP329, EP350, EP352, EP546
Barbanis S., EP1044
Barbanti M. C., EP1099
Barbarousi D., PB1516
Barbato A., EP694
Barbi E., EP1291
Barbieri M., EP921
Barbosa I., EP381
Barbui A. M., EP729
Barbui T., S158, EP1089
Barbullushi K., EP1099
Barbuto L., PB1770
Barcella L., S292
Barcella M., S259, S269
Barcellini W., S270, S271, S290, S291, S312, EP685, EP689, EP692, EP696, EP706, EP921, EP1099, EP1141, PB1621, PB1627
Bardas A., PB1379
Barella S., EP1307

Bárez A., EP350
Bargay J., S185, EP1012
Barham L., PB1750
Bari A., EP860, PB1550
Barilà G., EP611, PB1633
Barilka V., PB1353
Barillari M. R., EP1310
Barin C., EP898
Barisone E., EP348
Barkauskas D. A., S221
Barkhatov I., PB1612, PB1617
Barkhordar G. S., S128
Barnes G., EP911
Baron J., EP1026
Barone A., EP1155, EP1158
Barone F., S306, EP571, EP1152, EP1319
Barone G., EP665
Barosi G., PB1702
Barozzi E., EP1099
Barr P. M., S147, EP636
Barraco F., S157, EP494, EP1262
Barragán E., EP413
Barranco Lampón G. I., EP363, PB1724
Barrena S., EP329
Barrenetxea C., EP546, PB1526
Barreto V., S106
Barreto-Vargas C., S150
Barretta E., EP317
Barrientos J., EP635
Barrio S., EP408
Barros A. V. D., PB1732
Barros Lima C., PB1616
Barroso F., S263, EP1212
Barshack I., EP502
Barsic B., S304
Bartels M., S274, EP582, EP590
Bartlett N. L., S205, EP495, EP506, EP769, PB1441, PB1565
Bartoletti D., EP1079
Bartolucci P., EP1207
Bartzi V., PB1560
Baruchel A., S116, EP341, EP590
Barulli S., S154
Barve M. A., EP500, EP633
Baryakh E., EP1190
Barzaghi F., S258, EP741
Bas I., PB1523
Bas V., EP577
Basendwah A., EP1322
Basheer F., S129, EP470
Bashir Z., EP495
Bashton M., EP317
Bašić-Kinda S., EP561, EP826, PB1494, PB1539, PB1684
Basile F. G., PB1698
Basilico C., EP491
Basova O., EP935
Basquiera A. L., EP927, PB1380
Bassan R., S112, S114
Bassani B., S125
Bassawon R., S305
Bassermann F., S247, EP761, EP896
Basso M., EP795
Basso M., EP571
Basso-Ricci L., EP1298
Basso Zangirolami A., EP1213
Bassolli de Oliveira Alves L., EP818
Bast L., S245
Bast T., S100
Bastian L., EP318, EP375
Bastida J. M., EP1131
Bastos H., EP751
Bastos I. V. D., PB1745
Bastos J., EP488
Bastos M., EP546, EP726
Bastos-Oreiro M., EP870, EP1167, EP1168, EP1231, PB1791
Basu C., S192
Basu S., EP1220
Bat T., PB1547
Batai A., EP672
Bataller A., EP472, EP481, PB1642
Batcha A., S121
Batinić J., EP826, PB1539, PB1684
Batsis I., EP1232, EP1254, PB1583
Bauer H., PB1625
Bauer K., EP664, EP897
Baues C., EP779
Baum H., EP760
Baumann S., EP725
Baumeister J., EP1063
Bautista G., EP350, EP447
Baver S., EP1191, PB1477, PB1485
Baxter J., EP1058
Baykov V., EP544, EP556, EP770, EP771, PB1456
Baysal M., EP577
Bazarbachi A., S232, S233, S242, EP431, EP1228
Bchir M., PB1420, PB1556, PB1585, PB1731, PB1749
Beà S., EP606, EP858, EP872
Beach C., S131, S311, EP428, EP445, PB1398
Beachell J., EP703
Beale R., EP813
Bear J., S287
Beatriz C., EP1089
Beaubrun A., EP1201, PB1769
Beauvais D., S216
Bebeshko V., PB1366
Beccaria A., EP1307
Bechir M., PB1423
Becker H., EP467
Becker M., S109
Beconi M., EP841
Bednarek K., EP960
Bednarik D., EP740
Beeker A., EP1027
Beery E., EP1060
Beevi K., PB1541
Bega G., EP795
Beggiato E., S308, EP1079
Beguin Y., EP844
Beham-Schmid C., EP521
Behan S., EP765
Behlendorf T., EP979
Beider K., EP716
Beier Ommen H., S134
Beinarovich A., EP770
Bejar R., EP452, EP643, PB1391
Bejarano M., EP363, EP1335
Bekadja M. A., EP1159
Bekkers M., EP869
Bekris G., EP1189
Beksac M., S186, S189, EP975, EP982, EP988, EP1031
Belada D., EP496, EP506
Belateche K., PB1563
Belcher P., EP1339
Belen Vidriales M., EP457
Belhadj K., S180, EP1036
Belhadj R., EP1255, PB1629
Belia M., EP777, EP808, EP1272, PB1560, PB1577
Beliveau M., S302
Bell H., EP327
Bell N., EP876
Bell T., EP1025, EP1033, PB1665, PB1667, PB1668, PB1753
Bellesi S., EP394, EP1233
Bellesso M., EP818
Belli C., EP927, PB1380
Bellia M., EP774
Bellini M., EP1089
Bello C., PB1364
Bello López J. L., PB1734
Bellofiore C., EP1004
Bellosillo B., EP890, EP1089
Belloumi D., PB1690
Belotti A., EP449
Belousov A., EP501
Belousov K., EP1048, PB1500
Belyayeva A., PB1785
Ben Abdennebi Y., PB1373, PB1556, PB1585
Ben Ami R., S281, S284, S285
Ben Amor I., PB1363, PB1527, PB1562, PB1564, PB1592, PB1690
Ben Ayed M., PB1814
Ben Azaiz R., PB1649
Ben Barouch S., S288
Ben Batalla I., EP463
Ben Lakhal R., PB1556
Ben Neji H., PB1420, PB1423, PB1556, PB1585, PB1749
Ben Othmen T., PB1690
Ben Romdhane N., PB1814, PB1824
Ben Salah H., PB1564
Ben Yakar R., EP462
Benabdennebi Y., PB1423
Benakli M., EP1255, PB1629
Benaksas C., S126
Bénard S., S157
Benavente C., EP1346, PB1819
Benavente Y., EP612
Benbatoul K., EP452, EP643, PB1391
Benboubker L., S180, S193
Bencomo-Alvarez A., S150
Bendaña López Á., PB1734
Bendek G., EP663, EP665
Bendell J., EP480
Béné M., S180, EP897
Benedetti F., EP1267
Benedicenti F., S258
Bénédicte B., EP1208
Beneit P., EP447, EP479
Benekou K., EP1272
Benes V., EP853
Benesova A., EP661
Benet C., EP889
Benetti A., EP1108, PB1601
Benevolo G., EP1079, EP1089
Benghiat S., EP1208
Bengio R., EP659
Bengoechea E., EP1021
Benintende G., PB1506
Benitez Jerez J., EP1116
Benitez-Ribas D., EP734, PB1642
Benito R., S143, EP893, EP1131
Benjamin R., EP974, EP976, PB1654, PB1694
Benjamini O., EP502
Benjiba L., EP1089
Benlakhal R., PB1585
Benlakhel R., PB1423
Benner A., S183
Bennett C., EP1057
Bennett S., EP1212
Benoit F., EP1282
Benouatas R., PB1629
Benoun J., EP341
Bensinger W. I., EP969, EP1002, EP1163
Bent-Ennakhil N., EP994
Bentley J. H., EP1087
Bento C., EP700
Bento L., EP587, EP1231
Benyaich S., PB1536, PB1815
Benyamini N., S255, S284, S285
Bérard E., EP456, EP482
Berceanu A., S156, S157
Bercher C., EP1282
Berchialla P., PB1808
Berdeja J. G., S191, EP964, EP977, EP978, EP984, EP985, EP990, EP1019, EP1049
Bereczky Z., S303
Berentsen S., S291, EP689, EP1179
Beretta S., S249
Berg D., EP963
Bergamaschi M., S154
Bergantim R., EP488, EP1011
Berger A., PB1639
Berger D., EP902, EP1065, EP1066, EP1068
Berger K., PB1748
Berger M., EP679
Berger T., S288, EP1023, PB1528
Bergeron J., EP439
Berggren D., EP912
Bergmann A. K., EP325
Bergua J., EP329, EP350, EP447, EP546, PB1407
Bergua Burgues J. M., EP496
Berkman-Gottlieb T., EP463
Berkova A., EP948
Berlin J., PB1764
Bermann G., PB1476, PB1481
Bermúdez A., EP329
Bermúdez-Rodríguez M. A., S237
Berna-Erro A., EP1161
Bernal M., EP612
Bernal T., EP352, EP447, EP546, EP889
Bernal del Castillo T., PB1407
Bernal Sanchez M., PB1704
Bernard E., S133
Bernard H., EP665
Bernard V., EP853
Bernard-Pierrot I., S106
Bernardo Á., EP812
Bernardo M. E., S102, S258, S269, EP741, EP1298
Berneman Z., EP654
Berneš P., PB1684
Bernheisel C., EP1148
Berno T., EP1053
Berred E., PB1373, PB1423, PB1556, PB1585, PB1731
Berred R., PB1585, PB1731
Berrou J., S126
Berry T., EP910, EP1106
Bertani G., PB1387
Berthon C., EP407
Bertinato E. M., PB1387
Bertoli D., EP449
Bertoli S., EP416, EP456, EP482
Bertolini F., EP753
Bertoni E., EP1158
Bertoni F., EP883
Bertozzi I., EP1129
Bertrand Y., EP343
Bertsch U., EP968
Besemer B., S183, EP968
Besenbacher S., EP863
Besharatian B., EP515
Besiroglu B., PB1430
Besley C., EP498
Besser M., EP526, EP716
Besses C., EP890

Bessmeltsev S., PB1635, PB1783, PB1784, PB1779, PB1800
Besson C., S215
Bessonen K., S169
Best J. M., EP585
Bethge W., S242
Bettelheim P., S198, EP897
Betti S., EP1089
Beumer N., EP463
Beutel G., S139
Beverloo H. B., S123, EP666
Beyar-Katz O., S284, S285
Beyer C., EP398
Beyne-Rauzy O., S156, EP1125
Beynon V., S270, S271, EP696
Bezares R., EP625
Bezděková R., EP954, PB1677
Bezirgiannidou Z., PB1436
Bhak R., PB1485
Bhalla K., S132
Bhalla S., EP936
Bhat S., PB1780
Bhatia J., S267
Bhatnagar B., EP462, EP924
Bhattacharya D., EP611
Bhayadia R., S120, EP398, EP404
Bhella S., PB1662
Bhuller K., EP765
Bhutani D., S189
Bhutani M., S193
Biagetti G., EP1108, PB1601
Bianchi A., EP867
Bianchi P., EP686, EP691
Bianchi S., S306
Bianchini M., EP663, PB1509, PB1511
Biar O., S255
Biavasco R., EP1067
Bibeau K., EP706
Biderman B., EP626, EP631, EP799, PB1490, PB1785
Bidet A., EP451, EP456, EP482, EP652, EP898
Biemond B., EP1197, EP1221, EP1308
Biersack H., EP853
Biffi A., EP348, EP1201, PB1746
Bigliardi S., EP1184
Bijou F., EP783
Bila J., EP1031, EP1043
Bilal I., PB1377
Bilalis A., PB1681
Bilbao Sieyro C., EP662, EP1116, PB1495
Bilgin Y., EP1027
Bill M., EP392
Bill M., EP435
Billio A., EP1267
Billot J., EP682
Bilous N., EP615, EP623
Bindels E., S123, S170, EP378
Binder M., S219
Binota J., EP331
Binotto G., S154, EP673, EP1079, EP1124, EP1129
Binte Mohammed Zaini N., EP857
Biondo U., PB1397
Biran N., S188, EP1002, EP1008
Bird B., EP806
Bird R., S299
Birkballe Hansen T., EP888
Birkmose J., EP1191
Bishop M. R., S117, EP1010
Bishton M., EP514, EP529, EP532, EP797
Bisio V., S162, EP906
Bitencourt de Souza E. M., PB1823
Bittencourt R. I., EP1039
Bittrich M., EP1239
Bixby D., EP462
Björkholm M., EP856, EP1088
Björklöf K., EP1134, PB1652
Bladé J., S185, EP973, EP975, EP1012, EP1021, PB1642
Blair H., S105, EP317, EP876
Blais F., S262
Blaise D., S243, EP1228, EP1238
Blaker Y. N., EP856
Blanc A.-S., EP1095
Blanchard M.-J., S185, EP1012, EP1021
Blanco A., EP336
Blanco A., EP809
Blanco A., PB1526
Blanco L., EP809
Blasczyk R., EP757
Blaslov V., PB1684
Blau I. W., S183, EP968
Blau O., EP402
Blazar B., S239, S253
Blázquez-Goñi C., EP1131
Blein S., EP938
Blijlevens N. M., S155, EP803
Blizin D., PB1650
Bloberger N., EP736
Bloehdorn J., S144
Blomberg C., EP462
Bloom R., EP515
Bloor A., EP644
Blum W. G., S138, PB1415
Blumenberg V., EP547, EP725, EP749
Blyden G., S263
Boban A., EP573, PB1539
Bobba P., EP969
Bobba S., EP1085
Bobola M., EP1153
Bobruff Y., EP733
Boccadoro M., S182, EP985, EP994, EP1031
Bocchia M., S114, S154, EP529, EP622, EP673, EP1079
Boddy A., EP433
Bodmer N., S116
Bödör C., S143
Boelens J. J., EP727
Boellaard R., S208, EP517, EP766
Boer J. M., EP319
Boeree A., EP319
Boersma C., PB1676
Bogatyrev V., EP772
Bogdan I., PB1459
Bogdanov K., PB1402
Bogeska R., S246
Bogomolova T., EP822
Böhmer L. H., S220
Böhnke J., S196
Boichenko E., EP358
Boichuk I., PB1677
Boise L., EP956
Boissel N., S117
Bojanic I., EP1287
Bojarska-Junak A., EP1280
Bokemeyer C., S183, EP825
Bolaman A. Z., PB1778
Bolamperti S., S268
Bolaños E., EP1346
Bolaños Mnrroy B., EP1116
Boldizsar S., EP768
Boldorini R. L., EP603
Boletta A., EP1067
Bollard C., S221
Bollu V., EP510
Bologna S., S215
Bolomsky A., EP960
Boluda M., EP413
Bombelli S., EP658
Bomben R., EP860
Bombín Canal C., S293
Bomken S., S105, EP876
Bonacina A., EP665
Bonato S., EP1288
Bondarenko E., EP762
Bondarenko I., S211
Bondarenko S., S233, EP360, EP822
Bondaruk O., EP1349
Bonete M., PB1828
Bonetti F., EP1307
Bonfanti-Lombardi M., EP722
Bonfiglio S., S143
Bonifacio L., EP849
Bonifacio M., S112, S154, EP673, EP1079, EP1089
Bonifazi F., EP1309
Bonifazi F., S240
Bonifer C., S105, S122
Bonini C., S252, EP719, EP722
Bonnamain V., EP748
Bonnard G., S295
Bonnet C., PB1572
Bonnet D., EP813
Bonney D., S116
Bonney S., EP1339
Bonnotte B., EP697, EP705, EP1143
Bonomini S., EP949, EP1061
Bonuomo V., EP491
Boor P., S196
Boos J., EP342
Booth C., EP1214
Booth S., EP514, EP765
Boque C., EP670
Bör Ö., EP1216, EP1218, EP1316
Boral A., PB1709
Borate U., S168, EP917, EP926, EP1075
Borchert N. M., EP757
Borchmann P., S209, S225, EP516, EP764, EP767, EP779, PB1430
Borchmann S., S225, S307, EP779
Bordini J., EP600
Bordone J., EP665
Borget I., EP995, EP999
Borie C., EP898
Bories P., S216, EP456
Borisenkova E., EP360
Borisova A., PB1352
Borjon I., PB1438
Borlenghi E., S114, EP449
Bornhauser B., S107, S110
Bornhäuser M., EP431, EP436
Borrero Borrego A., EP1116, PB1561, PB1798
Borsani O., EP1098
Borsato J., PB1546
Borsellino Z., EP1307
Borte M., EP1340
Borthakur G., S113, S132, S136, S167, EP430, EP464, EP468, EP471, EP480, PB1415
Borzenkova E., EP544, PB1415
Borzooee F., S178
Boscarol G., EP1158
Bosch D., S170
Bosch F., S143, EP336, EP450, EP631
Boschero M., PB1808
Boscoe A., EP710
Bosdure L., EP720
Bose P., EP331
Bose P., S136, S201, EP1077, EP1085, EP1096
Bosi A., EP529
Bosi C., EP1079
Bosotti R., EP1298
Bosshard L., EP788
Botsa E., PB1829
Botta C., EP809
Böttcher S., EP632
Bottos A., PB1565
Bouabdallah K., S211, EP495, EP787
Bouarab H., EP1255, PB1629
Bouchard S., EP1176
Boucher R. H., EP1058
Bouchla A., PB1681
Boudjerra N., EP1159
Boudry A., EP385
Bougeon S., EP616
Bouhla A., PB1516
Boukla A., EP609
Bouman B., S245
Bounaix L., S216
Bouquet L., EP720
Boureau L., EP451
Bourgeois H., EP1176
Bourgeois M., S293
Bourhis J. H., S243, EP748
Bouronikou E., EP919
Bourquin J.-P., S107, S110, S116
Bousiou Z., EP1232, EP1256
Boutakoglou E., EP588
Boutboul D., EP1147
Boutsikas G., EP774
Boutsis D., EP774
Bove V., PB1675
Bowden C., EP692
Bowles K., S179, S181
Boy M., S162, EP906
Boyer H., EP1151
Boyer M., EP599
Boyle E. C., EP757
Bozic B., EP971
Bozzoli V., EP1184
Brach D., S176
Brackertz B., EP496
Brackman D., EP444
Bradai M., EP1159
Bradford E. S., EP1087
Bradley T., S135, EP480, EP1074
Braendle E., PB1712
Braester A., S288
Braga de Camargo P. J., PB1823
Bramanti S., EP729
Brambilla V., S259
Branagan A., EP784
Branca A., EP1053
Branca R., EP1281, PB1789
Brandão A., EP818
Brander D., EP635
Brás G., EP1274, EP1281, EP1290, PB1789
Brauer D., EP435
Braun N., EP739
Braun T., S126, S138, S311
Brauneck F., EP410
Braunstein E., EP1100
Braverman J., EP1178
Bravo-Pérez C., S303
Brayer J., EP739, EP1163
Breaster A., PB1663
Breccia M., S154, EP673, EP677, EP1079
Breen J., EP321
Breman E., EP739
Breña J., PB1679
Brendehaug A., EP396

Bresciani P., S240
Bresnick E. H., EP378
Bret C., EP950
Brett V.-E., EP898
Brevard J., S138, PB1764
Brice P., EP765, EP766
Bridgelalall S., EP899
Bridoux F., EP1011
Brieghel C., S143, EP602
Briggs A., PB1768
Brink M., S220, EP796, EP1020
Brinkman N., EP1200
Brissot E., S232, S233, EP1228
Bristogiannis S., PB1747
Brito R., EP820, PB1726
Britto Rêgo D. D. F., PB1823
Brkljacic B., S304
Broccoli A., EP793
Bröckelmann P., S225, EP764, EP779
Brodsky A., EP665
Broeks M., S274, EP582
Broijl A., S180, EP987
Bron D., EP654
Broner J., S156
Bronte L., S263
Brooks C., EP427
Broome C. M., S290, S291, S312, EP566, EP689, EP1179, EP1180
Brophy S., EP628
Broseus J., EP652
Brotto D., EP1310
Broussais F., S216
Brouwer R., PB1671
Browett P., EP783
Brown A., PB1753
Brown C., S260, PB1769
Brown E., PB1384
Brown F., EP861
Brown J. R., EP614, EP633
Brown K., EP365
Brown P. A., EP341
Brown R. C., EP1202, EP1219
Brown R., EP717
Brown S., S181
Broyl A., EP1020
Brožová L., EP954, EP1042, PB1677
Bruggemann R., S281
Brugger W., EP467, EP496, PB1451
Brugnara C., EP695
Brümmendorf T. H., S196, EP387, EP657, EP671, EP672, EP684, EP1063
Bruna R., EP543
Brunet T., EP933
Brunetti L., PB1409
Brunner A., S168
Bruno B., S235, EP1237
Bruno S., EP384, EP419, EP753
Bruscaggin A., EP603
Bruselles A., S258
Bruserud Ø., EP396
Bruslova K., PB1366
Bruwier A., EP1208
Bruzzone M. G., S259
Bryceson Y. T., PB1543
Brychtova Y., S142
Brzózka K., S164, EP455, EP480
Buadi F. K., EP963
Bucci M., EP385
Bucelli C., EP1099
Buchholz T. A., EP807
Buck C., EP1189
Buck M. C., EP896
Bucklan D., EP535
Bücklein V., EP547, EP725, EP749
Buckley S., PB1711
Buckstein R., EP915, EP920, EP931
Budaeva I., PB1402
Budde E., S222
Budde L. E., EP1235
Buechler M., S246
Buechner J., EP590
Buendía B., EP546
Bueno L., EP1304, EP1306
Buesa C., EP450
Bueso-Ramos C., EP471, EP1104
Buffardi S., S221
Bug G., S232, S233, S242, EP431, EP467
Bugarski D., EP759
Buhl E. M., S196
Bühler M., EP858
Buijs-Gladdines J., EP335
Buka R., PB1656
Bukhvald N., EP1349
Bukkems L., EP569
Bukumiric Z., EP833, EP1326
Bulabois C. E., S233, S235
Buldakov I., PB1491
Bulj N., PB1494
Bulla A., EP1004
Bullinger L., S133, S143, EP376, EP386, EP402, EP423, EP755
Bultmann M., EP318
Bumbea H., EP828
Bumma N., S189, EP1163
Bunn V., EP506
Buño I., EP726, EP870
Buonanno S., EP719
Buquicchio C., EP491, PB1461
Burakov V., EP1333
Buratta S., EP384
Burbury K., EP1057, EP1074, PB1723
Burch M., EP462
Burchert A., EP1239
Burda D., EP1264
Burger E., S219
Burger J., EP636
Burggraaff C. N., EP517
Burgos L., S185
Buriánková E., EP552, EP802
Burke G. A. A., S221
Burke J. M., EP496, EP642, EP643, EP969, PB1451
Burke L., PB1714
Bürkle D., EP979
Burnett A., S130, S133
Burns R., S299, PB1733
Burroni B., EP790
Burroughs Garcia J., EP949
Burrow R., EP592
Burrows F., PB1408
Buruiana S., PB1582
Burzdikaite P., EP486
Busca A., S240, S281, S308, EP474, EP491
Busch G., EP725
Busch H., EP853
Busch J., EP853
Buske C., S124, EP782, EP784
Busnego M. T., PB1679
Busque L., EP684
Bussel J. B., EP1150, PB1733
Bussolari J., EP869
Butaev L., S286
Butcher K., PB1381
Buthorn J., EP330
Butina E., EP1334, EP1347, PB1496, PB1836
Butler A., S133
Butler J., S210, S236
Butler K., EP685, EP706
Butler M., S107, S110
Butolina M., EP584, PB1549
Bütow M., EP387, EP657
Butrym A., EP612
Butt N. M., EP1058
Butta Coll N., EP1072
Buus R., PB1639
Bykova A., EP674, EP680, EP681
Byrd J. C., S145, S148
Byrgazov K., EP424, EP871
Byrne J., EP457
Byun J. M., EP1029

Caballero D., EP1234, PB1526
Caballero D., EP509, EP1231, EP1253
Caballero M. D., EP1234
Caballero Berrocal J. C., S293
Caballero-Velázquez T., S237, EP1237
Cabañas V., EP546
Cabero-Becerra M.-A., EP621
Cabero Martinez A., EP1234, EP1253, PB1575
Cabezas De La Cruz M., PB1561, PB1798
Cabezudo E., EP1192
Čabraja I., EP819
Cabral R., PB1399, PB1457, PB1701
Cabras M. G., S219
Cabrera A., EP1335
Cabrera J., EP625
Cabrera Ruiz F. J., PB1651
Cabrera-Serrano A. J., EP612
Cabrero M., EP350, EP1234
Cabrero Calvo M., EP1253
Cacace F., EP478, PB1790
Caccavari V., PB1550
Cacciola E., EP1094
Cacciola R., EP1094
Cachucho A., S106
Cadassou O., EP407
Caddell R., PB1588
Cadinanos Garai A., EP788
Caffin A.-G., PB1546
Cafforio L., EP624
Cagnetta A., EP459
Cahill M. R., PB1413
Cai J., EP512, EP537, EP549
Cai Q., EP512, EP537, EP549
Cai Y., S228, EP334, EP562, EP862, EP864, EP865, EP868, EP874
Cai Z., EP792, EP1024, PB1361, PB1670
Caignard A., S162
Caillat-Zucman S., EP540
Caillon H., S180
Caillot D., S180, EP705, EP1143
Caimi P. F., EP518, EP530
Cairns D., EP644, EP1259
Cairo M., S241
Cairoli R., EP650, EP1113, PB1387, PB1442
Cairoli S., EP1140
Caja T., PB1502, PB1628
Çakır A., PB1458
Calabretto G., EP611
Calabria A., S258
Calabro' F., EP815
Calabuig M., EP350, EP587
Calafiore V., PB1397
Calama Ruiz-Mateos V., PB1426
Calaminici M., EP854
Calasanz M. J., S143, EP329, EP411
Calbacho M., EP350, EP455, PB1793
Calbacho Robles M., PB1689
Calbi V., S258, EP741
Caldas J., EP418
Calderon-Lopez M.-T., EP1343
Calen A., EP828
Califano C., S114, EP651, EP860
Callanan M., EP790
Callander N., S188, EP990, EP1008, EP1026, PB1698
Callewaert F., EP1145
Çalliku E., PB1502, PB1628
Calo A., PB1819
Calon G., PB1394
Calore E., EP1238
Calvo G., PB1642
Calvo R., PB1434
Calvo X., EP606, EP890
Calvo Sánchez J., EP409
Calvo Villas J. M., EP578, EP1331
Camacho L., EP890
Camargo E., EP1335
Camargo P. J. B. D., PB1745
Cameron C., EP446
Cameron H., EP446, PB1395, PB1406
Cameron R., EP382
Camilleri D. J., PB1595, PB1682
Camilleri M., EP1189
Caminos N., EP546
Camisa B., S252, EP722
Campa D., EP612
Campagna D., S273
Campanella A., EP600
Campanini N., EP949
Campbell A., S260
Campbell C., EP736
Campbell G., EP555, EP559
Campbell P., S133
Campbell T. B., EP984, EP1009
Campestri R., PB1534
Campisi S., EP1307
Campo E., S143, EP858, EP872, PB1567, PB1568
Campos A., EP1281, PB1789
Campos V., EP750
Campos Jr A., EP1274, EP1290
Campos-Costa C., PB1701
Canaani J., EP487
Cañadas-Garre M., EP612
Canales M., EP530, EP807
Canales Albendea M. A., PB1518
Canaro M., EP1149
Canarutto D., EP741
Canbolat A., EP1218
Cançado R. D., EP1211
Cancela Pires J., EP488
Cancrini C., S258
Candoni A., S112, S240, S289, EP491, EP815
Cangialosi C., PB1397
Canichella M., S306
Canioni D., EP790
Cano I., EP450, EP479
Canonico F., EP348
Canonico V., EP665
Canpolat A., EP1216
Cantonetti M., EP793, EP883
Cantoni E., EP1067
Cantoni N., PB1517
Cantoni S., EP1113
Canzian F., EP612
Cao A., S211
Cao J., S206, EP792
Cao L., EP601, EP618, EP801, PB1497, PB1576

Cao L.-M., EP460, EP484
Cao L.-Q., PB1591
Cao P., EP339, EP414
Cao S.-B., EP460
Cao X., EP1248, PB1396
Cao X.-Y., EP1230
Cao X.-X., EP1117
Cao X., PB1625
Cao Y., EP1268
Cao Y., EP397
Cao Y., EP1225
Caocci G., S154, EP1079
Capasso A., EP634
Capasso M., S276
Capecchi M., EP1141
Capo-Chichi J.-M., EP1082, EP1083, EP1093
Capodanno I., S154
Capotondo A., S259
Cappelleri J., EP370
Cappelleri J. C., EP1025, EP1033, EP1175
Cappellini M. D., S101, S268, EP733, EP843, EP1304, EP1306, EP1307, PB1805
Cappellini M., EP783
Capra M., S211
Caprioli V., EP478, PB1790
Carabba M. G., S259
Carande Checa L., EP820
Carbó J. M., EP415
Carbonell D., EP726, EP870
Carcelero E., EP472
Carda J., EP1114
Carda J. P., EP630, EP1102, EP1121
Cardaci S., EP1067
Cardellino A., EP1171
Cardenas A., EP1320
Carfora R., EP1310
Cario G., EP325
Carlet M., S109
Carli G., EP1124, EP1129
Carlile D., EP501
Carlone G., EP1273
Carlo-Stella C., EP501, EP518, PB1440, PB1570
Carlson K., EP1051
Carlson K., S242
Carlsten M., EP718, PB1543
Carlucci F., S258
Carluccio V., PB1461
Carminati E., EP459
Carmo C. B. C. D., PB1745
Carmona-Torre F., EP809
Carneiro A., EP488
Carniti C., EP723, EP729, EP744
Caro A., EP812
Caro-Valenzuela J., PB1430
Carobbio A., S158, EP1089
Carotti A., EP1288
Carozza D., PB1498
Carpenter C., EP1051
Carpentier B., EP652
Carrabba M., EP729
Carrai V., PB1770, PB1771
Carranco Falcón A. R., PB1488
Carranza Jara J. M., EP1251
Carrasco-Alfonso M., S190, EP964, EP972, EP978, EP1003, EP1049
Carreno Gonzales M. J., S246
Carreño-Tarragona G., EP412, EP1089
Carreras M., EP481
Carriço F., PB1732
Carrillo-Tornel S., EP889
Carrizales Villarreal J. A., PB1438
Carroll A., EP317
Carroll C., EP736
Carter B. Z., EP379
Carter L., EP835
Cartron G., S212, S216, EP511, EP950
Carubbi C., EP1061
Caruso R., S258
Caruso V., EP1305
Carvalhais I., EP488
Carvalho A., EP425
Carvalho L. D., PB1745
Carvalho do Carmo C. B., PB1823
Carzavec D., PB1494
Casabonne D., EP612
Casadei B., EP729
Casado M. Á., EP1167
Casado-Izquierdo P., PB1383
Casado Montero L. F., EP670
Casais C., PB1457
Casale M., EP1158, EP1307
Casasnovas O., S212, EP497, EP511, EP705, EP1143
Casasnovas R.-O., S216, EP530
Casciano R., EP1005
Caserta S., PB1384
Casetti I., EP1098
Cashman H., EP1186
Casiraghi M., S258
Casneuf T., EP967
Cassaday R. D., S117, EP731
Cassanello G., PB1621
Cassin R., EP631
Cassina L., EP1067
Castagnetti F., S154
Castaigne J.-G., EP366
Castaman G., S256, EP730
Castaño-Diez S., EP472, EP479, EP481
Castella M., EP734
Castellani L., S292
Castellano E., EP721
Castelli F., S126
Castellino A., EP1184, PB1448
Castellino C., EP860
Castellón V. E., EP1320
Castells O., EP417
Castiglioni C., PB1766
Castilla García L., EP1327
Castillo C., EP734
Castillo J. J., EP784, EP805, EP1174
Castillo P., PB1642
Castillo R., PB1724
Castillo-Girón C. M., EP472, EP481
Castonguay M., S262
Castonquay V., PB1662
Castro B., PB1457
Castro F., EP519
Castro I., EP425
Castro M. B., PB1380
Castro N., EP986
Castro P., EP734
Casucci M., EP722
Casulo C., S213
Catalan M., EP665
Catalano G., EP420
Catalano J., S202
Catalano L., EP1034, PB1581, PB1678, PB1695
Cathers B., EP1198
Catherwood M., S143, EP631, PB1580
Catić- Đorđević A., EP588
Cattaneo C., EP449, EP491
Cattaneo D., EP673, EP1089, EP1099
Caulier A., EP1278
Cauwelier B., EP542
Caux C., S121
Cavalca F., EP1089
Cavalcante L., EP620
Cavalli F., S219
Cavalli G., EP1067
Cavallin M., EP477
Cavallo F., EP530, PB1575
Cavattoni I., EP1267
Cavazzana M., S257
Cavazzini F., S154, EP1079
Cavé H., EP343
Cavo M., S125, S182, S184, S186, EP384, EP405, EP419, EP753, EP963, EP973, EP980, EP981, EP1009, EP1016, EP1046, EP1079
Cayssials E., EP679, EP933
Cea M., S182, EP459
Cearley A., EP508
Ceballos P., EP1228
Ceballos-Bolaños C., EP492, EP574
Cebeira M. J., S293
Ceccato J., EP810, EP1124, EP1129
Cecchi N., EP1141
Ceccolini M., EP1034, PB1581, PB1678, PB1695
Çeçen E., PB1834
Ceci A., EP1309
Cedena M.-T., S185, EP1012
Cedena T., EP721
Cedena Romero M. T., PB1689
Cédile O., EP851
Cedillo de la Cerda J. L., PB1438
Ceesay M., S283
Cefis M., S292
Ceglie G., EP1127, EP1140, EP1203, PB1765
Ceidiene V., EP555
Celebrin L., EP665
Celico C., S219
Celik F., EP517
Celkan T., EP1216, EP1218, EP1316
Celkan T. T., PB1832
Cella D., S290, EP1179
Celli-Lebras K., EP385
Cen H., EP792
Cenci S., EP1067
Cenfra N., EP1184
Centore F., PB1460
Centurion M. E., EP665
Ceolotto G., EP1108, PB1601
Cepheid Y. L., PB1355
Cerchione C., EP827, EP1034, PB1581, PB1678, PB1695
Cerciello G., EP1166
Cerna L., EP1297
Cerrano M., S308, EP474
Cerretani E., S108
Cervantes F., S202, EP671, EP1084
Cervera J., S160, EP413, EP889
Cervera M., EP329
Cerveró C. J., EP447
Cesana D., S258
Cesaro S., EP348
Çetinoğlu S., EP704
Cetkovsky P., EP473
Chabaeva Y., S286, EP360
Chacim S., S278
Chadwick H., EP370
Chaganti S., EP498, EP504
Chaguar B., PB1598
Chahal M., PB1554
Chai S., PB1660
Chai Y., EP966, EP974
Chai-Adisaksopha C., EP1330, PB1437, PB1751
Chakrabartty J., PB1469
Chakraborty R., EP1015
Chakravarthy D., EP442
Chakroun A., PB1814, PB1824
Chalandon Y., S243
Chalbaoui A., PB1586
Chalkiadakis G. N., EP1153
Chamberlain C. X., EP1318, PB1805
Chamekh A., PB1824
Chammou D., EP631
Chamoun K., EP530, EP924
Chamuleau M., EP499, EP517
Chan E., S192
Chan H., EP783
Chan M., PB1554
Chan O., PB1394
Chan S., EP362, EP1082
Chan W. Y., EP983
Chan W., EP861
Chanan-Khan A., S145
Chandak A., EP1005
Chandra T., EP754
Chandrasekaran V., EP442
Chang A. H., S115, S119
Chang C., PB1614, PB1670
Chang K.-H., S251
Chang P.-Y., EP476
Chang T.-Y., EP483
Chang V., EP1190
Chang Y., S104
Chang Y.-J., S234, EP395, EP1142, EP1252, EP1265, PB1591
Chang Y.-H., S300
Chao M., PB1624
Chapchap E.-C., EP352
Chapiro E., EP898
Chappert P., S295
Chapuis A., EP731
Charania A., EP1130
Charef O., PB1423
Charfi M., PB1363, PB1452, PB1527, PB1562, PB1564, PB1690
Chari A., S191, S193, EP936, EP975, EP985
Charitaki I., S280
Charloteaux B., PB1483
Charlton J., EP711
Charry P., PB1649
Chartier L., EP790
Charvátová S., EP724
Chat L., S126
Chatain N., S159, S196, S197, EP387, EP657, EP1063
Chatterjee A., EP958
Chatterjee G., EP958
Chatzidavid S., PB1560
Chatzidimitriou A., EP609, EP631
Chatzidimitriou C., EP551, EP773, EP774, EP777, EP808, EP1272, PB1560, PB1577
Chatziioannou S., EP774, PB1560
Chatzikonstantinou T., EP631, PB1583
Chatzileontiadou S., EP631
Chatzilygeroudi T., EP1153
Chauchet A., S215
Chaudhri N., PB1796
Chaudhry A., EP642
Chauny J.-V., PB1742
Chauveau D., S189
Chauvel C., S126, EP906
Chavda S., EP983
Chaves M., EP1054, EP1286

Chavez J. C., S210, S213, S222, EP536, EP791, PB1364, PB1588
Chawla R., S173
Chawla R., PB1673
Cheah C. Y., EP500, EP525, EP633, EP638
Chebukina Z., EP1040
Chechetkin A., PB1491, PB1800
Chechulova A., EP1332, EP1333
Chelly M., PB1814
Chelmakov A., PB1785
Chelysheva E., EP674, EP680, EP681, EP756
Cheminant M., EP790, EP1147
Chen A., EP508
Chen B. E., PB1662
Chen C.-M., EP349, EP368
Chen C., S188, EP1002, EP1008
Chen C., S206
Chen C., EP1120
Chen C., S311, EP446, PB1395, PB1398, PB1406
Chen C., EP595, PB1471, PB1475, PB1477
Chen D.-Y., EP642
Chen F., EP1090
Chen G. L., S238
Chen G., EP565
Chen H.-M., EP349, EP368
Chen H., S234, EP1226, EP1252, PB1591
Chen J. M., EP786
Chen J., EP633
Chen J.-H., EP476
Chen K.-M., EP499
Chen L., EP528
Chen L., EP1271
Chen L., PB1648, PB1670
Chen L., EP1120
Chen L., S194
Chen L., PB1473
Chen M., EP1266
Chen M.-T., EP349, EP368
Chen M., EP593, EP598
Chen M., S187
Chen M., PB1786
Chen P.-H., PB1552
Chen Q., S231, S298
Chen R., S261
Chen R., EP548
Chen T., EP612
Chen W., EP859
Chen W.-M., EP347
Chen W., EP1050, PB1646, PB1648, PB1670, PB1685, PB1688
Chen X., S228, EP334, EP864, EP874
Chen X., EP962, EP1120, PB1670
Chen X., PB1781
Chen X., S206
Chen X., EP339
Chen X., EP1075
Chen Y., EP397, EP967
Chen Y., EP340
Chen Y., EP1252, PB1591
Chen Y., EP1120
Chen Y.-C., EP476
Chen Y., EP1277
Chen Y., EP583
Chen Y., EP338
Chen Y., EP694
Chen Y., EP962
Chen Y.-G., EP476
Chen Y., EP847
Chen Y.-H., S234, EP1226, EP1252, PB1591
Chen Y., EP1111
Chen Z., PB1648
Chen Z., PB1786, PB1795
Chen-Kiang S., EP861
Chen-Liang T.-H., EP889
Cheng T., EP1103
Cheng Y., EP847
Cheng Y.-F., EP1226, PB1591
Cheng Y., PB1481
Chenhua Y., EP454
Chennacrishnaiah S., S305
Cherait A., S156
Cherepanov D., EP985, PB1639
Cherkasova A., PB1638
Cherkasova E., EP1264
Cherniak E., EP699
Chernykh J., PB1500
Cherry M., EP437, EP541, EP643, PB1391
Cheung A., EP905
Cheung K., EP443
Cheung M. C., PB1662
Cheung R. S., EP442
Cheung S., EP638
Cheung V., EP1083, EP1093
Chevassut T., EP445
Chevli M., EP930, EP1315
Chevret S., EP497, EP540, EP818
Chèze S., EP1125
Chhabra S., EP990
Chia P. S., EP597
Chia V., PB1702
Chiacchio R., PB1460
Chianella G., S269
Chiang A. K., S221
Chiappella A., EP723, EP729, EP744, PB1448, PB1451
Chiarenza A. L., EP651
Chiaretti S., S112, S114
Chiba M., EP852
Chiba S., S226, EP438, EP441
Chicano M., EP726, EP870
Chien K., S132, EP676
Chien W.-C., EP476
Chifotides H., EP1096
Chihara D., EP881
Childs B. H., S211
Childs R., EP718, PB1543
Chim C. S., EP1024
Chin P. S., S122
Chinali M., PB1765
Chinea Rodríguez A., EP489, EP587
Ching T., EP632
Chiocca E., EP1155, EP1158
Chirila A. M., PB1379
Chistolini A., S306, EP571, EP1152, EP1319
Chitarrelli I., PB1460
Chiu G., EP1090
Chiurazzi F., EP651
Chiusolo P., EP394, EP729, EP1233
Chivers S., EP846
Chloé S., EP1278
Chng W.-J., EP857, EP961
Cho C., EP353
Cho H. J., EP936
Cho Y.-U., EP918
Chodirker L., EP931
Choeurng V., EP965
Choi D., S305
Choi E.-J., EP918, PB1417
Choi G., S233, EP1284
Choi M. Y., S140
Choi P., S299
Chonat S., S271, EP590, EP1194
Chong E., EP515, EP800
Chong S., EP1252
Chong S. L., PB1489
Chopra D., EP737
Choquet S., S215, S216, EP530
Chou H.-C., PB1552
Chou J., EP791
Chou W.-C., EP922
Choudhuri S., PB1659
Chowdhry S., PB1498
Choy A., S283
Christensen J. H., EP506
Christensen S., EP1107
Christian A., EP631
Christian R., S138
Christiansen C. F., EP1107, EP1126
Christoforidis A., PB1807
Christoforidou A., EP1044
Christoforidou B., EP1044
Christou G., EP931
Chromik J., EP457, EP463
Chu B., PB1647
Chu E., S140
Chu M., S192
Chu T., PB1739
Chua C. C., EP429
Chuah C., S153
Chuansumrit A., EP850
Chubukina Z., PB1800
Chudakov D., EP333
Chudinovskikh Y., EP1264
Chulián S., PB1584
Chumak A., EP615, EP623
Chunara U., EP1339
Chung C.-H., EP476
Chung J., EP861
Chung M., PB1440
Chung S., EP365
Chung T., PB1624
Chung W., EP1019
Chung Tsang Y., PB1760
Chupp G., EP1087
Churilova I., PB1784
Churkina M., PB1611
Churruca J., PB1793
Churruca O., EP411
Chuvin N., S121
Chyla B., S137, EP599
Ciancio A., EP1310
Cianciotti B. C., S252
Ciavarella S., EP1184
Cibeira M. T., EP1011, PB1642
Cibeira T., S189
Cibien F., EP645
Cicalese M. P., S258, EP741
Ciccarone M. V., EP1184
Ciccioli M., EP665
Ciccone G., PB1448
Ciceri F., S102, S233, S240, S252, S258, S259, S269, EP431, EP719, EP741
Cichocka T., PB1545
Cichoń T., EP724
Ciciarello M., S125, EP405
Cicinelli E., EP1188
Cid J., EP734, PB1642
Cid López M., PB1734
Cili A., PB1502, PB1628
Cilloni D., S138, EP1079
Cimino E., PB1706, PB1717
Cimminiello M., PB1460
Çınar G., EP1283
Cinetto F., EP810
Ciofini S., EP622
Ciolfi A., S258
Ciolli S., EP645
Ciortan S., EP828
Ciotti F., S102
Cirillo D. M., S279
Cirillo M., S225
Cirstea M., PB1379
Citrano M., EP1155
Ciudad J., EP329, EP352
Ciudad M., EP697
Ciulla D., S251
Civeira Marín M., EP578, EP1139, EP1331, PB1821
Cladera A., EP352, EP546
Cladiere C., EP697
Claessen M.-J., S294
Clappier E., S106, S126, S162, EP906
Clark B., EP711
Clark E., EP501
Clark F. J., EP1058
Clarke K., EP610
Clarke L., S263
Claudio J., EP1093
Clausen M., EP1107
Clavero E., EP612
Clavio M., EP459
Clear A., EP854
Clemente V., EP1127, EP1140
Clifford R., EP628, EP797
Clifton-Hadley L., EP788
Cloos J., EP458
Clot G., EP858
Clouser M., EP1126
Cluzeau T., S156
Cnossen M. H., EP567, EP569
Co M., EP783
Coates T. D., S101, EP1304, EP1306
Cobb P., EP643
Cocciardi S., EP376
Cochrane T., EP1086
Cocito F., EP1184
Cockerill P. N., S122
Cocks K., PB1747
Coelho A., S264
Coelho P., EP1274, EP1290
Coen-Herak D., EP573
Cogle C. R., EP1182
Cogliatti S., PB1708
Coha B., EP819, PB1605
Cohan D., EP975
Cohen A., S190, EP964, EP965, EP1003
Cohen A., EP642, EP805, EP1174
Cohen F., EP330
Cohen J. B., EP500
Cohen O., EP1000, PB1644
Cohen Y. C., S190, EP1023, PB1652
Coisne V., PB1742
Coiteux V., EP679
Cokic V., EP629
Colado E., EP809
Colak G., EP1077, EP1080, EP1085
Colás B., PB1819
Colby J. A., EP1318
Coleman D. J., S122
Coleman M., EP783
Colia M., EP634
Coll R., EP329, EP350, EP352
Coll Jorda R., PB1407
Coll-Vallier J., EP574
Collado R., EP563, EP616, EP631
Çollaku N., PB1502
Collins G., EP514, EP530, EP765, EP769
Collins R., EP693
Colmenares R., EP408
Colombatti R., S314, EP1201, PB1746, PB1762
Colombini A., EP348
Colombo C., EP1113

Colombo E., EP997
Colombo M. P., S125
Colombo N., EP459
Colomer D., EP1084
Colomo L., EP606
Colorado M., EP447, EP670
Colucci P., PB1714
Colucci S., S100, S275
Colvin R. A., S257, S266, EP1301
Combik M., S164
Côme C., EP863, EP888
Comenzo R., S189
Comont T., S156, EP416, EP1125, EP1147
Compagno F., EP1158
Comuzzi C., EP815
Conconi A., EP860
Conde Ausin M., PB1651
Condom M., PB1567, PB1568
Condorelli C., PB1766
Condori D., EP1329
Conliffe B., PB1475
Connarn J. N., EP1009
Connell A., EP693
Connelly S., S238
Connolly M., EP628
Connors J. M., S205, PB1554
Consiglieri G., S102, EP741
Consonni D., EP843
Constantin C., PB1379
Constantin O., EP828
Conte K., EP747
Contejean A., S157
Contento Gonzalo A., PB1407
Conter V., EP348
Conti A., EP1298
Conticello C., EP1004
Contreras T., EP1012
Contreras-Agudo M. J., EP1343
Cony-Makhoul P., S156
Cook G., S181, S187, EP985, EP1259
Cook R., EP455
Coombes C., PB1433
Coombs C. C., EP500, EP524, EP633
Cooney J. P., S235, PB1393
Cooper B. W., EP437
Cooper D., S256, EP730
Cooper D., EP1163
Cooper J., EP965
Cooper M., EP539
Cooper N., S299, EP1130, EP1133, EP1150, PB1733
Copeland T. S., PB1393
Copland M., EP682
Copley F., PB1383
Coppadoro B., EP1201
Coppell J., EP1058
Coppens M., S256, EP567
Corbacho A. J., EP1161
Corbacioglu A., EP376
Corbacioglu S., EP733
Corbett G., S148
Corby A., EP652
Cordoba Macuñano R., PB1791
Cordón L., S185, EP413
Coriu D., EP1119, EP1192, PB1379
Corman S., EP916, PB1738
Cormio C., PB1737
Cornejo Calvo M. E., PB1599
Cornelissen I., EP869
Cornelissen J., S232, S243, EP666, EP678
Cornell R. F., EP1046
Cornely O., S281, PB1504
Cornet-Masana J. M., EP415
Cornpropst M., EP585, EP589
Corona K., EP530
Corradi G., S125, EP384, EP405
Corradini P., S182, EP543, EP723, EP729, EP744
Corral J., S303
Corre J., S180
Correa J.-G., EP872, PB1567, PB1568
Correa M. E. P., PB1730
Cortes J., S138, S153, EP671, EP672, EP677, EP684
Cortes M., EP670
Cortes Rodriguez M., EP1253
Coscia M., EP631, EP634, EP645, EP650
Cosgrove D., EP643
Coşkun Ç., PB1372
Cosmopoulos K., S176
Cosset F.-L., EP939
Cossu A., EP1314
Cossutta M., PB1765
Costa F., EP418
Costa F., EP949
Costa G., EP1310
Costa I., EP421
Costa I. G., EP657, EP1063
Costa L. J., S191, EP747, EP990
Costa M. I., EP630, PB1350, PB1630
Costa M. J., EP354, PB1449
Costa Cordeiro A., EP1251
Costello C., S192, EP985
Costello D., EP1196
Coster L., EP898
Cotton F., PB1536, PB1815
Coucelo M., EP1102, PB1616
Courtright J., EP541
Coutinho J., PB1399, PB1457
Coutinho R., PB1457
Couto Caro C., PB1426
Coutre S., EP636
Coutre S., S148
Cowan R., EP509
Cowland J. B., PB1615
Cox S., EP754
Cozens K., S219
Craddock C., S232, S243, EP432
Craig A., PB1711
Cranco S., EP880
Crane G., EP1104
Crary S., S256
Cras A., EP1282
Craviotto L., EP949
Crawford R., EP370, PB1665, PB1667, PB1668
Crawley C., EP470
Creasey T., EP765
Crescenzi A., EP867
Criag Z., EP644
Crickx E., S295, EP1147
Crippa L., EP723
Crippa S., S269, EP1298
Crisà E., S154
Criscuolo M., EP491, EP793
Crisóstomo A. I., EP1102, EP1114, EP1121, PB1616
Crispin P., S282
Cristiano G., S125, EP384
Critoph D., PB1744
Cro L., EP921
Croset A., EP938
Cross M., S161
Cross N. C., EP660, EP682, EP1064
Cross S., EP760
Crosswell H. E., EP769
Crotty G., PB1413
Crotty G., EP628
Crugnola M., S154, EP1079
Crump M., EP501
Crusoe E., EP1054, EP1286, PB1631
Cruz J. C., EP437
Cruz K., EP1202
Cruz R., PB1449
Cruz Afonso M. J., EP1116
Cruz Contreras D., PB1438
Cruz Cruz N., PB1561
Crysandt M., EP467, EP657
Csoka M., S221
Cuadrado M., EP498
Cubal F., PB1701
Cubillas D., EP1346, PB1819
Cuccarini V., S259
Cuccurullo R., EP478
Cuéllar C., EP952
Cuellar Pérez-Ávila C., PB1689
Cuello M. T., EP665
Cuello R., S293
Cuesta-Casanovas L., EP415
Cueto D., EP713
Cuevas B., EP670
Čugurović J., EP1196
Cui J., EP1080, EP1085
Cui L., EP742
Cui L., EP717
Cui X., EP996, PB1801
Cuker A., EP1144
Cultrera J. L., EP642
Cumano A., S248
Cuneo A., S143, EP624, EP631, EP645
Cunha C., EP425
Cunha M., PB1701
Cunha Pires E., PB1538
Cunniff J., EP859
Cunningham D., EP499, PB1569
Cunningham I., EP917, EP926
Cunningham J., EP555
Cupedo T., EP943
Curcio F., S289
Curley D. C., EP1289
Curran E., PB1720
Curti A., S125, S138, EP384, EP405, EP753
Curtin N., EP1074
Curtin P., EP345, EP351
Curtis S., EP1206
Curto-Garcia N., EP1089, PB1719
Curtopelle A., EP1004
Custidiano M. D. R., EP663, EP880
Cutajar M., PB1682
Cuthill K., PB1654, PB1694
Cutler C., S238, S239
Cutts K., PB1398
Cvetkovic Z., EP1326
Cwynarski K., S219, EP765
Cymbalista F., S148, EP652
Cyr M., EP401
Cyteval C., EP701
Cytryn L., EP570
Czapla J., EP724
Czapla L., PB1805

D´Acunto M. C., EP665
D'Addona M., EP1170
D'Alba I., EP1158
D'Alessandro A., EP1067
D'Altri T., EP373
D'Ambrosio A., EP1166
D'Amico M. R., EP478, PB1790
D'Amore E. S. G., EP1124, EP1129
D'Amore F., EP810, EP1124, EP1129
D'Ardia S., S308, EP474
D'Onofrio V., S276
D'Sa S., S291, EP689
Da Costa V. A., EP1213
Da Cunha-Bang C., EP613
Da Silva Barros J. T., EP848
Da Silva Santos Duarte A., EP1213
Dadi N., EP531
Daffini R., EP449, EP1089
Dagna L., EP1067
Dahl M., EP863
Dahlke M., PB1476, PB1481
Dai M.-S., EP476
Dai S., EP636
Dai V., PB1570
Dail M., S137
Dal Bello R., S126
Dal Zotto C., EP1307
Dalal M., EP934, PB1738
Dalla Palma B., EP949
Dalla Santa S., EP316
Dallasta G., PB1534
Dalle J.-H., S157
Dallemagne J., PB1657
Dallmann L.-K., S128, S139
Dally N., S255, S288, PB1663
Dalovisio A., S192
Dalton N., EP1214
Daly J., EP941
Daly K., EP785, EP798
Dam M. J., S159
Damaj G., S212
Damas R., EP488
Damaschin C., S209
Dambrauskiene R., EP1115
Damerdji D., PB1835
Damianaki A., EP588
Damiani D., EP477
Damlaj M., EP830
Damm F., EP402, EP755
Damore M., S192
Damrah N., EP402
Danelyan S., EP1056
Dang L., EP695
Dang P., S151
Dang S., S150
Dani N., EP1220
Daniel E., EP1017, EP1018
Daniele A., PB1550
Daniele P., EP1025, EP1033
Danise P., EP827
Danylesko I., EP526, EP716
Dao F.-T., EP347
Daoud J., PB1564
Dardanoni G., EP1309
Darden T., EP1151
Dargenio M., EP491
Darif M., EP963
Darin S., S102
Darley R. L., EP388, EP393
Darmani I., PB1516
Darmon S., EP385
Darnahal M., PB1830
Darvalics B., EP1107
Das R., EP911
Dasgupta S., EP780
Dash A. B., S166, S184
Dashkevich E., EP1349
DasMahapatra P., EP1179
Datseris I., EP774, PB1560
Daukelaite G., EP486
Davainis L., EP486
Dave N., PB1709
Daver N., S132, S135, S136, S167, EP367, EP401, EP430, EP440, EP464, EP466, EP468, EP471,

EP676, EP1075, PB1405, PB1624
David S., S212
Davidis-van Schoonhoven M., EP1027
Davidkova I., PB1503
Davidkova Y., PB1421
Davidova Y., EP357
Davids M. S., EP633
Davidson M., EP1082
Davies A., EP504, EP530
Davies F. E., EP985, EP1013, EP1259, PB1673
Dávila J., EP893
Davis J., EP1224
Davis K. L., EP992
Davis L., PB1384
Davis R., EP1171
Davis R., EP1215
Davis Z., S143, EP631
Davydova J., EP360, EP1260
Davydova Y., EP361, EP1241
Dawidowska M., EP322
Dawoud A., EP1064
Day G.-J., PB1354
Dazzi F., EP738, EP1276, EP1279
Dbaibo G., PB1763
De Andrade Rezende M. J., PB1823
De Arriba F., EP1021
De Bastos I. V., PB1823
De Beleyr B., EP654
De Bessa Jr. J., PB1538
De Beuf K., EP566
De Boer C., S180
De Boer F., S149
De Boer R., EP608, EP873
De Botton S., S138, EP457, EP465, PB1408
De Braganca K., S190, EP1003
De Candia E., EP571
De Candia M. S., S154
De Castro C. M., S174, EP595, PB1471, PB1476, PB1477
De Deus Santos M. D., EP631
De Dios Soler M., EP927
De Dreuzy E., S251
De Fabritiis P., S182
De Falco F., EP620
De Farias M., EP1279
De Franceschi L., EP695, EP1307, PB1766
De Gennaro F., EP1127, EP1140
De Grande A.-C., EP456, EP482
De Groot M., EP1284
De Groot-Kruseman H., EP538
De Guibert S., EP495
De Haas V., EP319
De Haro N., EP889
De Heer K., EP608
De Jong D., EP517, EP766
De Jong M., EP943
De Jonge N., S281
De Keizer B., EP517
De Kerviler E., EP540
De Kraa R., PB1393
De La Cruz Benito B., PB1518
De La Cruz Vincete F., EP530
De La Fuente A., EP447, EP479
De la Fuente J., EP733
De la Fuente Graciani I., S293
De la Iglesia S., PB1495
De la Morena-Barrio B., S303
De La Morena-Barrio M. E., S303
De La Nuez Melián H., PB1495, PB1561, PB1798
De la Puerta Paula R., PB1689
De la Rosa M., EP616
De La Rubia J., S185, EP986, EP1012, EP1021, EP1046
De la Serna J., S143, EP587
De las Heras A., EP1167
De Lavallade H., S153, S283, EP1276, EP1279
De Leon Cantu R. E., PB1438
De Leonardis P., PB1357
De Lima M., EP353
De Linares Fernández S., EP1250
De Looper H., S170
De Lorenzo R., S279
De Luca G., EP1067
De Luca M. L., EP1152
De Luca M. L., EP793
De Lucena M. M., PB1823
De Marchi E., EP753
De Marco B., EP1267
De Martino A., PB1790
De Mel S., EP961
De Melo Campos P., EP1213
De Michele E., EP1307, EP1310
De Miguel Llorente D., PB1425, PB1450, PB1666, PB1692, PB1787
De Moerloose B., S116, EP343
De Montalembert M., S314, EP736, PB1762
De Nardi L., EP1291
De Novellis D., EP478, EP1166, PB1392, PB1790
De Novi L. A., EP860
De Oliveira C., EP1282
De Paoli L., EP603
De Passos Sousa R., EP1145
De Pater E., S170
De Paz R., EP670
De Paz Arias R., PB1518
De Propris M. S., S112
De Ramos J., PB1679
De Rueda B., EP329
De Sanctis V., PB1550
De Santana J. A., PB1823
De Santana Xavier G. A., PB1823
De Santis G., PB1461
De Santis S., EP419
De Simone G., EP478, PB1790
De Souza C., EP717
De Souza Medina S., EP1213
De Stefano V., EP987, EP1089
De Toledo M. A., S196, S197, EP1063
De Tute R., S181
De Vet H. C., S208, EP517
De Vos S., S213
De Waal E., EP1020
De Wilde B., EP1208
De Wit M., EP467
Deak B., EP768
Deak D., PB1684
Dean J. P., S147, EP636
DeAngelo D. J., S201
Deary I., EP754
Deau-Fischer B., S215
Debeljak N., EP1109
DeBonnett L., S314, EP1211
DeCastro A., EP974, EP1002
Dechow T., EP979
Deckert M., S219
Dedeken L., EP1208
Deeren D., EP739
DeFilipp Z., S239
Degelia A., S282
Degli Esposti L., PB1766
Degli Esposti S., EP1001, EP1026
DeGutis I., EP677, EP1182
Dei Tos A. P., EP1124, EP1129
Deininger M. W., S153, S201, EP671, EP684
Dejoie T., S180
Dekaj F., EP1047
Del Campo Garcia R., PB1575
Del Carpio D., PB1675
Del Fabro V., EP1004
Del Giudice I., EP624, EP860
Del Guerra de Carvalho Moraes B., EP818
Del Orbe R., EP889
Del Orbe Barreto R., EP712
Del Potro E., EP546
Del Principe M. I., EP491
Del Valle S., PB1793
Delabesse E., EP456, EP482
Delamer R., EP665
Delaporta P., EP1311
Delavallade H., EP738
Delfau-Larue M.-H., EP790
Delforge M., S180, S190, EP987, EP1009, EP1192, PB1653
Delgado E., EP1161
Delgado I., PB1649
Delgado J., S143, EP734, EP872, PB1567, PB1568
Delgado R., S221
Delgado V., PB1791
Delgado-Martínez J., EP415
Delia M., EP491
Delimpasi S., EP974, EP976, EP986, EP1014, EP1016, EP1028, EP1031, PB1515, PB1516
Dell'Orso G., EP1158
Della Porta M., PB1619, PB1626
Della Starza I., S114, EP860
Dellacasa C., S308, EP474
Dellatola M., PB1515, PB1516
Delmer A., EP646
Delord M., S215
Deltreggia Benites B., EP1213
Delumpa R., S167
Delwel R., S123, EP378
Demakos E. P., EP904
DeMarco D., EP499
Demchenkova M., EP556
Demerdash Y., S245
Demichelis Gómez M. R., EP1156
Demidenko A., EP1321
Demina A., EP358
Demina E., EP772
Demir A. M., EP577
Demosthenous C., EP631, EP1254, PB1583
Demuth I., EP755
Den Boer M. L., EP319, EP324
Den Hollander C., EP943
Dendle C., S282
Deng B., S115, S119, EP1269
Deng L., EP946
Denguir R., PB1824
Denis F., EP1176
Deniz Marrero I., EP1116
Denkers F., EP400
Dennis M., S130
Denny N., EP797, EP1199
Denotti A. R., EP1307
Deodato M., EP634, EP650
Deol A., EP495
Depaus J., PB1570
Depil S., S121
Deraedt W., EP964, EP978, EP1049
Derhaschnig U., S302
Derman B. A., EP1010
Dermikan F., EP631
Derolf Å., EP1081
Desamericq G., PB1742
Deschamps M., EP720
Deschatelets P., S174
Deshpande N., EP958
Desnica L., EP826, EP1263, EP1287, PB1539
Desnoyer A., EP1282
Despan C., EP828
Dettoraki A., PB1829
Deutschman E., S176
Devereux S., EP636
Devine J., EP1046
Devlin M., PB1709
Devlin S., S133
Devos H., EP542
Devos T., S202, EP1085
DeVries T., EP747
Dewilde V., PB1657
Dey D., EP553
DeZern A., S167
Dhanasiri S., EP1013, PB1673
Dheur M.-S., EP739
Dhillon H., PB1486
Dhodapkar M. V., EP1163
Dholaria B., S192, EP1235
Dhouaieb M. B., EP906
Di Bartolomeo P., S112
Di Bassiano F., PB1397
Di Battista V., EP827
Di Blasi R., S215, S216, EP540
Di Concilio R., EP1310
Di Cuonzo D., S308
Di Fazio A., PB1460
Di Giusto S., EP477
Di Marco A. M., EP604
Di Marco V., EP1309
Di Martino L., EP316
Di Mauro M., EP1203, PB1765
Di Meco F., S259
Di Micco A., S187
Di Micco R., EP1298
Di Modica S. M., S277, S279, EP1302
Di Molfetta S., PB1550
Di Paola A., EP348
Di Pierro E., EP843
Di Raimondo F., S114, EP651, EP1004, PB1409
Di Renzo N., EP463, EP651
Di Rita A., EP622
Di Rocco A., EP729, PB1448
Di Russo A., PB1550
Diaconu C. C., PB1707
Diakonov D., PB1431, PB1432, PB1446, PB1447
Diallo D., EP1205
Dialoupi I., EP993, EP1014
Diamanti I., EP1044
Diamantopoulos P. T., EP919, EP1153
Diamantopoulou P., EP763
Diamond E. L., EP330
Dias A. R., EP579, PB1693
Dias J., EP788
Dias M., PB1399
Dias M., EP837
Diavati S., EP808, PB1577
Diaz E., PB1362
Diaz G. A., EP694
Díaz-Beyá M., EP329, EP352, EP472, EP479, EP481, EP734
Diaz Couselo F., EP880
Díaz Crespo F., EP870
Díaz de Heredia C., EP336, PB1780
Diaz-Lopez A., EP447
Diaz Morfa M., PB1425, PB1450, PB1692, PB1787

Díaz Roldán B., PB1488
Diblasi R., EP497
Dickinson M., S210, EP501, EP519
Diditchenko S., EP1200
Diefenbach C., S214, S222
Diels J., EP972, EP977, EP978, EP1049
Diepstra A., EP766
Dierlamm J., EP767
Dietzfelbinger H., EP1157
Diez-Campelo M., EP889, EP893, EP907, EP910, EP915, EP920, EP1106
Díez Gallarreta Z., PB1526
Diez-Martin J., S233, EP726, EP870, EP1132, EP1168, PB1696
Dijk A., EP1027
Diklic M., EP629
Dilhuydy M.-S., EP652
DiLiberto M., EP861
Dillon J., EP1292
Dillon L., S128
Dillon R., S128, S133
DiMaria E., PB1573
Dimicoli S., S156
Dimitrova S., EP1123, PB1686
Dimopoulos M.-A., S184, S186, S280, S287, EP551, EP774, EP782, EP784, EP959, EP974, EP975, EP976, EP986, EP988, EP993, EP1011, EP1014, EP1016, EP1028, EP1031, EP1036, EP1041
Dimopoulou M., EP773, EP1272, PB1560
Dimou M., EP631, EP773, EP774, EP919, EP1153, EP1340, PB1560
Dimou-Besikli S., EP1254, PB1697
DiNardo C., S132, S136, S137, S167, EP429, EP430, EP439, EP440, EP457, EP464, EP465, EP466, EP468, EP471, EP676, EP909
Dinarello C. A., EP1067
Ding B., EP982
Ding C., EP548
Ding M., EP334, EP562, EP864, EP874
Dingli D., EP747
Dinmohamed A. G., S155, EP434, EP637, EP640, EP666, EP678, EP796, EP803, EP804, EP1020
Dinneen K., EP806
Dinnessen M. A., EP637, EP803
Dionisi M., EP1140
Dionisio F., S258
DiRaimo J., EP1154
Dirnberger-Hertweck M., PB1444
Disher T., EP446
Dispenzieri A., S189
Distefano G., EP1067
Divona M., EP420
Dixon S., S260
Djouadi K., PB1563
Djurasinovic V., S307, EP1043
Dlilali M., PB1563
Długosz-Danecka M., S205, EP638
Dmitrova A., EP1260
Do Y. R., EP1029
Dobay M. P., S107
Dobber J., S149
Doblas-Márquez A., EP1324
Dobo S., EP585, EP589
Dobrenic M., EP561
Dodero A., EP723, EP729, EP744
Doğan F., EP1283
Doğan Ö., PB1603
Doghmi K., PB1375, PB1551, PB1598, PB1680
Doglio M., EP722
Doglioni C., EP1067
Dogliotti I., EP860, PB1575
Doherty A., EP1026
Doherty D., EP797
Döhner H., S124, S131, S133, S137, S144, EP376, EP402, EP423, EP428, EP445, EP457, EP465, EP467, EP909
Döhner K., S124, S128, S133, EP376, EP402, EP423, EP467, PB1711
Doki N., EP1229
Dokshina I., EP607
Dolai T. K., EP591, EP976
Dolinski B., S177
Dolnik A., EP402, EP423
Doma S. A., EP575
Dombret H., S126, EP385, EP428, EP445
Domenech C., EP343
Domingo Domènech E., EP506
Domínguez C., EP1329
Domínguez-Andrés J., EP1067
Dominguez Muñiz O., PB1462, PB1464, PB1604, PB1794
Domínguez Muñoz M. Á., PB1426
Dominique B., PB1383
Domm J., EP733
Dompeling E., S149
Donahue R., S202, EP1081
Donaldson D., EP631
Donchev M., PB1421
Dong B., EP962
Dong C., EP769
Dong F., EP1050, PB1685
Dong J., EP1073
Dong J., S117
Dong Y., EP692, EP696
Dong Y., EP1006
Dong Si T., PB1709
Donia H., EP821, PB1410
Donnellan W., EP480
Doobaree I. U., EP1236
Doorduijn J. K., EP637, EP640
Dorado N., EP726, EP1168
Doran C., PB1379
Dorillo E., EP620
Dorofeeva A., PB1467
Doronin V., EP457
Dörr H., S225
Dorra B., EP1285
Dorra J., PB1374
Dorritie K., S222
Dos Santos G., EP631
Dosanjh J., PB1354, PB1355, PB1356
Dou X.-L., EP1142
Dou Y., EP372
Doubek M., S142, EP631
Doucerain C., EP1204
Doucey M.-A., EP938
Douganiotis G., EP1044
Dougherty S., EP910, EP1106
Douka V., EP1254, PB1697, PB1721
Douma S., EP1232
Dourado D., EP1054, EP1286
Dovern E., EP1197
Dovydenko M., EP1260
Dow J., EP480
Doward L., EP370
Dowling T. H., EP396
Doyen C., S180
Drachtman R., EP1206
Drago K., PB1475
Dragonetti G., EP491
Drake A., EP938
Drakopoulou E., EP939
Drakos E., EP882
Drakos G., EP1153
Drandakis I., EP1272
Drandakis J., EP551
Drandi D., EP860
Dransfield D. T., S176, EP859
Drayson M., S181, EP1259
Drees E., S225
Dreger P., EP431, EP1245
Dren N., EP1177
Drenou B., S215
Drescher R., S310
Dresse M.-F., EP1208
Dreta B., EP631, EP826
Dreyling M., S210, EP786, PB1444, PB1748
Driessen J., S208, EP766
Driessens M. H., EP567
Drijun J., EP1333, PB1618
Dritsa M., PB1807
Drize N., EP756
Drnovšek E., EP1109
Drobna-Śledzińska M., EP322
Drokov M., EP360, EP1260, PB1785
Druker B., S150
Drummond M. W., EP1058, EP1077
Drupad D., PB1501
Du J., EP962
Du M.-Q., EP857
Du Q., EP1266
Du T., PB1555
Du X., S204, EP1120
Du X., EP618, EP801, PB1576
Du Y., EP598
Du Y., EP516
Duan J., S115
Duan M., EP1120
Duan R., EP374
Duan Y., EP439, EP444
Duarte C., EP1032
Duarte D., S278
Duarte P., PB1675
Duarte R., S241
Duarte R., EP488
Duarte S., EP630, EP1102, EP1114, EP1121
Duarte T., S278
Dubbini M. V., S240
Dube H., S192
Dubin F., S186
Dubnyak D., EP1260
Dubois J., S149, EP599
Dubov S., S286
Dubov V., S286
Dubowy R., EP747
Duca L., EP843
Ducamp S., S273
Ducastelle-Lepretre S., EP494, EP1262
Duchmann M., S126, EP385
Dudebout J., PB1662
Dudnic C., PB1582
Dueñas A. B., EP1329
Dueñas M. E., PB1385
Duerig J., EP968
Duetz C., S163
Dufu K., EP1198
Dugan J., S165
Duh M. S., PB1485
Dujmovic D., EP561, EP826, PB1494, PB1539, PB1684
Duléry R., S215
Dulicek P., EP1076
Düll J., S175, PB1444
Dulphy N., S162, EP906
Dulucq S., S152
Dumagay T., PB1754
Duman M., EP1342
Duman N., EP1138
Dumas P.-Y., EP456, EP482
Dumezy F., EP407, EP432
Duminuco A., PB1409
Dummer R., PB1428
Dumont A., PB1445
Dumpis S., EP626
Dunaeva E., PB1700
Duncan K. W., S176
Dungarwalla M., EP649
Dunlea E., EP628
Dunne A., EP433
Dunnebach E., EP727
Dünweber A., S134
Duong V. H., EP913
Duployez N., S128, EP385
Duque M., S106
Durakovic N., EP1263, EP1287
Duran A., EP818
Duran-Ferrer M., EP858
Durand A., EP497
Durão S., EP1032
Durdu-Rayman N., EP1027
Durgam G., PB1719
Durham B. H., EP330
Dürk H. A., EP1239
Dürrenberger F., EP1204
Dussiau C., EP898
Dutari P., EP997
Duyster J., EP467
Dyagil I., EP615, EP623, EP672
Dybedal I., S201
Dytfeld D., EP960
Dziedzic K., S164
Dzierzak E., S170

Eadie L., EP321
Eagle G. L., EP610
Ebbo M., EP1125
Ebeling F., EP925
Ebert A., EP378, EP381
Ebner J., EP389
Ece D., EP355, PB1523
Eckert C., EP318
Eckley S. T., S176
Eclache V., EP898
Economou M., PB1376, PB1772, PB1807, PB1812, PB1816
Ector G. I., S155
Edahiro Y., EP1101, EP1105
Edavana V., EP740
Eder T., EP373, EP380, EP381
Edler M., EP1210
Eeckhoudt S., PB1815
Eertink J. J., S208, EP517
Efira A., EP1208
Efraim M., S299
Efstathopoulou M., EP631, EP773, EP774, EP808, EP1272, PB1560, PB1577
Eftychidis I., PB1721
Egic D. M., S246
Egidio B., EP1273
Egle A., EP971
Egyed M., S148, EP1076
Ehrencrona H., S152
Eichenauer D. A., S209, EP779

Eichhorst B., S144, S146, EP599, EP632
Eide C., S150
Eijsink J., PB1676
Eikenboom J., EP567
Einsele H., S175, S190, EP987, EP1003, EP1009, EP1031, EP1237
Eiring A., S150
Eisa N., PB1533, PB1578
Eisenwort G., S198, EP897, EP902, EP1065, EP1068, EP1070
Eiznhamer D., S239
Ejerblad E., EP912
Ek S., EP863
Ekels A., EP1162
El-Ashwah S., EP631
El Chazli Y., EP821, EP1185, PB1367, PB1811
El Demerdash D., EP1195, PB1479
El Fakih R., EP1276
El Fatmi R., PB1585, PB1749
El-Ghammaz A., PB1774
El-Gharbawi N., PB1818
El Gkotmi N., PB1516
El Haddad M., PB1551
El Hariri N., PB1763
El-Hassad E., EP797
El Hassadi E., EP806
El Husseiny N., PB1813
El Kassiss Y., EP515
El Maaroufi H., PB1375, PB1551, PB1598, PB1680
El-Najjar I., PB1654, PB1694
El Omri H., PB1377, PB1454
El Rassi F., S314, PB1762
El-Sherif N. H., EP702
Elalfy M., EP688
Elbieh E. A. S., EP715
Elbogdady M., PB1540, PB1773
Eldabah N., PB1811
Eldering E., S141, EP608, EP873
Eldfors S., EP396
Eleftheriou P., S263
Elemary M., EP931
Elemento O., EP861
Elena C., S154
Elena K., EP781
Elena N., EP781
Eleutherakis-Papaiakovou E., EP993, EP1041
Elgawhary S., PB1818
Elhassadi E., EP1341, PB1412, PB1413, PB1579, PB1580
Elia L., S112, S114
Elias A., EP881
Eliason L., EP1171
Eliopoulos A. G., EP600
Elkorashi S., PB1377
Ellervik C., S159
Elli E. M., EP1079, EP1089
Elliott B., EP499
Ellis M., S288, EP655
Ellison C., EP1261
Ellison T., EP1258
Ellonen P., EP856
Elloumi M., PB1363, PB1452, PB1510, PB1527, PB1562, PB1564, PB1592, PB1690
Elmaagacli A., S243
Elmusharaf N., EP649, EP797
ElRazzaz M., PB1774
Elsabah H., PB1454
Elsaid R., S248
Elsden E., EP1189
Elshinawy M., EP707
Emadi A., EP462, EP913
Emarah Z., PB1578
Emelina E., EP641, EP653, PB1524
Emile J.-F., EP330
Emiliani C., EP384
Emmerechts J., EP542
Emmrich S., EP398
Emna A., PB1374
Emna B., PB1374
Emna B., EP714, EP817, EP831, PB1586
Empson V., EP1076
Enard W., S127
Encinas C., EP1168, PB1696
Encinas J., EP721
Enciso C., PB1534
Enciso M. E., PB1675
Endakova A., EP1190
Endell J., EP879
Engelhardt M., PB1658
Engen C., EP396
Engert A., S209, S225, S307, EP764, EP767, EP779
England J., EP1082, EP1083
Enjuanes A., EP606
Enomoto T., S226
Enrico A., EP631, EP659, EP927
Enright H., EP806, PB1413
Ensari S., PB1445
Ensell L., EP788
Enshaei A., S111, EP317
Entrena L., S303
Eoli M., S259
Epifanovskaya O., PB1612, PB1617
Epstein R., EP916
Eradat H., EP503
Erba H. P., EP442
Ercan T., PB1705
Erdem M., PB1372
Eren F., PB1683
Erickson-Viitanen S., EP1075, PB1716
Erlacher M., S199
Ermini A., PB1602
Ernst M., PB1430
Eroğlu Küçükdiler H., PB1778
Erpelinck C., S123, EP378
Escalada González L., PB1507
Eschweiler J., EP1063
Escobar M. A., S256
Escoda L., EP329
Escoffre-Barbe M., S180
Escudero Vilaplana V., EP1168
Eshan S. H., PB1424
Eshel R., S285
Eshet Y., EP502
Eshoj H. R., PB1740
Eskelund C., EP863
Espada E., EP354, EP1032, PB1449
Español-Rego M., EP734, PB1642
Espehana A., S283
Espeli M., S162
Espigado I., EP587
Espinet B., S143, EP606, EP616, EP631, EP890
Espinosa Lara N., EP1139
Espinoza M., PB1675
Esposito O., S101
Essa M., EP369
Essam Y., PB1540, PB1773
Essel J., EP541
Essers M., S245
Estanek V., EP859
Estanislao A., EP814, PB1664
Estcourt L., PB1430, PB1756
Esteban D., EP472, EP481
Estepp J., S260, EP1202, PB1764
Esteve J., S138, S168, S232, EP329, EP415, EP472, EP479, EP481, EP546, EP734
Esteves G., EP354, EP1032
Estoppey C., EP938
Estornes Y., S121
Estrada N., EP670
Estrov Z., EP1096
Etienne G., EP679
Eto T., EP1229
Euzébio M., S106
Eva J., EP371
Evans M., EP1258
Eveillard J.-R., S180
Everden A., EP797
Evers L., S149
Evgeniya B., EP781
Evim M., EP1216, EP1218, EP1316, PB1372
Ewing J., EP1058, EP1074
Eyre T. A., EP500, EP504, EP514, EP524, EP633, EP649, EP797
Ezponda Itoiz T., EP907
Ezzat H., EP1220
Ezzat H., EP1312

Fabbiano F., S112
Fabbri A., S219
Fabbri F., EP384
Faber E., EP969
Fábián J., PB1641
Fabio G., EP491
Fabre S., EP915, EP920
Fábregas Ruano M. T., PB1584
Fabris M., S289
Fabrowski P., S100
Facchin G., EP815
Facchinelli D., EP795
Facchini E., EP1158, EP1314, PB1770
Facco M., EP645
Facon T., S180, EP976, EP980, EP981
Fadeev T., S295
Fadeeva N., EP1190
Faderl S., EP442
Fadhil S., EP834, PB1589, PB1729
Fadiga N., S262
Fadlallah J., S295
Fagerholt O., EP399
Faghmous I., EP366
Faguer S., EP1087
Fahd M., S157
Fahmy O., PB1479
Fain O., EP906
Faitova T., EP613
Faivre L., EP1282
Faiza T., PB1563, PB1835
Fakhfakh Y., PB1363, PB1452, PB1562, PB1564, PB1690
Fakhfekh Y., PB1527
Fakhri B., EP500, EP633, EP1235
Falanga A., S292
Falautano M., S219
Falciani F., EP610
Falini B., EP611, EP793
Falini L., S227
Falini B., S227
Faller D. V., S166, EP928, PB1407
Falqués-Costa T., EP406
Falvo P., EP753
Famengo B., EP1124, EP1129
Fan H., PB1416
Fan L., S207, EP548, EP601, EP618, EP801, PB1497, PB1576
Fan M., EP356
Fan X., EP905
Fan Z., EP356
Fanale M., S205, EP506, EP769
Fang B., PB1648, PB1670
Fang J., EP414
Fang Y., EP512, EP537, EP549
Fang Z., PB1648
Fang Z., EP1058
Fang X., EP787
Fang X., EP562
Fanin R., S240, S289, EP477, EP815
Fann R. J., PB1489
Fanning S., EP541
Fante M., EP364
Fantl D., PB1675
Farady C., S161
Farahat N., PB1410
Faraj S., EP834, PB1589, PB1729
Faraoni I., EP420
Fardella E., EP723
Fareed J., S307, EP1326
Farhadfar N., S238
Farias D. L. C., EP1039
Farina F., S259
Farina G., EP651
Farina L., EP634
Farmaki E., PB1772
Farmer M., EP585, EP589
Färnegårdh M., EP871
Farooq A., EP1001, EP1026
Farooq U., EP495
Farrajota Neves da Silva P., EP882
Farrell J., EP930, EP1315
Farrelly E., EP934
Farrer A., EP930, EP1315
Farrow N. A., S176
Farruggia P., EP1155, EP1158
Farrugia D., PB1682
Farrugia M., PB1595
Faryal R., EP797, PB1545
Farzaneh F., EP788
Fastenau J., EP1031
Fastova E., EP756
Fathi A. T., EP443, EP457, EP465, PB1408
Fattizzo B., EP713, EP921, EP1099, EP1141, PB1621, PB1627
Fattori G. C., EP1058
Faustino P., S264
Fava C., S154, EP661, EP673
Favini C., EP603
Fay B., EP693
Fazal S., EP455
Fazio F., S182
Fazlic Dzankic A., EP886
Fé A., PB1460
Fechina L., EP358
Feder K., S124
Federico M., EP860, PB1575
Federti E., EP695
Fedorova D., EP576
Fedorova L., EP544, EP770, EP771
Fedrigo M., EP1053
Fei X., PB1594, PB1797
Feigenson M., EP758
Feingold J., EP518
Fejes Z., EP572
Feki W., PB1452
Felber B. K., S287
Feld J., EP904
Feldkamp J. D., EP755
Feldman S., PB1528
Feldman T., S205, EP506
Feldman T., EP391
Felices M., EP326
Feller A. C., EP853
Feller F. M., EP910, EP1106

Fellner M., EP378, EP381
Fenaille F., S126
Fenaux P., S138, S156, S162, EP906, EP909, EP910, EP915, EP920, EP1106, PB1408, PB1619
Fenercioglu S., PB1832
Feng C., EP366, PB1735
Feng F., EP372
Feng J., EP397
Feng J., S206, S211
Feng R., EP513, EP639, EP789, PB1685
Feng S., EP505
Feng S., EP639, EP642
Feng S., EP728, EP1257, PB1781
Feng X., S115
Feng X., EP1271, EP1303
Feng X., EP580
Feng Y., EP505
Feng Z., EP344
Fenk R., EP968
Fenouille N., S126
Fenske T. S., EP500, EP535
Fenton K., S205, EP506, EP769
Fenwarth L., EP385
Fenyvesi F., EP572
Feres C., EP550
Ferguson G., EP797
Ferguson P., EP649
Fermont J. M., EP1222
Fernandes Â., EP425
Fernandes I., PB1701
Fernandes M., EP820
Fernandes M., S106
Fernandez A., S265, PB1407
Fernández I., EP1320
Fernandez I., EP663, EP665
Fernandez S., EP734
Fernandez S., EP994
Fernández-Alonso M., EP809
Fernandez-Aviles F., EP472, EP481
Fernandez-Caldas P., PB1495
Fernández-Caldas González P., PB1561, PB1798
Fernandez Carazo R., PB1483
Fernandez de Larrea C., EP734, PB1642, PB1649
Fernández-Ibarrondo L., EP890
Fernandez-Leyva H., PB1672
Fernandez Luis S., EP587
Fernández Melid E., PB1734
Fernández-Moreno A., EP350
Fernández Mosteirín N., EP578, EP1331
Fernandez-Pol S., EP717
Fernández-Rodríguez C., EP890
Fernández Rodríguez M. Á., EP1345, PB1507
Fernandez-Ruiz A., EP670
Ferra C., EP1231, PB1493
Ferrand C., EP720
Ferrant E., S148, PB1546
Ferrante M., EP860
Ferranti A., S219
Ferranti M., PB1761
Ferrara F., S114, EP1034, PB1392
Ferrara I., EP1170
Ferrara J. L., S238
Ferrari G., S249, S268, S269, S277, EP1302
Ferrari L., EP665
Ferrarini I., EP795
Ferrarini M., EP1067
Ferrario A., EP634
Ferreira C., PB1449
Ferreira F., EP488
Ferreira G., EP820
Ferreira R. B., EP1274, EP1290
Ferreiro Ferro R., PB1734
Ferrel B., EP396
Ferrer A., EP606, EP1320
Ferrer-Marin F., EP1161
Ferreri A. J., S219
Ferrero D., S308, EP474
Ferrero E., EP1067
Ferrero G. B., PB1808
Ferrero S., EP860
Ferretti A., EP571, EP1152
Ferretti V. V., EP1098
Ferri V., EP603
Ferriera V., S256, EP730
Ferroli P., S259
Ferro-Perez de Guzman S., EP1343
Ferrua F., S258, EP741
Ferster A., EP343, EP1208
Feugier P., S212, S215, EP497, EP646, EP652
Feuring-Buske M., S124
Fevereiro M., EP820
Fevraleva I., EP1325, PB1414
Fiallo Suárez D. V., EP1116, PB1495
Fianchi L., EP491, EP793
Fidarova Z., PB1467
Fidone C., EP1307
Fiedler W., EP376, EP410, EP439, EP463, EP748, EP825
Fields P., EP504, EP514
Figeac M., EP385
Figueiredo D., PB1350, PB1630
Figueiredo V. L. D. P., EP1039
Figueiredo Costa S., EP818
Figuera A., PB1799
Figuera-Alvarez A., EP445
Figueredo Y., PB1675
Figueroa M. F., EP665
Figueroa Mora R., EP649
Fijnvandraat K., EP567
Filanovsky K., S255
Filardi N., PB1460
Filatova L., EP1264
Filik Y., EP664
Filipovics A., EP1095
Filisetti C., S102
Fillet M., EP844
Fillitz M., S198, EP971
Filosa A., S101, EP1307, EP1309, PB1810
Filshie R., EP433
Fina P., PB1602, PB1771
Finazzi M. C., S158
Finciuc V., PB1582
Fine B., EP965
Finelli C., S172
Finitsis S., EP1254
Finizio O., EP491, PB1392
Fink A., S146, EP632
Fink A.-M., S144
Fink D., EP967
Fink M., EP1109
Finke J., S219, EP431
Finn N., EP931
Finnegan P., EP1235
Finocchiaro G., S259
Finotto S., EP795
Fiocchi C. A., PB1766
Fiorcari S., EP617
Firatli Tuglular T., PB1683
Firsova M., EP1270
Fischer K., S144, S146, EP632
Fischer L., EP786
Fischer L., S161, EP896
Fischer T., EP1059
Fisher A., EP1189
Fisher F. M., EP758, EP839, EP840, EP842
Fishman J., EP1191
Fitzgerald K., EP1046
Fiumara P. F., PB1409
Fjelstrup S., EP863
Flace A., EP1204
Flaishon L., EP462
Flament A., EP739
Flanagan K., EP945
Flasinski M., EP398
Flavin R., EP806
Flegarić-Babok R., PB1605
Fleming M., S273
Fletcher R., EP1058
Fleury I., EP516
Flick E. D., EP1182
Flinn I. W., S148, EP500, EP642, EP787, PB1553
Flodrova P., PB1637, PB1640
Flores M. G., EP665
Flores R., PB1767
Flores Ballester E., EP1327
Flores-Montero J., S185
Florido Ortega Y., EP662, EP1116, PB1495
Florinskiy D., EP576
Flotho C., S199
Flowers M., S235
Flygare J., S164
Foà R., S112, S114
Foà R., S154, EP624, EP645, EP673
Foard D., EP1000, PB1644
Födermayr-Mayerleitner M., EP897
Foell J., EP733
Fogelstrand L., S128
Fogliatto L. M., S148, EP807
Fok H., S263
Fokina E., EP607
Fokkema C., EP943
Foley M., PB1709
Follmann M., EP779
Follows G., S148, EP530, EP765, EP857
Foltz L., EP1077
Fominykh V., EP358
Foncillas M. A., EP350, EP1089
Foncuberta M. C., EP663, EP880
Fong C. Y., EP917, EP926
Fonseca C., EP1054
Fonseca G., EP1019
Fonseca M., EP1234
Fonseca R., EP965
Fonseca e Silva D., EP1281
Font C., EP1320
Font P., EP910, EP1106
Font López P., EP1168
Fontan J., S180
Fontana M. C., S125
Fontana M., EP1000, PB1644
Fontana R., EP1170
Fontanes Trabazo E., PB1734
Fontanili I., EP1155
Fonte Feal C., PB1604
Foran J. M., EP1078
Forcade E., S117, S157, S236, S243
Forestieri G., EP603
Forget A., S126
Forjaz Lacerda J., EP354
Forman S., EP345, EP351
Fornero L., EP950
Forni G. L., S101, EP688, EP1307, PB1766
Forrest B., EP592
Forrest D., EP365
Försti A., EP612
Forsyth S., EP1202
Forsythe A., EP1025, EP1033
Forte D., EP384, EP405
Forté S., S262
Fortini M., EP1307
Fortune A., EP806, PB1413
Foss F. M., S218
Fossard G., EP494, EP1262
Fossati C., S258
Foster M., EP709
Fotiou D., EP993, EP1016, EP1036, EP1041
Fotzi I., EP1155, EP1158, PB1771
Fouzia O., PB1558
Fowler N. H., S210
Fox C., S219, EP504, EP514, EP532, EP539, PB1451, PB1738
Fox M. L., EP1089
Fox S., EP1058
Fracchiolla N., S112, S137, EP491, PB1357
Fraczkiewicz G., EP1073
Fradette C., EP1312, PB1760
Fraeman K., PB1639
Fraga C., EP579, PB1693
Fragiadaki I., EP588
Fragoso R., S106
Frairia C., S308, EP474
Fram R. J., S166, EP928
Frampton J., EP373
Franceschetti S., PB1550
Franceschini A., PB1765
Francis S., EP1058
Francis-Gibson B., S314, PB1762
Francisco Trafane L., EP1213
Francis Grigoropoulos N., EP857
Franco I., EP1032
Francois C., S174
Frangoul H., EP733, EP736
Frank M., EP1224
Frank P., EP1172, PB1743
Frankfurt O., EP457, EP462
Frederic B., EP844
Frederiksen H., S296, EP690, EP1107, PB1740
Frederiksen M., PB1740
Freeman B., EP642
Freeman C., PB1554
Freeman S., S130, S133, EP432
Fregnani A., EP855, PB1633
Freilone R., S308
Freitas J., EP663
Freitas M. J., EP665
Frello M., EP459
Frenquelli M., EP600
Fresa A., EP631, EP645, PB1506
Freue J. M., PB1509, PB1511, PB1534
Freund T., S285
Freyer L., S248
Frick M., EP755
Fridthjof K., S134
Fried S., EP526
Friedlander S., S166
Friedman J. D., PB1553
Friedrich C., EP652
Frigo A. C., EP810
Frigola G., EP872
Friis L. S., EP359
Frikha I., PB1363, PB1527, PB1562, PB1564, PB1592, PB1690
Frikha R., PB1510, PB1527
Frisch A., EP487
Frison L., EP810
Fröhlich L., EP547, EP725, EP749
Fruchtman S., EP904

Frustaci A. M., EP650, EP793
Fryzek J., EP1180, EP1193
Fu B., EP565
Fu C., PB1670
Fu H., S104
Fu H.-X., EP1142, EP1252
Fu H., EP1277
Fu R., EP583, EP894, EP895, EP900, EP901, EP946, EP947, EP953, EP1050, PB1472, PB1478, PB1636, PB1646, PB1647
Fu R., EP1103, EP1111
Fu S., EP742
Fu W., S184, EP792, EP962, EP1024, PB1670
Fuchs M., S209, EP764, EP767
Fuente M. L., EP880
Fujii S., EP942
Fujimaki K., EP667, EP668
Fujimoto A., EP507
Fujino T., S300
Fujisawa M., S226
Fujita K., EP522
Fujiwara S., PB1587
Fukuda T., S244, EP507
Fukuda-Kurahashi Y., EP875
Fumagalli F., S102, EP741
Fung H. C. H., S213
Fung K., EP317
Fung M., S238
Fuqua T., EP1209
Füreder W., S301, EP589
Furey S., EP694
Furman R. R., S145
Furtado M., EP649, EP765
Fuster-Tormo F., EP329
Fylaktou A., EP609
Gaartman A., EP1221
Gaba S., PB1656
Gabaldo M., S258
Gabbasov Z., EP1328, PB1638
Gabdoulline R., S128, S139, EP402, EP757
Gabeeva N., PB1785
Gabellier L., EP950
Gabra H., EP463
Gabriel C., EP897
Gachev J., EP592
Gacina P., PB1494
Gack L., S120
Gadaud N., EP456
Gafter-Gvili A., S309, EP1247
Gage-Bouchard E. R., PB1498
Gaglioti C., EP1307
Gagne K., S162
Gahrton G., EP1237
Gaião Santos J., PB1616
Gaidano G., S143, EP543, EP603, EP624, EP631, EP634, EP650, PB1444
Gaidzik V. I., EP376, EP423
Gainaru G., EP551
Gajra A., EP737
Galactéros F., S270, S271, EP692, EP696
Galanopoulos A. G., EP919, EP1153
Gale R. P., PB1786
Galimberti S., S154, EP631, EP860
Galinsky J., EP1192
Galinsky K., S166
Galiulin R., S211
Gallagher M., S261
Gallagher R. C., EP694
Gallamini A., S205
Gallardo Delgado M., EP374
Gallego C., EP481
Gallego-Hernanz M. P., EP933
Gallego Murillo J., S294
Gállego Pérez-Larraya J., EP1003
Gallego-Villar L., S199
Gallì A., EP588
Galli E., EP540, EP793, PB1506
Galli-Tsinopoulou A., PB1376, PB1378
Gallipoli P., S129
Gallo M., S177
Gallo V., S258, EP741
Gallur L., EP336
Galmés B., EP1149
Galopoulos D., EP551, EP774, EP777, EP808, EP1272, PB1560, PB1577
Galstyan G., S286
Galtier J., EP482, EP497
Galtseva I., EP357, EP360, EP361, EP1241, EP1260
Galunic-Bilic L., EP561
Galvano C., EP625
Gamal M., EP702
Gaman A. M., PB1707
Gaman M.-A., EP1119, PB1707
Gambacorti-Passerini C., EP658, EP672, EP684
Gambale A., EP688
Gamberini M. R., EP1307, EP1313
Gamberini R., EP1305
Gámez I., EP612
Gamez Jimenez E. M., EP823
Gamperl S., EP1070
Gan D., EP338
Gandhi M. D., PB1440
Gandhi S., EP589, EP738, EP1276, EP1279
Gandini D., EP566
Gandolfi L., EP1267
Gangat N., S169
Ganguly S., EP1019
Ganly P., EP963
Ganser A., S128, S133, S139, EP376, EP402, EP423, EP467, EP748, EP757
Ganster C., S128
Ganwo I., PB1377
Ganzel C., EP462, EP1023
Gao L., S194, EP962
Gao Q., S207
Gao S., EP469, EP493, EP639, EP789, PB1416, PB1670
Gao X., EP805, EP1174
Gao Y., PB1542
Gao Y., EP525
Gaponova T., EP1241
Garbers C., EP1059
Garcés J.-J., S185, EP809
García A., EP952
García C., EP413
Garcia J., S136, S137, EP917, EP926, EP1078
García J. M., S303
Garcia J., PB1654, PB1694
Garcia K. C., S253
García M., EP479, PB1828
Garcia M. C., EP1168
Garcia O., EP546
García P., EP612
Garcia P., PB1654
Garcia-Albornoz M., EP813
García Arias Salgado E., EP1072
García-Arroba Peinado J., PB1791
García-Ávila S., EP890
García Bacelar A., S293
García Barcenilla S., EP1072
Garcia-Belmonte D., EP546, PB1791
García Bosque I., PB1518
García-Boyero R., EP352, EP447
García-Cadenas I., EP329, EP350, EP352, EP546, EP587
García-Calderón C., S237
Garcia Cereijo P. M., PB1604, PB1794
García de Coca A., S293
García de Herreros M., EP1320
Garcia de Labanca A., EP663
García Delgado R., PB1651
García-Díaz C., EP1131
Garcia-Donas G., PB1828
García-Escobar I., EP1320
García Gala J. M., EP1345
Garcia-Gisbert N., EP890
Garcia-Guiñon A., EP350, EP352, EP546, PB1649
García Gutiérrez V., EP489, EP670, EP1089
Garcia-Hernandez C., EP670
Garcia-Horton V., EP710
García-Malo M. D., EP616
Garcia-Manero G., S113, S136, S165, S167, S168, EP367, EP401, EP430, EP464, EP915, EP917, EP920, EP926, EP1104, EP1182, PB1619, PB1624, PB1626
Garcia-Marco J. A., S145, EP621, PB1493
García Ortego A. J., EP1139, EP1331, PB1821
García-Ortiz A., EP721
García-Pagán J. C., EP1084
Garcia-Pintos M., PB1649
Garcia-Rey E., EP734
Garcia Rivello H., EP927
Garcia Ruiz A., PB1826
Garcia-Ruiz C., S160
García Sánchez R., PB1651
García-Sanz R., EP782, EP1012
García-Serra R., EP563, EP616, EP631
García Suárez J., EP1327
García Torres E., PB1788
García Valdés M., PB1704
Garcia-Vela J., EP621
García-Vicente R., EP408, EP412
Gardelegui Perez de Villarreal I., PB1722
Garderet L., S180, EP963
Gardin C., S126
Gardiner B., EP1052
Gardner T., EP1175
Garfall A. L., S193
Garg M., S181, S299, EP974, EP976
Garg V., EP784
Garibaldi B., PB1409
Garidi R., S180
Garifalos F., EP1166
Garifullin A., EP1040
Garikipati A., EP911
Garmash A., PB1785
Garofalaki M., PB1515, PB1516
Garramone M., S259
Garrett A., EP977
Garrido-García V., EP412, EP721
Garris R., S113, EP367
Garrote M., EP1084, EP1089
Garzon F., EP784
Gasior Kabat M., EP1072, EP1089
Gasiorowski R., EP433
Gasparetto C., S188, S192, EP1002, EP1008
Gasparini V. R., EP611
Gastinne T., S216, EP766
Gat E., S216
Gater A., EP1175, PB1753
Gatopoulou X., EP1052
Gatt A., PB1682
Gatt M., S189, EP1023
Gattei V., EP624, EP860
Gattillo S., EP741
Gauci L., PB1682
Gaudiano M., EP869
Gaudin C., S156
Gaudio F., EP1188
Gauthier J., EP508, EP731
Gavanji R., EP446
Gavillet M., EP688
Gavin P., EP649
Gavini F., EP994
Gavriatopoulou M., S280, EP959, EP974, EP976, EP993, EP1014, EP1016, EP1041
Gavriilaki E., EP1153, EP1232, EP1254, EP1256, PB1804
Gavriilaki M., EP1232
Gavrilina O., S286, EP357, EP360, EP674, PB1785
Gavrilova L., S286
Gay F., S182, S184, EP987, PB1653
Gaysultanova Y., EP762
Gazeau N., EP508
Ge J., EP962
Ge M., EP581, PB1492
Ge Z., EP453, PB1386
Geary B., EP388
Gebauer J., EP853
Gebauer N., EP853
Geddes M., EP931
Geelen I. G., EP666, EP678
Geerts P., PB1676
Geffroy S., EP385
Geib J., PB1764
Geiger H., EP761
Geiger K. R., EP1060
Geisler C., EP863
Geissler K., S198, S211
Gemdzhian E., EP799
Gendlin G., EP641, EP653, PB1524
Genel F., EP704, PB1820
Genescà E., EP329, EP352, EP546
Geng D., EP1003
Geng H., PB1648
Geng Y., EP505
Gengrinovitch S., EP462
Genovese P., S252, EP1298
Gentile M., EP624, EP645, EP651, EP1307
Gentili S., EP1314
Gentilini Cacciola E., EP1094
Gentinetta T., EP1200, EP1210, EP1215
Gentner B., S102, S259, EP741
Genuardi E., EP860
George R., EP887
George T. I., S201
George-William J. N., EP604
Georgescu D., EP828
Georgiev P., EP1076
Georgopoulos N., EP777
Georgopoulou A., EP777, EP1272
Geraldes C., PB1630
Gerard L., PB1573
Gerardi C., PB1550
Gercheva-Kyuchukova L., EP1076
Gerds A., S202, EP480, EP1074, EP1075, EP1086, PB1711

Gerecitano J., EP869
Gergely V., EP994
Gerike T. G., PB1702
Germain J., EP1125
Germano C. R., PB1461
Germing U., EP467, EP897, EP910, EP915, EP920, EP1106
Gernsheimer T., S299, EP1144, EP1148, PB1733
Gerotziafas G., S307
Gerrie A., PB1554
Gerson J. N., EP500, EP633
Gerss J., EP342
Gerull S., EP1242
Gesk S., EP853
Getsy J., PB1706, PB1717
Getu H., PB1671
Geyer S., EP908
Gezer D., S196, EP1063
Ghali H., EP834, PB1589, PB1729
Ghandili S., EP825
Ghanim M. T., EP439
Ghanima W., S299, EP566, EP1126, PB1733
Ghanzin M., EP1264
Gharaibeh O., EP1220
Ghassoul Y., PB1563
Ghazaryan N., EP1056
Ghazy H., PB1578
Ghedira F., PB1824
Ghedira H., PB1443
Gherli A., S108
Ghesquiere T., EP697
Ghesquières H., EP451, EP494, EP1262, PB1546
Gheuens S., S270, S271, EP692, PB1805
Ghia E. M., S140
Ghia P., S143, S145, S147, S148, EP500, EP600, EP631, EP633, EP634, EP636
Ghiaur A., PB1379
Ghiggi C., EP860
Ghilotti F., EP972
Ghione P., PB1498
Ghirardi A., S158, EP1089
Ghita B., PB1466
Ghobadi A., S117
Ghoghale S., EP958
Ghorashian S., S116
Ghorbel M., PB1690
Ghosh M., S210
Ghosh N., S222, EP635
Giaccone L., S308, EP474
Giagounidis A., S165, EP467
Giai V., S308, EP474
Giakoumi X., EP774, EP808, PB1577
Giammarco S., EP394, EP491, EP1233
Gianakoulas N., PB1681
Gianesin B., EP1307
Giannakopoulou A., PB1697, PB1721
Giannakopoulou N., PB1560
Giannakou A., EP777
Giannelli S., S258
Giannikos T., EP773, EP808, EP1272, PB1577
Giannini M. B., EP827
Giannopoulos K., EP503, EP638
Giannotta J. A., EP921, EP1099, EP1141, PB1621, PB1627
Giannoukos G., S251
Giannouli S., EP1153
Giansily Blaizot M., EP701
Giatra H., EP551
Gibaja V., EP859
Gibb A., EP797
Gibbons D., EP1122
Gibbs S., S189
Gibert J., EP890
Gibson K., EP682
Giebel S., S232, S233, EP724, EP1228
Giere I., EP663, EP665, PB1380
Gigantes S., PB1515, PB1516
Gil A., PB1666
Gil C., EP329, EP350, EP352, EP447, EP546
Gil J. V., EP413
Gil L., EP960
Gil M., EP665
Gil-Alzugaray B., EP809
Gil Cortés C., PB1407
Gil Esparraga E., PB1488
Gil Manso R., PB1689
Gil Perez A., PB1425, PB1450, PB1692, PB1787
Gilbert J. C., S302
Gilbertson M., S282
Giles F., EP400, EP620
Gilham D. E., EP739
Gilis L., EP494, EP1262
Gilkes A., S133
Gill H., EP1074
Gill N., EP555
Gille H., EP846
Gillessen S., EP764, EP767
Gillett A., EP628
Gillham C., EP1292
Gillmore J., EP1000, PB1644
Gilmore R., PB1545
Gilreath J., PB1625
Gilroy K., EP696
Gimenez A., EP408
Giménez R., PB1369
Giménez-Conca A., EP352, PB1380
Giménez-López M. J., EP1183
Giménez-Pérez T., EP350
Gimeno E., EP546, EP606, EP616
Gimsing P., EP963
Gindele R., S303
Giné E., EP734, EP786, EP858, EP872, PB1567, PB1568
Gini G., EP1184, PB1550
Ginzburg Y., S200
Ginzel C., EP879
Gioacchino E., S170
Giona F., EP1155
Giordano A. M., EP651
Giordano C., EP1166
Giordano P., EP1155, EP1158
Giotopoulos G., S129
Giovangrossi P., EP1313
Giraldes J., EP841
Giraldo P., EP670
Giralt S., S241, EP353, EP1235
Giraud J.-T., S156
Girgis S., S191, S193, EP967
Gironella M., PB1649
Girshova L., PB1402
Gisslinger H., EP1076
Giudice V., EP1170
Giudici G., EP658
Giugliani R., EP694
Giuliani N., S182, S184, EP949, PB1633
Gjærde L. K., EP359
Gjertsen B. T., EP383, EP396, EP399, EP403, EP417, EP458, EP463
Gjoklaj M., EP646
Gkagkaridou S., EP609
Gkaitatzi M., PB1368
Gkirkas K., PB1516
Glader B., EP691, EP696
Glait-Santar C., S285
Gleeson M., PB1654, PB1694
Gleich G. J., EP1087
Gleixner K., EP461, EP902, EP1065, EP1068, EP1070
Glenthøj A., S270, S271, EP686, EP691, EP692
Glinshchikova O., PB1352
Glover R., EP1058
Glovier S., S150
Gnani D., EP1067
Gobbi G., EP1061
Godeau B., S295, EP1125, EP1147
Godfrey A., EP470, EP1058
Godwin J., EP541
Goedhart T., EP569
Goel S., EP1075
Goergen H., S209, EP767
Goffredo B. M., EP1140
Gogia A., S143
Goh Y. T., EP672, EP1081
Gohil S., EP649
Göhring G., S139, EP325, EP402
Gokarn A., EP958
Gökbuget N., EP318
Gökçe N. Ö., PB1820
Golbano N., PB1666, PB1692, PB1787
Golbano López N., PB1425, PB1450
Gold R., S255, S284, S285
Goldberg A., PB1391
Goldberg J. D., S191, S193, EP967
Goldkuhle M., PB1430
Goldschmidt H., S183, S190, EP968, EP972, EP987, EP1009, EP1245
Goldschmidt N., S255, EP502
Goldstein D., S288
Golenkov A., EP1048, PB1500
Golfier C., PB1546
Goller K., S164
Gołos A., EP1091
Golub A., PB1582
Golubic Cepulic B., PB1539
Golvano E., S293
Gomes E., EP421, EP630, PB1350, PB1630
Gomes R., EP1102, EP1114, EP1121
Gómez A., PB1369
Gomez E., S256
Gomez M. S., EP665
Gómez M., PB1819
Gomez V., EP670
Gómez Aguado F., EP1072
Gómez Alonso J., EP374
Gomez-Arevalillo S., EP1343
Gómez-Arteta E., EP574
Gómez Casares M. T., EP662, EP1091, EP1116, PB1495, PB1561, PB1798
Gómez-Centurión I., EP350, EP352, EP1168, PB1696
Gomez-Espuch J., EP1231
Gómez García L., S293
Gomez Gutierrez R., PB1728
Gomez-Hernando M., EP472, EP481
Gomez Llonin A., EP606
Gomez Martínez A., EP578, EP1139, EP1331, PB1821
Gomez-Perdiguero E., S248
Gomez-Rosas P., S292
Gómez-Úbeda S. P., EP1234
Gonçalves A. C., EP421, EP630, PB1350, PB1630
Gonçalves C., PB1457
Goncalves K., EP1224
Gonçalves L., EP975
Gonçalves N., S278
Gonçalves Pereira S., EP418, PB1726
Goncalves Ramos I., EP1251
Gonchar L., PB1366
Goncharova N., EP1349
Gong C., EP857
Gong J., EP465
Gong M., EP1266
Gong X., PB1706, PB1717
Gong Y.-P., PB1647
Gonzalez A. P., EP587
González A., PB1642
Gonzalez B., S116
Gonzalez E., EP578
González E., EP413
González F. A., PB1819
Gonzalez J., EP665, EP927
González M. S., EP587
Gonzalez M., S150
González T., EP329
González Y., EP1021, PB1649
Gonzalez Barca E., PB1444
González de Villambrosía Pellón S., PB1575
González-Campos J., EP329, EP350, EP352, EP546
González del Castillo L. M., PB1798
González-Farré B., EP872
González Fernández F. A., EP712
González-García H., EP1131
González-Gascón-y-Marín I., EP631
González-Gil C., EP329
González Gómez E., EP1139, EP1331, PB1821
González-Haba E., EP1168
Gonzalez-Haro C., EP1343
González-Martín J. M., EP1091
González Martínez T., EP907
Gonzalez-Navarro E. A., EP734
González Pérez M. S., PB1734
González Pinedo L., PB1798
González-Porras J. R., EP1131
Gonzalez Rodriguez L., PB1604, PB1794
González San Miguel J. D., EP662
González-Sierra P. A., EP612, EP823, EP1250
González Tarancón R., EP578
González Vicent M., EP587
González Zorrilla E., EP1072
Gonzalo Benito H., S293
Gooding S., PB1671
Goodman A., EP743
Gooljarsingh T., EP703
Goonasekera H., PB1806
Gooneratne L., PB1596
Gopal A., EP731, PB1572
Goranova V., PB1522
Göransson M., EP688
Gorbach O., EP776, PB1691
Gorbacheva S., EP681
Gorbatchevsky I., S214, PB1569
Gorbenko A., EP647, EP1110
Gordeuk V., S263
Gordillo Valencia N., EP411
Gordon-Walker D., EP523
Gorio C., EP1158
Görner M., S183, EP436
Gorreo Renzulli L., S112

Gorsh B., EP1171
Goryainova N., EP935
Goryunova E., PB1402
Gossage J., S103
Goswami B., EP553
Göthert J., EP1074
Gotlib J., S201, PB1713
Goto H., EP852
Gotoh A., EP903, EP1101, EP1105
Gottardi E. M., EP661
Gottardi M., EP491
Gottipati R. M., PB1718
Gottwaldova E., PB1640
Götz M., EP386
Götze K. S., EP376, EP467, EP761, EP896
Goulielmos G., EP1146, PB1351
Gourevitch A., EP462
Goursaud L., EP385
Goy A. H., EP495, EP530, EP787
Goyal G., S224
Goyal L., EP341, EP495, EP791
Goyal S., S261
Goyama S., S300
Gözmen S., EP704
Gozzelino R., EP848
Gozzetti A., EP622, EP631
Gozzini A., S154, EP673
Grace R. F., S270, EP691, EP692, EP696, EP1194
Gracia Vela M., PB1793
Graeven U., S183, EP968
Graf I., EP461
Graf L., PB1708
Graham T., EP1164
Grahlyova L., PB1530
Grainge M. J., EP532
Gramegna D., EP449
Granacher N., EP1077, EP1085
Granada I., EP329
Granados E., PB1445
Granados M. P., EP1161
Granell M., EP970, EP1021, EP1237, PB1649
Granier C., PB1565
Granot G., EP655
Grardel N., EP343
Gras I., EP1320
Gras L., S243
Grasedieck S., S178
Grasselli G., EP843
Grassi A., EP1228
Grassi L., EP1058
Grassi S., EP860
Grasso A., EP1273, EP1291
Grasso M., S182
Grau M., EP872
Grausenburger R., EP752
Gray K., EP969, EP1051
Graziadei G., EP1307
Graziano F., EP1155
Grebenkin D., EP681
Grebien F., EP373, EP380, EP381, EP389
Grech M., PB1682
Greco A., EP651
Greco R., PB1387
Green D., EP731
Green S., EP876
Gregersen H., EP1035, PB1740
Gregorová J., EP954
Greil R., EP971
Greiner G., S198, EP461, EP1065, EP1070
Greiner J., EP386
Greinix H., S235, EP521
Greipp P., S169
Grentzelias D., EP551
Gressin R., S212, EP511, EP790
Grey W., EP813, PB1383
Gribanova E., EP360
Gribben J., EP539, EP854
Grienay N., EP705, EP1143
Gries K. S., EP1031
Griessinger E., EP399
Grifa E., EP604
Griffin J. D., S313
Griffin M., S174, S301, EP589, EP592, EP594, EP595, PB1471, PB1477
Griffith J., EP514
Grifi F., EP1159
Grifoni A., EP867
Grigg A. P., EP769
Grigorie A., EP828
Grillo G., S236, PB1442
Grimaldi F., PB1392
Grimley M., EP745
Grimm J., EP404, EP435
Grinblatt D., EP1010, EP1182
Grinev V. V., S105
Grisariu S., S288
Griselli M., EP1288
Grishina O., EP467
Grishunina M., S286, EP360
Griskevicius L., EP486
Grispou E., PB1515
Gritsaev S., PB1447, PB1618, PB1635, PB1779, PB1783, PB1784, PB1800
Gritsayev S., EP836
Grob T., EP378
Groen K., EP1020, EP1027
Grogan L., EP806
Grønbæk K., EP863, EP888, EP913, PB1615
Gronroos E., PB1383
Gros F.-X., S216, EP497
Gröschel S., S123
Grosicki S., EP636, EP974, EP976, EP1028, EP1081
Gross T. G., S221
Gross Z., EP494
Groß-Langenhoff M., EP448
Grossi F., S174
Grossman A., S309
Grosso A. R., S106
Grote L., EP988
Grouzi E., S287
Grove C., S138
Grube M., EP1239
Grubic Z., EP1287
Grudeva-Popova Z., PB1522
Grundy M., PB1381
Grünschläger F., S245
Grupp S., EP736
Grzasko N., EP963
Gsottberger F., EP887
Gstettner C., EP521
Gu J., PB1795
Gu S., PB1386
Gu X., EP792
Gu Z., EP351
Guajardo M. L., PB1438
Guan H., EP346
Guandalini G., EP795
Guardia-Alés S. J., EP1183
Guarente V., EP631
Guariglia R., EP1170
Guarina A., EP1155, EP1158
Guarini A., S112, EP624
Guarini A., PB1550, PB1737
Guarnera L., EP793
Gubitosa J., EP703
Gubkin A., PB1785
Gudelsky A., EP758
Gudgin E., EP470
Guelbert N. B., EP694
Guenova M., PB1421, PB1503
Guerci-Bresler A., EP679
Guerneri S., PB1357
Guerra A., S258
Guerra M., PB1701
Guerra Domínguez L., PB1798
Guerrero M. V., EP665
Guerveno C., S156
Guezguez B., S129
Guffon N., EP694
Guglielmelli P., S158, EP1092
Gugliotta G., S154
Guidetti A., EP723, EP729, EP744
Guidez F., S162
Guidez S., S212, EP511
Guièze R., EP646, EP652
Guijarro F., EP415, EP472, EP481, PB1642
Guilbert F., S262
Guilhot J., S152
Guillaume T., S156
Guillen H., PB1666
Guillen Garcia H., PB1425, PB1450, PB1692, PB1787
Guilmet C., EP995, EP999
Guimaraes V., EP1286
Guimarães J., S278
Guindo A., EP1205
Guinn B.-A., PB1384
Guiot M., EP720
Gujral S., EP958
Gul E., EP989, EP1038, PB1643, PB1662
Gulbis B., EP1208, PB1536, PB1815
Güler S., PB1372
Gülez N., PB1820
Gulino A., S125, S249
Gulkirkas O., EP1316
Gullaksen S.-E., EP396, EP399
Gültekin S., EP897
Gumeni S., S280
Gumruk F., PB1365
Gumulec J., S299
Gunawan A., EP514
Gunduz E., PB1403, PB1775
Gunsilius E., EP971
Guo H., S299, PB1733
Guo H., S207, EP639, EP789
Guo R., PB1360
Guo R., S257, S266, EP1301
Guo S., S277
Guo Y., EP901
Guo Y., EP1007
Guobyte A., EP1178
Guolo F., EP459
Gupta A., EP800
Gupta D. G., EP331
Gupta I., EP1001, EP1026, PB1698
Gupta M., EP331
Gupta N., EP928
Gupta R., S143
Gupta S., EP1015
Gupta S., S196
Gupta S., S200
Gupta V., S202, EP362, EP1077, EP1082, EP1083, EP1085, EP1092, EP1093, PB1723
Gür Kırkaş Ö., EP1216, EP1218
Gurageva A., PB1611
Gurianova M., EP674, EP680, EP681
Gurion R., S255, EP502, EP530, EP1247
Gürkan E., EP1216, EP1218, EP1316, PB1755
Gurney M., EP941, PB1545
Gurung B., PB1571
Gussinklo K., S170
Gusto G., EP1005
Guthrie T. H., EP642
Gutierres G. P., PB1745, PB1823
Gutiérrez A., EP1231
Gutierrez G., EP1231
Gutiérrez L., EP812
Gutierrez M., EP635
Gutiérrez N. C., EP1021
Gutierrez S., EP450
Gutierrez X., EP408, EP708
Gutiérrez-Adán A., S160
Gutiérrez Jomarrón I., EP1327
Gutrin J., EP407
Gutwein O., S255, PB1505
Gverić-Krečak V., EP819, PB1605
Gyan E., S156, S212, EP511
Gyula Szabo A., EP1035
Ha X., EP915
Haaber J., EP851
Haage T. R., EP1059
Haase D., S128
Habboubi N., EP427
Hackanson B., EP467
Haddad F., PB1763
Haddad P., EP531
Hadebache R., EP720
Hadiji S., PB1562, PB1564, PB1690
Hadjiev E., PB1421
Hadrup S. R., EP609
Hadzijusufovic E., S198, EP664, EP1070
Haefliger B., EP972
Haenel M., EP767, EP968
Haenig J., S172, EP1150
Haertle L., S175
Haferlach C., S123, S175, S310, EP892
Haferlach T., S123, S128, S310, EP373, EP892, PB1514
Häfner N., EP897
Hagar R., S263
Hagelaar R., S107, EP335
Hagenbeek A., S225, EP766
Haghighi S., PB1830
Haghverdi L., S245
Hagin D., S285
Hagleitner M., EP538
Hagner P., EP1062
Hagström-Andersson A. K., EP406
Haidary A. M., PB1532, PB1535
Haifa R., EP714, EP817, EP831, PB1586
Haioun C., S212, EP501
Hajar K., PB1466, PB1597
Hájek R., EP724, EP816, EP954, EP970, EP975, EP985, EP986, EP994, EP1011, EP1042, EP1297
Hakimi Z., EP1191
Hakobyan Y., EP1056
Hall A., S181
Hall L., EP693
Hall T., S153
Hallard D., PB1445
Hallek M., S144, S146, EP632
Hallensleben M., EP757
Halligan S., EP532
Halloun J., S288
Hallworth P., EP1175
Halperin D., EP649

Halpern A., EP1074, EP1086
Halter J., EP1242
Hamad N., EP1186
Hamada A., PB1557
Hamadani M., EP518, EP528, EP535, PB1440
Hambleton H., EP835
Hamblin M., EP559
Hamdi S., EP1159
Hamdoun M., PB1585
Hamdy M., PB1818
Hamed A., PB1578
Hamed A., S211
Hamerschlak N., EP550
Hamiyet O., PB1809
Hamladji R.-M., EP1255, PB1629
Hammami E., PB1824
Hammond D., EP429
Hamza M. T., PB1479
Han B., EP593, EP598, EP929, PB1481
Han C., EP962
Han J., EP1092, EP1219
Han L., S196
Han M., EP953
Han M., EP1257, PB1781, PB1803
Han Q., EP453
Han T., EP847
Han T.-T., EP1142, EP1252, PB1591
Han W., S234, EP847, EP1226, EP1252, PB1591
Han X., EP516
Han X.-F., EP1030
Han Y., EP605, EP627, EP862, EP864, EP866, PB1544
Han Y.-Q., EP957
Han Y., EP1120
Han Y., EP962
Hanáčková V., EP552, EP802
Hanamoto H., EP914
Handa H., EP928
Handgretinger R., EP733
Hänel G., EP725
Hänel M., S183, EP436
Haney S., EP945
Hankins J. S., EP736
Hann W., EP1212
Hanna Wakim R., PB1763
Hannachi H., PB1585
Hanoun M., EP436
Hänselmann S., S310
Hansen D. L., S296, EP690
Hansen M. H., EP851
Hansen M., S294
Hansen S., S251
Hansen S. V., EP851
Hansson M., EP963
Hantrakool S., EP1330, PB1437
Hänzelmann S., EP318, EP375
Hao D., PB1648
Harada T., EP942
Harb J., EP1078
Harbi S., PB1664
Harchalakis N., EP919
Harchowal J., EP529
Harder L., EP853
Hardi A., PB1641
Harhalakis N., PB1515, PB1516
Hari P., EP747, EP964, EP972, EP990
Harieche F., EP1255
Harigae H., S210
Harikrishnan H., PB1541
Harlev S., S255
Harlin O., EP973
Harmenberg J., EP973
Harnett M., EP1017, EP1018
Haro-Cañada S., EP1343
Haroche J., EP330, EP1067
Harris E., EP1058
Harris R. S., S178
Harris S., EP754
Harris Z., EP1100
Harrison C., PB1719
Harrison C., S111, EP317
Harrison C., S203, EP1058, EP1074, EP1077, EP1078, EP1080, EP1085, EP1086, EP1089, PB1702, PB1711, PB1723
Harrison S., EP965, EP1046
Harrop S., EP631
Harrup R., EP433
Hart A., EP559, EP1130, EP1133
Hartley J., EP788
Hartmann B., EP971
Hartmann L., S128, EP896
Harwin W. N., PB1441
Hasabou N., EP438, EP441, EP448
Hasan M., EP457
Hasegawa A., S254
Hashim H., PB1664
Hashimoto Y., EP1101, EP1105
Hashino S., EP852
Haslene-Hox H., EP417
Hassab H., PB1367
Hassan E., EP1185
Hassan M. F., EP702
Hassanein M., EP1276, EP1279
Hassani K., PB1680
Hasselbalch H. C., S159, EP1076, EP1107
Hasselgren C. F., S134
Hassoun H., EP973
Hata T., EP667, EP914
Hatcher H., PB1744
Hatfield K., EP1296
Hatjiharissi E., EP1014, EP1016
Hatton C., EP514
Hattori K., S226
Hatziharisi E., PB1681
Hatzileontiadou S., PB1681
Hatzimichael E., EP551, EP631, EP774, EP919, EP955, EP1153, PB1681
Hatzipantelis E., PB1368, PB1376, PB1378
Hatzl S., EP521
Haubner S., S250
Hauns B., EP782
Hausmann D., EP896
Hauswirth A., EP461
Havelange V., PB1404
Haverich A., EP757
Havermans M., S123, EP378
Havet A., S157
Hawkes E., EP783
Hawkins E., S278
Hawkins P., S270, S271, EP692, EP696
Hawkins P., EP1000, PB1644
Hay A. E., PB1662
Hay K., EP365
Hayat A., EP797, PB1413, PB1545
Hayden A., PB1554
Hayden P., S243
Hayes A., EP1178
Hayes-Lattin B., EP508
Hayette S., EP451
Hayman T., EP1057
Hazenberg C., EP1284
Hazenberg M., EP1197
Hdijji S., PB1363, PB1527
He A., EP962
He G., EP1225
He G., PB1480
He K., PB1709
He Q., PB1614
He R., S169
He S., EP518
He X., PB1542
He X., S250
He Y., EP1257, PB1781
He Y., EP1271, EP1303
He Y., S104, S298, EP1142, EP1252
Healy J., PB1753
Heaney M. L., S201
Heath J., S251
Heatley S., EP321
Hebart H., EP648
Hecker J. S., EP761, EP896
Heckl D., S120, EP328, EP398, EP404
Heckman C., EP396, EP424, PB1383
Heeney M.M., EP1222
Heerema N., EP317
Heesom K., EP760
Heffner L. T., EP782
Hegab H., PB1774
Hege K., EP1009
Hegenbart U., EP1011, EP1245
Heiblig M., EP451, EP494, EP1262
Heidel F. H., EP1079, PB1723
Heidenreich O., S105, S122, EP317, EP382, EP876
Heijmans C., EP1208
Heil G., EP467
Heim D., EP1242
Heimeshoff L., S175
Heindorfer A., EP816
Heitmüller C., EP879
Hejazi A., EP1322
Hekimci Ozdemir H., EP355, PB1523
Helali I., EP407
Held G., EP423
Helleberg C., PB1740
Hellemann G., EP1217
Heller G., EP422, EP752
Hellesøy M., EP383, EP396, EP399, EP417, EP463
Hellmann I., S127
Hellmich C., S179
Helmig-Mason J., EP861
Heltai S., EP634
Hemmaway C., S219
Hemmer M. T., EP353
Hemminki K., EP612
Hencklain Fonseca G. H., EP818
Hend B. N., PB1373, PB1374
Henderson C., EP944
Hendrik Veelken J., S232
Hengel S., EP944
Henke O., PB1514
Hennessy B., EP797, EP806, EP1341, PB1412, PB1413, PB1579, PB1580
Henrick P., S138
Henrique M., EP820
Henry G., S162
Henson K. E., PB1600
Hentze M. W., S275
Henzlová L., EP552, EP802
Heo I., S310
Heras I., EP587
Herbaux C., S212, EP511, EP782, EP950
Herishanu Y., S148, S255, S284, EP631, PB1505
Hermann C., EP1340
Hermans C., S256
Hermansen E., EP1035
Hermine O., S201, EP790, EP1095, EP1304, EP1306
Hermiston M. L., EP341
Hermosín L., EP889
Hernández F., EP563
Hernandez F., EP889
Hernández G., S272
Hernandez I., EP698
Hernández M.-T., S185, EP1012, EP1021
Hernandez-Aldama L., PB1753
Hernandez Boluda J. C., EP670, EP1089
Hernández Frausto A., EP1156
Hernandez-Gea V., EP1084
Hernandez-Ilizaliturri F. J., PB1498
Hernández Mata C. F., EP578, EP1139, EP1331, PB1821
Hernández-Mohedo F., EP612, PB1704
Hernandez-Rivas J., PB1793
Hernández Rivas J. M., S143, EP893
Hernández-Rivas J. M., EP329, EP350, EP546, EP893, EP1131
Hernández Sánchez A., EP893, EP1234
Hernández-Sánchez M., S143, EP374
Hernandez Valdes R., PB1438
Herndlhofer S., EP461
Herold T., S109, S121, S127
Herppich A., PB1761
Herquelot E., EP1207
Herráez S., PB1526
Herranz A., EP1168
Herranz M. J., PB1649
Herrera P., EP350, EP546, EP1231, EP1237
Herrera Puente P., EP489, PB1407
Herrera Robles K., S293
Herrero Martin S., PB1425, PB1450, PB1692, PB1787
Herrero Velasco B., S116
Herrmann H., S198
Hershkovitz-Rokah O., EP330
Hertenstein B., S219
Hertzog-Tzarfaty K., EP1023
Herzig J., S128, EP376, EP423
Herzog E., EP1210, EP1215
Herzog Tzarfati K., S288, EP502
Heshusius S., EP1308
Hess B., EP518, PB1570
Hess G., S219, EP786
Hettler F., S247, EP761
Heubel - Moenen F. C., EP567
Heunis T., PB1385
Heuser M., S128, S139, EP376, EP402, EP423, EP463, EP467, EP748, EP757
Hewapathirana R., PB1806
Hexner E. O., S201
Heyes A., PB1665, PB1667, PB1668
Heyes E., EP373
Hiasa M., EP942
Hicham H., PB1466, PB1597
Hicks E., EP590
Hicks L. K., S201
Hidalgo-Calleja C., S237
Hidalgo Gómez G., EP336
Hiddemann W., S121
Hiemenz J. W., EP973
Hiemeyer F., S211

Higashino H., EP818
Higgins E., EP806
Higgins K., S145
Higgins L., EP1292
Hijas M., S293
Hijiya N., EP341
Hilberink J., EP1284
Hildebrandt M., EP547
Hilder B. W., S191, EP967
Hildyard C., EP514
Hilgendorf I., S242
Hilger J., EP525
Hill A., S301, EP1337
Hill B., EP530, EP787
Hill J. E., EP437
Hill K., EP916
Hill Q. A., S290, S312, EP1179
Hillebrand P., PB1679
Hillengass J., S190
Hilli A. K., EP614
Hillmen P., S145, S174, EP592, EP599, EP610, EP636, EP644, PB1471
Hills R., S130, S133
Hilsøe M., EP1107
Hińcza K., S128
Hines P., PB1761
Hinge M., PB1740
Hinterschied C., EP861
Hippenmeyer J., EP1134, EP1157
Hirabayashi K., S254
Hirai T., S253
Hiremath M., PB1415
Hirjan R., PB1379
Hirsch C., EP1045, PB1756
Hivert B., EP652
Hiwase D. K., S138, S151, EP445
Hjertner Ø., EP1022
Hjorth-Hansen H., S152
Hlaz A., PB1782
Hlozkova K., EP320
Ho A., EP364, EP1245
Ho C.-L., EP476
Ho L., PB1553
Ho P. J., PB1660
Ho S.-J., EP783
Ho T. W., EP733, EP736
Ho V., S241
Hoang T., EP745
Hobbs G., EP1075, EP1085
Hobbs W., EP689, EP733, EP736
Hochhaus A., S152, S153, EP660
Höchsmann B., S100, S174, EP595
Hockaday A., EP644
Hoda D., S238, EP541
Hodanova L., EP948
Hodgkinson A., EP432
Hodson A., EP504, EP555, EP559
Hodson D., EP857
Hoebarth G., EP1210, EP1215
Hoekstra O. S., S208, EP517
Hoell J. I., EP328
Hoermann G., S198, EP461, EP897, EP1065, EP1066, EP1070
Hofbauer L., S161, EP896
Hofer K., EP1169
Hoff F. W., S107
Hoffman D., EP917, EP926
Hoffman J. E., EP1163
Hoffman J., EP911
Hoffman R., S200, EP1077, EP1085, EP1106
Hoffmann A., S229
Hofmann S., EP386
Hofmann W.-K., S152
Hofmeister-Mielke N., S100
Hogan W., S169
Hogdal L., EP917
Hohman R., PB1753
Hoischen A., EP616
Hok R., EP390
Hokland P., EP392
Holbro A., PB1708
Holderried T., EP458
Holes L., EP1078
Holik H., EP819, PB1605, PB1684
Holkova B., PB1698
Hollak C., EP694
Holland-Letz T., S246
Holm C. K., EP392
Holmes H., EP503, EP787
Holstein S., EP945
Holte H., EP856
Hong M., PB1593
Hong V., EP841
Hongeng S., S257, S266, EP1301
Hooda N., EP1193
Hoogenboezem R., S170, EP378
Hoogendijk A., S294
Hoogendoorn M., S149, EP666, EP678, EP811, EP1027
Hoogkamer A. Q., EP319, EP324
Hopkins C. R., S184
Horder J., EP1189
Horesh N., EP487
Hormann F. M., EP319
Horowitz N. A., EP475, EP502, EP503, EP1023
Horst H. A., EP423
Hortal Benito-Sendín A., EP1131
Horton S. J., S129
Horvat N. P., PB1394
Horváth-Puhó E., EP1193
Horwitz N., S255
Horwitz S., S218, EP506, PB1453
Hose D., EP968
Hosing C., PB1415
Hosokawa K., S171, EP580
Hosono N., EP438, EP441, EP448
Hosoya H., EP1224
Hoster E., EP547, PB1748
Hou H.-A., EP483, EP922
Hou J., EP1024, EP1030
Hou J.-Z., EP439
Hou R., EP505
Hou Y., EP656
Hounsome L., EP504
Houot R., S117, S212, S216, EP511, PB1735
Hourigan A., EP1341
Hourigan C. S., S128
Houtenbos I., S149
Hovland R., EP396
Howard D., EP644
Howard J., S263, PB1764
Howe S., S176
Howell H., EP1224
Howell S., EP452, EP643, PB1391
Hoyos M., EP423
Hoyos Brea A. M., PB1584
Hrdinka M., EP724
Hristopoulos M., S222
Hristoskova R., PB1530
Hsiao F.-Y., EP349, EP368
Hsieh W.-T., EP483
Hsu C.-L., EP922
Htut M. M., EP740
Htut M., EP747
Hu B., EP783
Hu E., EP1173
Hu J., S206, EP323, EP337, EP338, EP340, EP397, EP639, EP789, EP1120, PB1786, PB1795
Hu J.-D., S204
Hu K., S217, EP505, EP533, EP1007, PB1435
Hu P. C., EP374
Hu R., PB1416
Hu S., EP598
Hu S., S228, EP562, EP862, EP864, EP865, EP866, EP868, EP874
Hu X., S287
Hu X., EP605, EP627, PB1499, PB1544
Hu Y., S194, PB1542
Hu Y., S204
Hua Y., EP951
Huang D., EP857
Huang D., EP553
Huang F., EP910, EP1106
Huang F., EP356
Huang H., S206, EP639
Huang H., S194, EP512, EP537, EP549, EP1275, EP1277, PB1361, PB1542
Huang H., EP520, EP1024
Huang H.-H., EP1030, PB1531
Huang H., PB1648
Huang H.-H., EP349, EP368
Huang H., EP512, EP537, EP549
Huang J., S207, EP525, EP639, EP642, EP783, EP789
Huang J. S.-Y., S186
Huang J., EP1120
Huang J.-W., S204
Huang J., PB1492
Huang J., EP1083
Huang L., EP1009
Huang Q., EP635
Huang Q.-S., EP1295
Huang R., EP601, EP801, PB1576
Huang T.-C., EP476
Huang W. H., PB1660
Huang W.-R., PB1647
Huang W., S214, PB1569
Huang X., EP356, EP560, EP669, EP847, EP1246
Huang X.-J., S230, S231, S234, EP347, EP395, EP460, EP484, EP656, EP1226, EP1240, EP1252, EP1265, PB1591
Huang X., S113
Huang Y., EP337, EP340
Huang Y., EP453
Huart A., EP1036
Hubberstey H., PB1486
Hübel K., EP807, PB1572
Huber M., EP387
Hudgens S., EP1178
Huelsenbeck J., EP648
Huen A. O., PB1439
Huerga Encabo H., EP813
Huerta-Aragonés J., EP1131
Hueso T., S215
Huet S., EP451
Huettmann A., EP767
Hughes C., EP915, EP920
Hughes M., S151
Hughes M., EP515
Hughes O., EP1175
Hughes T. P., S151, EP321, EP332
Huguet F., EP671, EP679
Huhn S., EP968
Hui L., EP344
Hui W., EP1120
Huijbregts J. E., EP517
Hulin C., S180
Huls G., EP434, EP1284
Hultberg A., EP566
Hultcrantz M., EP1088
Humpe A., EP547
Humphrey J., EP1080
Humphrey K., EP501
Hunault-Berger M., S243, EP385, EP652
Hungria V., S189, EP975, EP985, EP1039, EP1046, EP1054
Huntly B. J., S129, S133, EP470
Huntrakool S., PB1751
Huo J., PB1492
Huo X., EP961
Huot L., PB1546
Hüper S., S175
Huppunen M.-E., EP424
Hurtado A. M., EP889
HurtadoDoce A., EP1135
Hus I., EP1280
Hus M., S202, EP1280
Husainova G., EP1190
Husby S., EP863
Huscher D., EP1340
Husnain M., EP1015
Hussein S., EP1118
Hutchings M., S205, EP499, EP501, EP766
Hutti J. E., EP1078
Hüttmann A., EP506
Huuhtanen J., EP580, EP611
Huvarova L., EP1297
Huw L.-Y., S222
Huynh V., EP341
Huys I., EP1192
Huzjan Korunic R., EP886
Hveding Blimark C., EP1035, PB1634, PB1653
Hwang I., EP861
Hwang S. M., EP1160
Hwang S.-H., EP918
Hwang W., EP905
Hyrenius-Wittsten A., EP406
Iacoboni G., EP501, EP631
Iacono G., S294
Iacucci Ostili R., EP1288
Ianakieva V., PB1652
Iannalfo M., EP478, PB1790
Ianotto J.-C., EP1091
Iastrebner M., EP927
Iatcenko I., EP695
Iatsemyrskyi S., PB1366
Ibáñez F., EP563
Ibáñez M., EP413
Ibrahim F., PB1377
Ibrahim I., PB1547
Ichikawa M., EP914
Ichinohe T., S244, EP507, EP1229
Idink C., S149
Idoine A., EP642
Idowu M., EP1206
Ielmini N., S219
Iglesias-Rodriguez M., EP1179, EP1180
Ignatieva S., EP822
Iida S., EP522
Ikegame K., EP1229
Ikezoe T., EP694
Iland H. J., EP433
Ilari C., EP624
Ilariucci F., S219
İleri T., EP1316, PB1755
Ilett E. E., EP613
İlhan G., EP1216, EP1218
Iliakis T., EP773, EP774, PB1560
Iliasova A., EP876
Ilic I., EP561
Iliescu L., EP828
Illerhaus G., S219

Illés A., S137, S145, S205, EP506, EP975, EP1076, EP1081, PB1641
Illidge T., EP506
Illman J., EP925
Ilonczai P., S303
Im E., PB1698
Imada K., S244
Imaizumi Y., S218
Imam Y., PB1710
Imamura T., EP937
Imbaby S., PB1811
Imbusch C. D., EP463
Imoto N., PB1587
Imren S., EP736
Inamdar N., EP958
Inati A., S260, EP1220
Ince I., EP1316
Ince B., EP1216, EP1218
Ince D., PB1834
Ince I., EP1216, EP1218
Infante M. S., S303
Ingleson E., S181
Ingoglia G., EP1204
Iñigo B., EP1021, EP1346
Iñigo M.-B., EP1012
Iñiguez R., EP708
Inniss M., S177
Innocenti I., EP604, PB1506
Inns J., PB1385
Inogés S., EP809
Inoue Y., EP942
Inserra E., EP1310
Intermesoli T., S154
Intzes S., PB1436
Inusa B., S260, S314, EP1214, PB1762
Inzoli E., EP658
Ioakeimidou N., EP1311
Ioannidou L., PB1829
Ioannidou M., PB1368, PB1376, PB1378
Iolascon A., S276, EP688, EP695
Ion S., EP828
Ionescu B., PB1379
Ionova T., EP1187, EP1190
Iordan A., PB1652
Iori A. P., S240
Iovino G., EP474
Iqbal F., S299
Iqbal M., EP835
Iqbal Z., PB1827
Iqbal Z., EP911
Iraca T., PB1743
Iraheta S., PB1493
Iraqi W., EP1052
Ireland R., EP504
Irimia R., EP1192
Irish J., EP396
Iriyama N., EP667, EP668
Irmela J., S109
Irrera G., S240
Irving J., EP327
Isaeva N., EP607, PB1549
Ishida F., EP580, EP611
Ishikawa M., PB1455
Ishikawa T., EP807
Ishio T., EP852
Ishitsuka K., S218
Ishiyama K., S171
Ishizawa K., EP439, EP1006
Ishmatova I., EP1264
Isidori A., EP1079
Isiksoy S., PB1403
Isinova G., EP357, EP360, EP361
Iskas M., EP609, PB1368, PB1697, PB1721
Iskas M., EP631
Iskas M., EP1254
Iskrov I., PB1590
Israel M. R., S309
Issa D., S149
Issa G., S113, S132, EP401, EP464, EP468, EP471, EP676, PB1408
Issa H., S120, EP398
Issa J.-P., EP913
Issaoui L., PB1731
Istvanffy R., S247
Itchaki G., S255, S288, PB1505
Ito R., PB1587
Ito R., EP915, EP920, PB1619
Ito S., EP1006
Ito T., EP1101, EP1105
Itzykson R., S126, EP385, EP906
Iurlo A., S154, EP673, EP1079, EP1089, EP1099
Ivan M., EP781
Ivana V. L., PB1684
Ivanac G., S304
Ivanaj A., PB1502, PB1628
Ivanov D., S198
Ivanov H., PB1522
Ivanov V., EP439, EP1190, PB1402
Ivanova I., PB1421
Ivanushkin V., EP1134
Iversen L., PB1428
Ivic M., S304, EP886, PB1684
Iwama A., S300
Iyengar S., EP765
Iyer S. P., EP506, EP881
Izakova S., EP948
Izhaki N., EP475
Izmailova E., PB1612
Izquierdo Álvarez S., EP578
Izquierdo García I., EP1139, PB1821
Izutsu K., S218, EP807, PB1434
Jaatinen T., EP580
Jabbour E., S113, S132, S136, EP367, EP401, EP430, EP464, EP468, EP676, EP677
Jaber D., PB1373, PB1556
Jabr D., PB1423, PB1585
Jabri A., PB1814
Jaccard A., S189, EP1011
Jachiet V., S156
Jackson A., EP432, EP1058
Jackson C., EP964, EP972, EP978, EP990, EP1003, EP1049
Jackson E. R., EP1199
Jackson G., S181, EP1259
Jackson N., PB1698
Jackson S., S147, EP963
Jacob A. S., EP767
Jacob R., PB1463
Jacobasch L., EP975
Jacobs R., S147
Jacobsen E. D., S218
Jacobsohn D., S235
Jacobson C. A., S213, EP495, EP787, EP791
Jacoby E., S116, S233, EP526, EP716
Jacoby M., EP917, EP926
Jädersten M., EP912
Jaeger U., EP461, EP516, EP530
Jagadeesh D., S214, EP515, PB1453
Jagannath S., S187, EP936, EP964, EP972, EP974, EP977, EP978, EP984, EP990, EP1049, EP1163
Jagasia M., S239
Jäger U., EP685, EP706
Jaglowski S., EP787
Jagurinoski M., PB1503
Jahn N., EP376
Jaidi R., PB1420, PB1423, PB1443
Jain H., EP958
Jain M., EP1058
Jain M., EP536
Jain N., S113, EP367
Jain R., EP341
Jain S., EP566, EP1148
Jain S., S314, PB1762
Jakić Bubalo M., PB1684
Jakob T., PB1756
Jaksic O., EP631, PB1494
Jaksik R., EP322
Jakubowiak A., S192, EP964, EP982, EP1003, EP1010, EP1026
Jalel B., EP817, EP831, PB1586
Jamal E., PB1540
James A., EP437
James J., S314, PB1762
James Hampton R., PB1486
Jamieson C., EP1078
Jang J. H., S137, S173, EP910, EP1106
Jang J., S172
Jang J.-H., EP909
Jang S., EP918
Janin A., EP695
Janjan N., PB1520
Janning M., EP463
Janoudi T., S251
Jans J., S274, EP582
Jansen A., S299
Jansen P. M., S220
Janssen J. J. W., S152, S155, S168, EP666, EP678
Janssen L., S163
Janssen S. R., EP631
Janssens A., S148, EP654
Janssens R., EP1192
Jansson D., PB1634
Jansson Blixt C., PB1655
Janusz K., EP893, EP907
Jaquet T., EP387, EP657
Jarchowsky O., S288, EP1023
Jarchum G., EP997
Jarchum S., EP997
Jarden M., S134, PB1740
Jarkovský J., EP954
Jarmuż-Szymczak M., EP960
Jarvis M. C., S178
Jasielec J., EP1010
Jasminka S. P., PB1684
Jaspers A., EP844
Jastaniah W., S314, EP369, EP1220, PB1762
Játiva C., EP563
Jauch A., S183, EP968
Jauk F., PB1380
Jauković A., EP759
Javaid M. K., PB1671
Javelot M., EP995, EP999
Jawhar M., EP1065
Jawniak D., EP1280
Jayarajan J., S195
Jayavelu A. K., S127
Jelinek T., EP724, EP816, EP1042, EP1297, PB1677
Jeney V., EP572
Jeng B., EP1001, EP1026
Jenkins R. E., EP610
Jennane S., PB1375, PB1551, PB1598, PB1680
Jenner M., S181, EP1259
Jenni S., S107
Jennings P., EP559
Jensen B. A., PB1740
Jensen C. F., S134
Jentzsch M., S201, EP435
Jeon M., PB1417
Jeong J.-O., PB1513
Jeremias I., S127
Jerez A., EP612, EP889
Jerkeman M., EP786, EP856, EP863
Jerling M., EP1028
Jerome Clay E. L., EP1206
Jevremovic D., S169, EP908
Jeyakumar V., EP1135
Ji J., EP593
Ji J., EP789
Ji M., EP639
Jia B., EP1024
Jia L., S118
Jian L., EP923
Jiang Q., S204
Jiang A., PB1554
Jiang D., EP1144
Jiang E., EP1257, EP1268, PB1781, PB1802
Jiang H., EP347, EP460, EP484, EP656
Jiang H., EP962
Jiang K., EP1010
Jiang L., PB1805
Jiang P., EP337, EP338
Jiang Q., EP347, EP460, EP484, EP669, EP1120
Jiang R., EP988
Jiang X., EP1180
Jiang X., S290, S291, S312, EP1179
Jiang X., EP689
Jiang Y., S144, S146, EP599, EP632
Jiang Y., EP562
Jiang Z., EP490
Jiang Z.-X., S204
Jiang Z., EP356
Jiao Y., PB1670
Jibril A., S179
Jie K.-S., S180
Jilma B., S290, S291, S302, EP689, EP1179
Jiménez A., EP546, PB1793
Jimenez M. J., EP889
Jimenez M., PB1649
Jiménez R., PB1642
Jiménez T., S293
Jiménez Chillon C., EP489, EP1338
Jiménez Morales A., PB1704
Jiménez Solas T., EP907
Jimenez Ubieto A., EP786, PB1575, PB1791
Jimenez-Velasco A., EP670, EP677
Jimenez-Vicente C., EP472, EP481
Jiménez Yuste V., EP1072, PB1518
Jimenez-Zepeda V., EP989, EP1038, PB1643
Jin C.-H., S204
Jin J., S108
Jin J., S204, S206, S211, EP783, EP789, EP792, EP1024, PB1648
Jin Y., EP452, EP643, PB1391
Jindra P., EP473, EP1228
Jing H., EP1050, PB1648, PB1670, PB1685
Jing H.-M., PB1647
Jo D.-Y., PB1513
Joan Alfons S., PB1649
João C., EP1011
Jobes J., EP1017, EP1018
Jofra-Hernandez R., EP1298
Johannesen T. B., EP1022
Johansen M., EP443
Johansson A. L., EP1088
John G., PB1383

John L., EP1045
John M., S175
John M. V., EP902, EP1068
Johnson B., EP745
Johnson B., EP535
Johnson L., EP495
Johnson P. W. M., S219, EP499
Johnson R., EP498
Johnson S., S133
Johnston A., S282
Johnston L., EP1224
Jolly A., S245
Joly B., S215
Joly F., S290, S312, EP1179
Jonas B. A., S137, S138, EP444
Jonasova A., EP948
Jonassen I., EP399
Jones A., EP1074, EP1086
Jones C., EP498
Jones G. K., EP703
Jones J., EP1259
Jones R., EP592
Jones R., S258
Jones S. A., EP694
Jones S. G., EP765
Jongejan A., S141
Jongmans M., EP538
Jonkers J., S163
Joosten L. A., EP1067
Jordan I., EP734
Jorge J., EP421, EP630, PB1350, PB1630
Jørgensen J., EP856
Jørgensen M., EP613
Joris M., S216
Joshi N., EP916
Jost E., EP387, EP436, EP467
Josten K. M., EP1157
Joudinaud R., S126, EP385
Jouvin M.-H., EP713
Jozami C., EP665
Juan M., EP734, PB1642
Juárez L. M., EP1168
Jude F., PB1383
Jude J., EP381
Judge M. P., S270
Juergens D., EP1010
Juliusson G., EP909
Jun K., EP454
Jung S.-H., EP1029
Junge G., S173
Jungova A., EP816, EP1042
Juni M., EP663, EP665
Junqueira Atanazio M., EP1251
Jurado M., EP587, EP612
Jurado Chacon M., EP823, EP1250, PB1704, PB1826
Jurcic J. G., S138, EP437, EP917, EP926
Jurczak W., S145, S148, S211, EP500, EP503, EP524, EP633, EP638, PB1444, PB1569
Jurek S., EP829
Jurinovic V., S127
Jurisprudencia C., EP430
Justo P., EP952
Juszczynski P., S164
Juul Vangsted A., EP1035
Jylhä C., S143
Kaare A., S242
Kaare K., PB1757
Kabanova A., EP622
Kabir S., PB1712
Kacar A. G., PB1832
Kacem K., PB1373, PB1423, PB1556, PB1585
Kada A., EP1101, EP1105
Kadia T., S132, S136, EP430, EP440, EP464, EP466, EP468, EP471, EP676, EP1104
Kadıköylü G., PB1778
Kadiyala V., PB1355, PB1356
Kagawa K., EP942
Kahl B. S., EP518, PB1434, PB1571
Kaies H., EP1278
Kaila S., EP1051
Kairisto V., S152
Kaiser M., S181, EP987, EP1259
Kaisermann M., PB1698
Kaiyan L., EP454
Kajaste-Rudnitski A., EP1067
Kako S., S244
Kalafati E., EP939
Kalakonda N., EP504, EP530, EP539
Kalantaridou S., EP777
Kalayu Yirga S., EP323
Kale H., EP916
Kalfa T., EP1202
Kaliafentaki V., EP1153
Kalicińska E., EP631
Kalleda N., EP1204
Kallel F., PB1363, PB1592
Kallel F., PB1527
Kallianos A., EP993
Kalmar P., EP521
Kalmer M., S196, S197
Kalomoiraki M., EP763
Kaloyannidis P., EP814, PB1664
Kalpadaki C., EP551
Kalpatthi R., S260
Kaltenbach S., EP790
Kamachi K., EP875
Kamaeva I., EP762
Kamalakar R., EP1046
Kamar D., S157
Kamate J., EP1205
Kambhampati S., S311
Kamdar M., S148, S222
Kameda K., S244
Kaminskaitė U., EP700
Kammoun F., PB1562, PB1564
Kamoun H., PB1510
Kampfenkel T., S180, EP1031
Kampmann P., S134, S256
Kanagal-Shamanna R., EP464, EP468, EP1104
Kanaka-Gantenbein C., PB1829
Kanakura Y., EP914
Kanda J., S244, EP1229
Kanda Y., EP441
Kanellias N., EP774, EP959, EP993, EP1016, EP1041
Kanellou P., EP588, EP1153
Kang H., PB1417
Kang Y.-A., PB1417
Kang Y., EP990
Kanno H., EP691
Kanoun R. Y., PB1585
Kanoun S., EP511
Kansagra A., EP984, EP990, EP1009, EP1010, EP1173
Kantarjian H., S113, S132, S136, S167, EP367, EP427, EP430, EP440, EP464, EP465, EP466, EP468, EP471, EP676, EP1096
Kanter J., S261, S263, EP1217
Kanters S., PB1571
Kao C.-J., EP922
Kapinos K., EP1173
Kaplan Z., S299
Kaplanov K., S286, EP360, EP1190
Kapnang R., EP1005
Kapp-Schwoerer S., EP376
Kappelmayer J., EP572
Kapranov N., EP361, EP1241, EP1260
Kapsali E., EP955
Kapsimali Z., PB1829
Kapustin S., EP1332, EP1333, PB1618, PB1635
Kapustova V., EP1297
Kapuvari B., EP768
Kapuza E., EP762
Kara M., EP587
Karachunskiy A., EP358
Karadaş N., EP355, EP1316, EP1317, PB1523, PB1809
Karakaş Z., EP1216, EP1218, EP1316, PB1755
Karakasis D., PB1515
Karakatsanis S., EP551, EP774, EP919
Karakatsoulis G., EP631
Karakaya N., EP704
Karakuleli G., PB1750
Karakus V., EP631
Karaliota S., S287
Karaman K., EP1316
Karanth M., EP555
Karapınar D., PB1372
Karapınar T. H., EP704, PB1372, PB1820
Kardum Paro M. M., EP932
Kargl D., EP585, EP589
Karianakis G., EP551
Karima K., PB1374
Karjalainen R., EP396
Karlath F. A. P., PB1541
Karlin L., S180, S193
Karlsen L., EP614
Karlsson K., S148
Karmali R., EP530
Karmiris T., EP551, PB1515, PB1516
Karnabeda O., EP776
Karni C., S285
Karp K., PB1757
Karpova O., EP776
Karrison T., EP1010
Karunanayake P., PB1596
Karunanithi K., PB1656
Karve S., EP1046
Karypidou M., EP609
Kasanen T., EP580
Kashlikov M., PB1663
Kaskel P., EP764
Kasow K. A., S261
Kassam S., EP530
Kassar O., PB1363, PB1452, PB1527, PB1562, PB1564, PB1690
Kastritis E., S189, S280, EP782, EP959, EP993, EP1011, EP1014, EP1016, EP1036, EP1041
Kataeva E., EP1048, PB1500
Kataoka K., EP507
Kater A. P., S141, S145, S149, EP599, EP608, EP631, EP637, EP640, EP873
Kater J., EP325
Kato G., EP1200, EP1210, EP1215
Kato K., S218
Kato K., S210
Kato S., PB1703
Katodritou E., EP551, EP1014, EP1016, EP1031, EP1044
Katsaouni P., EP551
Kattamis A., S101, EP733, EP1304, EP1306, EP1311, EP1312, PB1805
Kattamis C., EP1311
Katz D., EP975
Katz P., EP596, PB1486
Katzilakis N., EP1146, PB1351, PB1468
Kauffman M., S188, EP530, EP924, EP1002, EP1008
Kaufman J., EP747
Kaufmann M., EP436
Kaur G., EP1173
Kaur Singh S., EP403
Kavalerchik E., EP1235
Kavazovic I., S141
Kavelaars F. G., EP378
Kaverina O., EP1190
Kawabata H., EP914
Kawai N., PB1455
Kawakami T., EP580, EP611
Kawakita T., EP1229
Kawamata T., S218
Kawamura T., PB1703
Kawano Y., EP1006
Kawichai S., EP1330
Kay N., S145
Kay S., S285
Kaya B., EP1212
Kaya Z., EP1244
Kayadibi H., PB1775
Kayal N., EP1051
Kaygusuz Atagunduz I., PB1683, PB1705
Kayser S., EP364
Kazanci E., EP1316
Kazanowska B., S221
Kazantzi A., EP1047
Kazey V., EP681
Kazi J. U., EP406
Kazianka L., EP897
Kazmi M., PB1654, PB1694
Kazmi S. R. S., S256
Ke X., S217, EP783, EP1007, PB1435
Keane N., PB1545
Keating M.-M., EP931
Keats J., EP859
Kebbaj D., PB1680
Kebriaei P., EP353
Kedmi M., EP502
Keegan A., S282
Keeping S., EP366, EP786
Kefi S., PB1373, PB1556, PB1585, PB1731, PB1749
Keil F., S198
Keith J., S265
Kelkka T., EP580, EP611
Keller A., S198
Keller P., EP1077, EP1080
Keller U., S219
Kellermann L., EP972
Kellermayer Z., EP943
Kelly C., PB1545
Kelly P., EP1202
Kelly R., EP592, EP1236
Kenion M., EP1276
Kenkre V., S214
Kennedy B., EP649
Kennedy D. G., EP1289
Kennedy J., EP1082, EP1083, EP1093
Kent A., EP429
Kent M., EP545
Kentsis A., EP378
Kenyon M., EP1279
Keohane C., EP797

Keramaris K., EP777
Keramidioti K., EP1044
Keränen M., EP580
Kerbauy M., EP550
Kern W., S310, EP892
Kerr C., EP580
Kerre T., EP748
Kersten M. J., S208, S210, S220, S294, EP495, EP510, EP766, EP787, EP796, EP803, EP804, EP873, PB1575
Kersting S., S149
Keska K., S164
Kessler P., EP816
Kettyle L., PB1381
Ketzer J., EP853
Kevie van der - Kersemaekers A.-M., S149
Key N. S., S256, EP730
Khachatryan A., EP1236
Khafaja S., PB1763
Khainfir A., PB1564
Khalaf D., EP931
Khalaila A. S., EP475
Khaled S., EP351
Khalifa L., PB1363, PB1527
Khan I., EP835
Khan J., PB1698
Khan M., EP881
Khan N., EP432
Khan U. T., EP610
Khan W., EP677, EP915, EP920
Khanka T., EP958
Khanna S., S200
Kharabi Masouleh B., EP366, EP387, PB1735
Kharasova Z., PB1500
Kharrat R., PB1420, PB1423, PB1556, PB1585, PB1749
Khatib A., EP475
Khattry N., EP958
Khatun A., EP1047
Khayati Y., PB1556
Khazieva A., PB1700
Khelif A., EP1304, EP1306
Khelifa L., PB1562, PB1564, PB1690
Khetib Tiaiba R., EP1159
Khimani F., EP536
Kho B., EP631
Khoduleva S., EP1321
Khoo L., EP433
Khwaja A., S130, S138
Kibbelaar R., EP811
Kicinski M., EP343
Kiem H.-P., EP731
Kikozashvili N., S284, S285
Kiladjian J.-J., S174, S202, S203, EP1076, EP1080, EP1081, EP1089, EP1106, PB1477, PB1702, PB1711, PB1713, PB1723
Kim D., S261, EP1261
Kim H.-J., EP438, EP457
Kim H. J., EP1029
Kim H., EP568
Kim I., EP439, EP1046
Kim J. J., EP495
Kim J. S., EP1006, EP1029, PB1660
Kim K. Y., PB1424, PB1825
Kim K., S189, EP1006, EP1024, PB1660
Kim K.-H., EP1029
Kim M. K., EP1029
Kim N., PB1424
Kim N. H., PB1825
Kim R., S106, S162
Kim S., EP740
Kim S., EP529
Kim S., S146, EP632
Kim S. Y., S144
Kim S.-H., EP1006, EP1029
Kim W. S., S205, EP506
Kimura F., EP1101, EP1105, PB1703
Kimura S., EP875
Kimura T., S244, EP1229
Kin A., EP740, EP1010
Kindler T., S129, EP376
Kindrakevych O., EP776, PB1691
King A., EP470
King J., EP1164
Kingsley E., EP642, PB1570
Kipps T. J., S140, S147, EP599, EP636
Kirgner I., EP1081
Kirill L., EP781
Kirito K., EP1101, EP1105
Kirk A., EP508
Kirkiz S., EP1244
Kirkizlar O., EP577
Kirkup C., EP1051
Kirkwood A., EP498, EP514
Kirschner K., EP754
Kirtsoni M.-C., EP773, PB1560
Kiselev P., EP1182
Kiseleva A., EP1334
Kiseleva M., EP1190
Kishimoto J., EP914
Kishore B., EP994
Kistler K., EP1318
Kit O., EP762
Kitamura T., S300
Kitara S., S108
Kitko C. L., EP341
Kiyoi H., EP667, EP668
Kizhakeyil A., EP857
Kjaer L., S159
Kjærsgaard A., EP1107
Kjeldsen L., S134
Kjems J., EP863, EP888
Klade C., EP1076
Klamova H., EP661
Klampfl T., EP752
Klamroth R., S256
Klapper W., S225
Klarskov Andersen M., PB1615
Klausen T. W., EP1035
Kleftogiannis D., EP399
Klei T., S294
Klein E., EP456
Klein G., EP665
Klein L., S245
Klein S., S180, EP1027
Klement P., S128, S139
Klencke B., EP1081
Klimko N., EP822
Klimontov V., EP778
Klingbiel D., EP807
Klink A., EP737
Klinten Grand M., S134
Klinushkina E., PB1500
Klitochenko T., EP1190
Klodzinskiy A., EP838
Klonizakis F., EP1153, PB1804
Kloos I., EP787
Klöpfer P., EP496
Klostergaard A., PB1740
Klusmann J.-H., S120, EP328, EP398, EP404
Klussman K., EP944
Kmetyuk Y., EP776
Knapp A., PB1565
Knapper S., S130, S168
Knapper S., EP1058
Knauf W., EP529
Knechtova Z., PB1677
Knepper T., EP536
Knight R. D., EP740
Knoch J., S195
Knoebl P., EP461
Knoechel B., S108
Knop S., S187, EP971
Knowles S., PB1453
Knupp J., EP924
Knut-Bojanowska D., EP1035
Ko B.-S., S173, S235, EP349, EP368, EP483
Ko Y.-D., S183
Kobayashi A., PB1703
Kobayashi H., S244
Kobayashi S., EP1229, PB1703
Kobbe G., S243
Koblihova J., EP661
Koçak Ü., EP1244
Kocaturk E., PB1775
Kockerols C. C., EP666, EP678
Koeck S., PB1777
Koekkoek S., PB1521, PB1661
Koene H., S149
Koenig L., EP1245
Koenigsmann M., EP979
Koeppel L., EP764
Koh K., PB1780
Koh Y., EP980, EP981, EP1006
Kohalmy K., EP768
Kohla S., PB1377
Kohlhofer U., S124
Köhn M., EP409
Kohri M., PB1455
Koide S., S300
Koike M., EP1101, EP1105
Koinig K., PB1777
Kok C. H., S151
Kokke A., EP1308
Koković I., PB1610
Kolacevic Zeljkovic M., PB1494
Kolambage C., PB1806
Koldej R., EP1243
Koleci N., S199
Kolesnichenko S., EP838
Kolesnikova M., PB1389
Koletsos N., EP1232
Kolgaeva E., EP1260
Koller E., S198
Koller P., EP351, PB1391
Kollmann K., EP422
Kollmann S., EP752
Kolodny S., EP1148, EP1151
Kolovou A., EP1153, PB1516
Kolstad A., S210, EP863
Kolupaev O., EP1181, PB1645
Komatsu N., EP1101, EP1105
Komkov A., EP333
Komninaka V., EP773, EP1272, PB1560
Komrokji R., EP899, EP915, EP920, EP1078, EP1106, EP1182, PB1394, PB1619
Kondakova E., EP544, EP770, EP771, PB1456
Kondo E., S244, EP507
Kondopidou F., EP774
Kondratchik K., EP358
Könecke C., S139
Konenko A., PB1579
Kong I., S278
Kong J., EP656, PB1591
Kong Y., S230
König T., EP342
Konis G., EP1202
Konishi T., EP937
Konopleva M., S113, S132, S136, S167, EP367, EP401, EP427, EP429, EP430, EP440, EP464, EP466, EP468, EP471, EP676, EP909, EP1068
Konova Z., EP1260
Konstantinidou P., EP1044
Konstantinou E., EP551, EP808, EP1272, PB1560, PB1577
Konstantinou I., EP773, EP774, EP777
Konstantinou E., EP631
Konstantinova T., EP360
Konstantopoulos K., EP773, EP777, EP939, PB1560
Konstantopoulos K., EP551, EP774, EP808, EP1272, PB1577
Kontopidou F., EP919
Kontos C. K., EP959
Kontro M., S168
Konuma T., EP1229
Koo R. M., EP1243, PB1433
Koontz M. Z., EP643
Koonyosying P., EP1330
Koopmansch B., PB1483
Kooshesh M., EP717
Kopeckova K., EP496
Koprivnikar J., EP457, EP462, PB1475
Kopsaftopoulou A., EP777, EP1272
Koren-Michowitz M., S288, EP631, PB1505
Koreth J., S238
Korin L., EP880
Kořístek Z., EP473, EP724, EP1297
Kornblau S., EP374
Kornblau S., S107, EP401
Kornblihtt L., EP927
Kornblit B., EP359
Kornreich L., EP343
Koroleva D., PB1785
Koroleva O., EP1260, PB1785
Korompoki E., S287
Korotaeva L., EP1321
Kortüm K. M., S175, EP992
Koschmieder S., S159, S196, S197, EP387, EP657, EP1063, EP1089
Koschmieder S., EP1074
Kosinski M., EP1179
Kosinski P., EP695
Kosmalska M., EP322
Kostal M., S299
Kostalova L., S142
Koster A., EP1027
Kostiukevych O., PB1691
Kostiukova N., PB1691
Kostroma I., PB1618, PB1635, PB1779, PB1783, PB1784, PB1800
Kostrzewska-Poczekaj M., EP960
Kosuri S., EP1010
Kota V., EP462, EP934
Kotanidou A., S287
Kotaskova J., S143
Kotašková J., EP631
Kotb R., S188, EP989, EP1002, EP1008, EP1038, PB1643
Kotchetkov R., PB1573
Kothari J., EP514, PB1671
Kotova E., EP357, EP361
Kotowski A., S256
Kotsi P., EP773
Kotsianidis I., EP631, EP919, EP1153, PB1436, PB1681
Kotsopoulou M., EP774

Koubaa A., PB1363
Koukou D., PB1829
Koumarianou A., EP774
Koumasi K., EP1311
Koumpis E., EP955
Kourakli A., EP919, EP1153
Kourti G., EP551
Kouvatsi A., EP1299
Kovacevic K., S302
Kovačević S., EP819
Kovacs J., EP768
Kovacsovics A., S120
Kovacsovics T., PB1625
Kovalchuk S., EP793, EP1184
Koviazin A., EP1264
Kovrigina A., EP564, EP799
Kowalik A., S128
Kowalski M., S202
Koyunlar C., S170
Kozhevnikova Y., EP558, PB1352, PB1414
Kozich Z., PB1650
Kozlov A., EP770
Kozlov V., EP776
Kralik M., EP561
Kralovics R., S198, EP1076
Kramer M., EP436
Krampera M., S219, EP1267
Kraus S., EP436
Krause S., S219, EP436
Krauter J., S138, EP467
Krauth M.-T., EP971
Kravchenko S., EP558, EP564, EP756, EP799, EP884, PB1574
Krawczyk J., PB1413, PB1545
Krayem B., EP487
Krečak I., EP819, PB1605, PB1684
Kredátusová A., EP802
Kreissl S., S209, S225, EP767, EP779
Kreitman R. J., EP631
Krejcy K., EP1076
Kremer B. E., PB1698
Kremers S., EP467
Kremyanskaya M., S200, EP1075, EP1077, EP1085
Kreuzberger N., EP1187
Kreuzer K., S146, EP632
Kreuzer K.-A., S144
Krevvata M., S180
Krhovska P., EP994, EP1042, PB1637
Kriachok I., EP557, EP776, EP974, EP976, PB1575
Kricheldorf K., S197
Kriegsmann K., EP1239
Kriemler-Krahn U., S172
Krimpenfort R., S163
Krippner-Heidenreich A., EP382
Krishnamurthy P., S283, EP738, EP1276, EP1279
Krishnamurti L., S261
Krishnan A. Y., S191, S193, EP977, EP978, EP1049
Krishnan S., PB1485
Krishnevskaya E., EP698
Kristan A., EP1109
Kristensen L. S., EP863
Kristo F., EP934
Krochmalczyk D., EP1076
Kroeze E., EP335, EP538
Kröger N., S232, S242, S243, EP431, EP1239
Kropf P., EP913
Krsnik I., EP1012
Krueger A., S166
Krueger J., EP341
Kruip M. J., EP567
Kruse A., EP1154
Kruse C., EP1150, EP1154
Kruse-Jarres R., S256
Kruss M., EP665
Kryachok I., PB1691
Kryuchkova I., EP986
Krzywinski A., EP625
Kseniia S., EP884
Ksienzyk B., EP896
Ku N. C., EP500, EP524, EP633
Kuang X., EP1120
Kuball J., EP727
Kubarova V., EP935
Kubasch A. S., S161, EP896
Kubesova B., EP1063
Kubicek S., EP1066
Kubicki T., EP960
Kuchenbauer F., S178, EP365
Kudari M., S258
Kueenburg E., S187
Kühn M. W., S129
Kuhnl A., EP498
Kuhnowski F., S180
Kuiavovych B., EP935
Kuijk C., EP1308
Kuiper R. P., S107, EP538
Kukreti V., PB1662
Kulaeva E., PB1548
Kulagin A.
Kulagin A., EP544, EP556, EP590, EP594, EP770, EP771, EP822, PB1456
Kulasekararaj A. G., EP589, EP590, EP594, EP738, EP1276, EP1279, PB1476, PB1480
Kulenkampff E., PB1517
Kulikov S., S286, EP360
Kulikowska de Nałęcz A., EP1091
Kulis M., EP858
Kulkarni A., S177
Kullmer J., EP436
Kulozik A., S100, S257, S266, EP1301
Kumar A., EP785, EP798
Kumar A., EP331
Kumar K., PB1687
Kumar M., EP694
Kumar R., EP1261
Kumar R. K., PB1469, PB1718
Kumar S., EP806, EP1341, PB1412, PB1413, PB1579, PB1580
Kumar S. K., EP963, EP990, EP1046, EP1051, EP1224
Kumar Verma N., EP857
Kunacheewa C., PB1419
Kündgen A., EP467
Kundi M., EP461
Kung C., EP695
Kungwankiatichai S., PB1419
Künstner A., EP853
Kunz C., EP1239
Kunz C., EP968
Kunz J., S100
Kunz W., EP547
Kunzweiler C., PB1485
Kuo K., S262, S267, S271, EP691, EP692, EP696, EP1194, EP1306, PB1805
Kuo W.-L., S101
Kuo Y.-Y., EP922
Kupesiz A., EP1316, PB1755
Küpper J., EP435
Kurahashi S., PB1587
Kurahashi Y., EP875
Kurakin V., EP1190
Kurata M., EP667, EP668
Kurian T., EP899
Kurman M. R., EP443, EP1017, EP1018
Kurochkin D., PB1700
Kurokawa T., EP1101, EP1105
Kurt Yüksel M., EP1283, PB1603
Kurtulus S., S168
Kusakabe M., S226
Kusano M., EP441
Kusec R., S304, EP886
Kuss B., S147
Kustanovich A., EP358
Kusumoto S., S218
Kuter D. J., S299, S312, EP687, EP689, PB1733
Kutlar A., EP1202
Kutok J. L., S176, EP859
Kutyna M. M., S151
Kuvshinov A., PB1491
Kuykendall A., S200, PB1394, PB1714
Kuypers F., EP1202
Kuzan D., EP510
Kužat L., PB1684
Kuzmina L., EP360, EP1241, EP1260, PB1785
Kuznetsov Y., EP770
Kuzyaeva A., EP1040
Kwak J.-Y., EP1029
Kwan J., EP433
Kwiatkowska A., PB1545
Kwiatkowski J. L., S257, S261, S266, EP1301
Kwon M., EP587, EP726, EP870, EP1168, PB1696
Kwong B., EP717
Kye S., EP917, EP926
Kyriakopoulou D., EP1311
Kyriakou C., EP983, EP1047, PB1747
Kyrtsoni M. C., EP774
Kyrtsonis M.-C., EP1016
Kytölä S., EP925
La Barba G., S154
La Marca G., S102
La Morella M., EP1004
La Motte-Mohs R., EP1062
La Rosée P., S219
La Starza R., S108
La Torre I., S131, S311, EP428, EP445, PB1398
Laane E., EP1187, PB1725, PB1757
Laas C., EP711
Labarque V., EP1208
Laber D. A., EP1136
Labopin M., S232, S233, S242, EP431, EP1228
Labotka R., S184, EP963
Labrador J., EP447, EP631, PB1407
Labuhn M., EP398
Labussière-Wallet H., S232, EP494, EP1228, EP1262
LaCasce A. S., EP769
Lacey R., EP797
Lachey J. L., EP758, EP839, EP840, EP842
Lachmann H., EP1000, PB1644
Lachmann R., EP694
Lachowiez C., S136
Lad D. P., EP631
Ladetto M., EP634, EP860
Ladicka M., EP994
Ladis V., EP1311
Ladogana S., EP1158
Ladygina E., S286
Lafaurie M., EP1125
Lafuente M., EP890
Lagana A., EP936
Laginestra A., EP753
Lahiry A., EP496
Lahoz Alonso R., EP578
Lahuerta J.-J., EP1012, EP1021, PB1793
Lai C. K., EP402
Lai X., EP1275, EP1277
Lai Y., EP669
Laidou S., S143
Laille E., EP457
Lakehal S., EP1159
Lakhdari N., EP1159
Lakhwani S., EP670
Lakos G., EP1160
Lakshminarayanan M., PB1714
Lal A., S257, S266, S267, EP1301
Lalancette M., PB1662
Lalayanni A., EP1254, PB1583
Lalayanni C., PB1697
Lalou E., EP777, EP1272
Lam H. P. J., PB1694
Lam W., EP1261
Lamanna N., EP500, EP524, EP633
Lamarsalle L., EP995, EP999, EP1207
Lambert F., PB1483
Lambert J.-F., PB1517
Lambert J., S180
Lambert J., EP786, EP797, EP1077
Lambert M., EP718
Lambert M. P., PB1733
Lamia A., PB1371, PB1373, PB1374
Lamia T., EP1285
Lampe J. W., S176
Lamprou M., PB1368
Lamure S., S215
Lan J., EP1277
Lan Y., EP951
Lancellotti S., EP571
Lancet J., EP899, PB1364, PB1394
Landecho M. F., EP809
Lander C., EP691
Landesman Y., EP936, EP966
Landgraf K., EP879
Landgren O., EP982
Landi S., EP612
Landspersky T., S247, EP761
Lane A., EP427
Lane S., EP433, EP1086
Laney J., EP737
Lang C., EP625
Lang T., EP1192
Lang T. J. L., EP755
Langemeijer S., EP594
Langer P., EP1045
Langerak A. W., EP599, EP637, EP640
Langley M., S177
Langlotz M., S100
Langseth Ø., EP1022
Lanping X., EP454, EP1300
Lanvers-Kaminsky C., EP342
Lanza F., EP353
Lanzarone G., S308
Lapa B., EP421, EP630, PB1350, PB1630
Lapalombella R., EP861
Lapeyre-Mestre M., EP1125
Lapietra G., EP571, EP1152
Lapin V., EP360
Lapotentova E., EP358
Lara J., S150
Larcher L., EP906
Larcher M.-V., EP494, EP1262
Largeaud L., EP456

Larghero J., EP497, EP540, EP1282
Laribi K., S156, EP439, EP529, EP652
Larijani M., S178
Lario Arribas A., EP489
Larionova O., EP1190
Larocca A., EP973
Laros - van Gorkom B. A., EP567
Larráyoz M. J., S143, EP411, EP606
Larripa I., EP659
Larsen J., S187
Larsen M. K., S159
Larsen S., EP1086
Larson R. A., EP438, EP457
Larson S., EP747
Larsson K., PB1655
Lasica M., EP638
Lasorsa V. A., S276
Lassandro G., EP1155, EP1158
Latagliata R., S154, EP673, EP1079
Latif A.-L., EP498
Latorre-Crespo E., EP754
Lattimore S., S256, EP730
Laubach J. P., EP963, EP975
Laude M. C., EP720
Lauf J., EP897
Laurence J., S241
Laurendon A., EP938
Laurent C., S212
Laurent D., EP455
Laurent M., EP995
Laurenti E., EP751
Laurenti L., EP394, EP604, EP631, EP634, EP645, EP1233, PB1506
Lavarda M., EP997
Lavaud A., EP652
Lavi A., S288
Lavi N., S288, EP1023
Lavilla-Rubira E., EP447
Lavorgna S., EP420
Lavrinenko A., EP838
Lavrova T., PB1504
Law A., EP1261
Law E., EP317, EP327
Law S., EP1000, PB1644
Layton D. M., S267, S270, EP691, EP692, EP696, PB1805
Lazareva D., EP1190
Lazarian G., EP652
Lazaridis A., EP1232
Lazaridou A., EP1254, EP1256
Lázaro P., EP1234
Lázaro del Campo P., PB1518
Lazaroiu M., S211, EP1081
Lazaryan A., S239, EP536
Lazzarino C., EP927
Lazzarotto D., S240
Le G., EP628
Le L., PB1542
Le P. Q., EP1208
Le Bras F., S216
Le Calloch R., EP646
Le Clech L., S156
Le Coutre P., EP677
Le Dû K., EP1176
Le Goff M., EP1176
Le Gouill S., S212, S216, EP500, EP511, EP790
Le Meur G., EP1262
Le Nouveau P., EP1013
Leader A., PB1528
Leahy M., PB1393
Leal A. R., EP579, PB1693
Leal I., PB1526
Leal J., EP1054, EP1286
Lear S., EP965
Leary H., EP797
Lebedev T., EP426
Lebedev Y., EP333
Lebedinsky C., PB1712
Leber B., EP931
LeBlanc R., S188, EP989, EP1002, EP1008, EP1038, PB1643
Leblanc T., S157
LeBlanc T. W., PB1753
Leblond V., EP646, EP782
Leboeuf C., EP695
Lebon D., S157
Lecat C., EP983
Lech-Marańda E., S202, S205, EP524, EP633, EP829, EP975
Lechauve C., S265
Lechevalier N., EP898
Leckenby A., EP393
Leclerc Teffahi S., S157
Ledda A., S182
Ledoux-pilon A., EP652
Lee A., EP859
Lee C.-C., EP483
Lee D. W., EP341
Lee D., EP731
Lee G., EP628, EP806, EP1292
Lee G.-W., EP1029
Lee H. K., EP568
Lee H., S189, EP985
Lee H. S., EP1029
Lee H. J., PB1553
Lee H.-J., PB1513
Lee J. H., EP1029
Lee J., EP568
Lee J.-H., EP918, PB1417
Lee J.-J., EP1024, EP1029
Lee J., S213
Lee J. H., EP1029, PB1660
Lee J. W., S301
Lee J.-H., EP918, PB1417
Lee K., EP747
Lee K., EP1019
Lee K.-H., EP918, PB1417
Lee L., EP983, EP1047
Lee M., S290, S291, EP689
Lee M.-W., PB1513
Lee N., EP527, EP619
Lee P., S135
Lee S., EP731
Lee S., EP924
Lee S., EP522
Lee S., S239
Lee S., EP1144
Lee Y., S235
Lee Y. N., EP529
Lee Y.-S., PB1417
Leebeek F. W., S256, EP567, EP730
Leetrakool N., EP1330
Lefaki M.-A., EP1272
Lefebure M., EP599
Lefebvre C., EP898
Lefort C., PB1546
Legieć W., EP1028, EP1280
Legnani F., S259
Legrand O., S138
Leguay T., EP456, EP482
Lehmann C., EP767
Lehmann F. F., EP739
Lehmann F., EP424, EP871, EP945
Lehmann S., EP912
Lehmann T., PB1708, PB1723
Lehrhaupt K., EP1191
Lei F., PB1594, PB1797
Leiba M., S255, S288, EP1023
Leiba R., EP487
Leibovici L., S309
Leijonhufvud C., PB1543
Leip E., EP671, EP672, EP684
Leitch C., EP403
Leitch H., EP931
Leite L., EP1274, EP1281, EP1290, PB1789
Leivas A., EP721
Leleu X., S180, S186, EP933, EP973, EP974, EP976, EP985, EP1005, EP1013
Lema E., EP758, EP842
Lemaire P., EP540, EP906
Lemanzyk R., S197
Lemes Castellano A., EP1116, PB1495
Lemoli R. M., EP459, EP463, EP1079
Lemons R., S256
Lemos M., EP820
Lendvai N., EP1003
Leng Y., PB1648
Lenhoff S., EP1228
Lenk L., EP375
Lennon H., EP1207
Lentell I., EP555
Lentes J., EP325
Lentzsch S., S188, EP966, EP1002, EP1008, EP1163
Lenz G., PB1434, PB1451
Lenzi C., EP600
Leo M., PB1461
León A., PB1679
Leonard N., EP1292
Leone J., EP672
Leone V., EP651
Leonetti Crescenzi S., S154
Leongamornlert D., S133
Leonidakis A., EP1014
Leonidopoulou T., EP551, PB1516
Leonova N., PB1784
Leoz B., EP812
Lepik E., EP770, PB1456
Lepik K., EP544, EP556, EP770, EP771, EP1190, PB1612, PB1617
Lepistö M., EP856
Leporace A. P., EP673
Leppä S., EP856
Leprêtre S., S145, EP646, EP652
Lerario G., PB1461
Lerbs T., EP717
Lereclus E., S162
Lerma A., PB1793
Leroy H., EP456
Lersch F., EP465
Leshchenko V., EP936
Leshchuk O., PB1459
Leslie L. A., S213
Lesokhin A., S192
Lessi F., EP491, EP1053
Letourneau-Guillon L., S262
Leung N., S241
Leung Y. T., EP1276, EP1279
Leuzzi L., PB1442
Levati G. V., EP921, PB1621
Levato L., S154, EP651
Levenga H., S149, EP1027
Levi I., S288, EP462, EP502, EP503
Levin M.-D., S149, S180, EP631, EP637, EP640, EP666, EP678, EP1020, EP1027
Levine M., S133
Levis M., S135, EP437, EP438, EP442, EP443, EP448
Levitch R., PB1476
Levy C., PB1665, PB1667, PB1668
Levy E. M., EP663
Levy I., S288, EP631, PB1759
Levy M., S192, EP452, EP462, EP642
Levy V., EP646
Lewandowski K., EP1091
Lewis D. J., EP499, EP500, EP524, EP633
Lewis E., EP1001, EP1026
Lewis J., PB1405
Lewis K. L., EP500, EP638
Lewis R., S281
Leypoldt L., S183
Leys R., EP1027
Li A., EP733
Li C.-C., PB1565
Li C., EP565
Li C., EP1303
Li C., S194
Li C., EP1003
Li C., S184
Li D., PB1572
Li D., EP1120
Li F., S204, EP792, PB1670
Li G., PB1542
Li H., EP1103, EP1111
Li J.-L., EP483
Li J., EP1030
Li J., EP1117
Li J. T., EP513
Li J., EP548, EP601, EP618, EP636, EP639, EP801, PB1497, PB1576
Li J., EP337
Li J.-L., EP460, EP484
Li J., EP1223, PB1473
Li J., EP1163
Li J., S118
Li J., EP998, PB1648
Li J., PB1660
Li J., EP792
Li K., S173
Li L., PB1688
Li L., EP583
Li L., EP962
Li M., EP747
Li M., EP965
Li Q., EP490
Li R., EP505
Li S., EP966
Li S., PB1801
Li W., S207, S211, EP1024
Li X., EP742
Li X., EP783
Li X., EP998, PB1648
Li Y., S204
Li Y., EP612
Li Y., EP513
Li Y., EP527, EP619
Li Y., EP1293
Li Y., EP1024
Li Z., EP639
Li Z., PB1646
Li Z.-L., PB1647
Li Z., S194
Li Z., EP792
Li Z., EP1223, EP1269, EP1294
Li Z., EP512, EP537, EP549, EP792
Li Z., EP414
Li Z., S139
Li Z.-H., PB1531
Liacos C. I., S280, EP959
Liang C., EP490
Liang M.-Y., S298
Liang R., EP1120
Liang S.-W., EP476
Liang X., PB1416
Liang Y., EP565
Liao J., EP1303
Liao K., S192

Liao L., EP528
Liao M. Z., EP632
Liao N., PB1660
Liao-Zou H., EP1198
Liapi D., EP774, EP1153, PB1516
Liapis I., PB1681
Liapis K., EP919, PB1436, PB1681
Liaskas A., EP773, EP774, PB1560
Liassou D., EP737
Libao B., EP1010
Libby E., S189
Liberati A. M., EP988, PB1444
Libura M., S128
Lidonnici M. R., S269, S277, EP1302
Lidove O., EP694
Lieberman C., S165
Liebman H., EP1144, PB1733
Liedtke M., EP1017, EP1018
Liem R., S260
Lien P.-W., PB1552
Lievin R., EP540
Liguoro I., EP1214
Lihou C., PB1720
Likold E., EP626, PB1490
Lillard J. W., EP956
Lim A., EP980, EP981
Lim J. Q., EP857
Lim J., PB1433
Lim K., S151
Lim M. A., EP515
Lim S.-T., EP857
Lima I., EP848
Lima M., PB1439, PB1701
Limbrick-Oldfield E., PB1571
Limongello R., S227
Lin C.-C., EP922
Lin D., EP356
Lin F., EP847
Lin F.-J., PB1552
Lin H., EP469, EP493
Lin H., PB1660
Lin H., EP397
Lin H.-M., S201
Lin K., PB1786
Lin P. L., EP992, EP1005
Lin P.-Y., S253
Lin R., EP356
Lin T. L., EP437, EP442
Lin T., EP969, EP1051
Lin T., EP356
Lin T., S206, S211
Lin X., EP1219
Lin X., S118
Lin Y., PB1473
Lin Y., S117, EP495, EP964, EP984, EP990
Lin Y., EP346
Lin Y.-W., PB1552
Lin Z., EP346
Linares M., EP408, EP412, EP952
Linares M., EP563
Lincango-Yupanki M., PB1380
Linch D., EP788
Linder M., EP1126
Lindsay J., EP988
Linev A., PB1522
Ling F., S126
Ling W., EP1249
Ling Z., S115, S119
Lingaraj T., PB1566
Linhares Y., PB1440
Linnikov S., EP1040
Linton K., S219, EP499, EP783, EP786
Lioe H., EP1210
Lion T., EP897
Lioure B., S157, EP1228
Lipe B., S188, EP1002, EP1008
Lipilkin P., PB1548
Lipilkina T., PB1548
Lipman K., PB1769
Lipton J. H., S153, EP675, EP1261
Liquori A., S160, EP413
Lis M. J., EP563
Lisa Battista M., EP1238
Lise Menard A., S232
Lisi R., EP1307
Lissenberg-Witte B., EP1027
Little C., EP745
Little M., S205
Litwak D., EP975
Litzow M., S135, S169
Liu A., PB1646
Liu A., S297
Liu A., EP1090
Liu B., PB1478
Liu C., EP469
Liu C., PB1478
Liu D., EP346
Liu D., EP1248, PB1396
Liu D.-Y., EP1230
Liu D., EP1103
Liu F., EP1225
Liu F. F., EP1165, EP1169, EP1178
Liu F., S104, S231
Liu F.-Q., S298
Liu G., EP527, EP619
Liu H., EP505
Liu H., EP601, EP618, EP801, PB1576
Liu H., EP339, EP414
Liu H., EP1303
Liu H., EP513, EP583, EP877, EP901, EP946, EP947, EP953, PB1685
Liu J., EP962, PB1360
Liu J., S228, EP334, EP562, EP862, EP865, EP866, EP868, EP874
Liu J., EP372
Liu J., S194, S204, EP1226, PB1670
Liu K., EP847
Liu K.-Y., S234, EP347, EP395, EP460, EP484, EP656, EP1226, EP1240, EP1252, PB1591
Liu L., EP728, EP962
Liu L., EP792
Liu L.-X., EP484
Liu L., EP1277
Liu L., EP395
Liu M., PB1499
Liu P., EP512, EP537, EP549
Liu P., PB1647
Liu Q., EP356
Liu Q., EP1050
Liu Q., EP469, EP493
Liu Q., EP1303
Liu R., S205
Liu R. D., EP766
Liu R., EP805, EP1174
Liu S., EP1050, PB1685
Liu S., EP346
Liu S., EP710
Liu S., EP1271, EP1293
Liu T., S207
Liu W., EP1111
Liu W., S257, S266, EP1301
Liu W., EP1024
Liu X., EP1103, EP1111
Liu X., EP1120
Liu X., S300
Liu X., PB1706, PB1717
Liu X., EP1271, EP1303
Liu X.-F., EP395, EP1265
Liu Y., S297
Liu Y.-K., EP1265
Liu Y.-R., S234, EP347
Liu Y., S206
Liu Y., PB1520
Liu Y., PB1354, PB1356
Liu Y., S118
Liu Y., EP894
Liu Y., EP519
Liu Z., EP583, EP895, EP900, EP901, EP946, EP947, EP953, PB1636
Liu Z., EP1120, PB1670
Liudmila F., EP781
Livia L., EP1251
Lizcova L., EP948
Llop M., EP413
Llorca J., EP612
Llorente L., EP350, EP352, EP546
Llorin-Sangalang J., S214
Lo A., PB1554
Lo C., EP745
Lo Presti V., EP727
Lobo D., EP555
Lobry C., S126
Locatelli F., S116, S257, S258, S266, EP733, EP1301, PB1780
Locke F., EP536, EP787
Lodvir Hemsing A., EP1296
Loeffen J., EP538
Loffreda A., EP1067
Logan A. C., S117
Loges S., EP463
Loghavi S., S132, S136, S167, EP440, EP464, EP468, EP471, EP1104
Logie J., EP1122
Loginsky V., PB1358
Loglisci G., S154
Logothetis C. N., EP1136, PB1394
Loh M., EP317
Loh X., EP857
Lohmeyer J. K., S253
Lohrmann E., EP496
Loja T., S142
Lokare A., S181
Lokau J., EP1059
Loke J., S232, EP432
Lomaia E., S153, EP674
Lomas O., EP797
Lombardi A., EP1108, PB1601
Lombardi R., EP843
Londhe A., EP977
Lonez C., EP739
Long M., EP861
Longarón R., EP890
Longo F., EP1307, PB1808
Lonial S., S187, EP975, EP984, EP1026
Loo S., S168
Lopes C., EP354, PB1449
Lopes M., S278
Lopez A., EP447
López C., EP858, EP872
López J. A., PB1407
Lopez M., PB1462, PB1464
López M. E., EP546
Lopez N., EP708
Lopez Abadia E., EP1089
Lopez Ansoar E., PB1462, PB1464
López-Cadenas F., EP889, EP893, EP907
López-Corral L., S237, EP1234, EP1237, EP1253
López de Hontanar Torres G., EP1327
López de la Guía A., EP1021
López De Ugarriza P., EP1345, PB1507
López-Díaz de Cerio A., EP809
López-Fernández E., EP612, EP823, EP1250
López Fresneña M. C., EP1168
Lopez-Garcia A., EP631
Lopez-Godino O., EP479, EP1231
López-Guerra M., EP1084
López-Guillermo A., EP872, PB1567, PB1568
López Jaime F. J., EP1324
Lopez-Jimenez F. J., EP1338
López Jiménez J., EP489
López-Lorenzo J. L., EP350, PB1407
López-Menargues P., EP563
López-Nevot M. Á., EP612
López-Parra M., EP1234, EP1253
López-Pavia M., EP563
López Peña A., EP578, EP1139, EP1331, PB1821
López Rodriguez J. F., EP662, PB1561, PB1798
López Rubio M., EP1327
Lörch T., S310
Lorè N. I., S279
Loren A. W., S238
Lorenc K. R., EP1163
Lorens J. B., EP463
Lorenzo Algarra J., PB1407
Lorenzo Perez M., EP1116
Lorocca A., EP988
Lorusso B., S108
Loscertales J., PB1493
Losem C., EP648
Loseto G., PB1550, PB1737
Lossos I., S214, S222
Lou F., EP460
Louar F., PB1629
Loubert A., EP1171
Louis C. U., EP1182
Loukari E., EP777
Lourou M., EP1146, PB1351
Loutsidi N., PB1516
Louzada M., EP989, EP1038, PB1643
Low M., PB1660
Low Z. S., EP857
Lowdell M., EP788
Lowe H., EP788
Lowsky R., EP1224
Lozano M., EP734, PB1642
Lozynskyy R., PB1459
Lu D.-P., EP1230
Lu J., S189
Lu J., EP962
Lu J., PB1786
Lu M.-Y., EP349, EP368
Lu M.-Q., PB1647
Lu P., S118
Lu P.-H., EP1230
Lu Q., EP437, EP438, EP441, EP448
Lu Q., PB1786
Lu T., EP334, EP562, EP864, EP868
Lu T., EP632
Lu V., S153
Lu W., PB1594, PB1797
Lu X., EP1024
Lu Y., EP733, EP736
Lu Y., PB1542
Lu Y., EP1230, EP1248
Lübbert M., EP376, EP467
Luca S., EP741

Lucas L., EP1054, EP1286, PB1631
Lucchesi A., S154, EP827, EP1034, PB1581, PB1678, PB1695
Lucchini E., EP543, EP795
Lucena M. M. D., PB1745
Luchinin A., EP1181, PB1645
Luchkin A., PB1467
Luciano L., EP673
Luciano L., S154
Lucijanic M., S304, EP886
Luck T. J., EP376, EP423
Ludek P., PB1677
Ludovico P., EP425, EP612
Ludvigsen M., EP392
Ludwig H., EP960, EP971, EP994, PB1658
Lufkin J., S263
Luft T., EP1245
Luger S., EP462
Lugtenburg P. J., EP499, EP517, EP766, EP803
Lugthart S., S263, EP1199
Luhanga M., EP1322
Lühmann J., EP325
Lukanov R., PB1686
Lukes J., EP320
Lukianova A., PB1358
Luksic I., S304
Luminari S., EP543, EP860, PB1572
Luna A., EP670
Luna de Abia A., EP489
Lundberg L., EP501
Lundgren S., EP580
Lunghi F., S154, EP1089
Lunghi M., S112, S114
Luo J., S206
Luo T., EP535
Luo X., PB1795
Luo Y., EP1275, EP1277, PB1361
Luo Y., PB1786
Luo Y., EP392
Luponio S., EP1170
Luppi M., EP612, EP617
Luptakova K., EP1077, EP1080, EP1085
Luque Paz D., EP652
Luquet I., EP456, EP898
Lura M. P., S144
Luts Khoroz I., PB1793
Lutska Y., EP969
Lutwak E., S255, EP1023
Lutz C., EP364
Lutz P., EP343
Lutz R., S183
Lützner J., EP896
Lux P., EP1199
Luzardo-Henriquez H., EP1116, PB1495, PB1561
Luzi D., S154
Luzna P., PB1640
Lv F., S207, S211, EP789
Lv M., S230
Lwin Y., PB1747
Ly N., S177
Lyall M., PB1665, PB1667, PB1668
Lyamkina A., PB1512
Lyashenko L., PB1366
Lykkegaard Andersen C., PB1740
Lymboussakis A., PB1575
Lymp J., EP541
Lynch M., S267, PB1805
Lynch R., EP731
Lynes J., EP539
Lysenko I., EP762, EP1190
Lyu Z.-S., S230
M'sadek F., PB1443
Ma F., S168
Ma L., PB1648
Ma L., EP891, EP923
Ma Q., PB1781
Ma R., S234
Ma S., EP512, EP537, EP549
Ma X., EP339, EP414
Ma X., EP530, EP924
Ma Y., PB1646
Ma Y., EP1246
Ma Y., EP1225
Ma Y., EP1225
Maaoui F., PB1752
Maas C. C., S155
Mabe P., EP694
Macaulay D., EP710
Maccari C., S158
MacDonald D., EP782
Macé S., EP981
Macedo D., EP1335
Machacek M., EP846
Machairas A., EP1272
Machherndl-Spandl S., EP897, EP971
Machová Poláková K., S152, EP660, EP661
Maciejewski J., EP580, EP596, PB1481
Macintyre E., EP790
Mackay S., EP401
Mackensen A., EP887
Maćkowska N., EP322
Maclean B., EP1205
Macoin J., EP938
MacPherson C., EP613
Macro M., S180
Madan S., S188, EP1002, EP1008
Maddaloni D., PB1602
Madden T., EP443
Maddocks K. J., PB1444
Madduri D., S190, EP936, EP964, EP1003, EP1009, EP1163
Madeiros N., EP842
Madelaine I., EP497, EP540
Madera E., EP363, EP1335
Madero L., PB1369
Madinaveitia Ochoa A., EP893
Maeda T., PB1455
Maeda Y., EP441, EP914
Maeda Y., EP580
Maekawa T., PB1703
Maerevoet M., EP530
Maertens J., S243, EP748, PB1404
Maes P., EP1208
Maestro A., EP1273, EP1291
Maffei R., EP612, EP617
Magalhães N., EP421, EP630, PB1350, PB1630
Magalhães Rego E., EP818
Magaz M., EP1084
Magdalena L., EP960
Magen H., EP1023
Maggi A., EP651, EP673
Maggio A., EP1158
Maggio A., EP1307, EP1309, PB1810
Magliano G., PB1387
Maglinte G. A., EP786, PB1735
Magnani T., S259
Magnani Z. I., S252, EP722
Magnano L., EP734, EP872, PB1567, PB1568
Magni M., EP723
Magnusson T., S224
Magomedova A., EP564, EP756, EP884
Magrath C., PB1744
Magro Mazo E., EP1089
Mahaklan L., EP850
Mahdi F., EP834
Mahe B., EP782
Mahe P., EP701
Maher L., EP930, EP1315
Mahévas M., S295, EP1125, EP1147
Mahjoub S., PB1814
Mahlberg R., EP968
Mahmood S., EP983, EP1000, EP1047, PB1644
Mahon F.-X., S152
Mahtat E. M., PB1375, PB1551, PB1598, PB1680
Mahtôt R. A., EP567
Mahuzier B., S236
Mai E. K., EP968, EP1245
Maia C., EP809
Maié T., EP657, EP1063
Maier G., EP443
Maier J., S172
Maier S., EP784
Maierhofer B., EP784
Mailankody S., EP747
Maillet T., EP697
Mainda A., EP774
Maiolino A., EP986
Maira D., EP843
Maisel C., EP973
Maisnar V., EP816, EP970, EP1042, PB1652
Maisto G., EP478
Maiti A., S132, EP430, EP440, EP466, EP676
Majdouline B., PB1597
Majhail N., PB1415
Majlufc A., EP1335
Major S., EP1010
Majunder M. M., EP396
Mak D., EP379
Mak P. Y., EP379
Makarik T., EP1071, PB1352
Makarova O., EP358
Makeeva L., PB1524
Makinde A. Y., EP1182
Makita S., S218
Makkeyah S., EP702
Makofske J., S168
Maksimov O., PB1496
Malagola M., EP1267
Malak S., S215
Malandrakis P., EP959, EP993, EP1041
Malaney P., EP374
Malara A., S249
Malato A., S154, PB1397
Malcovati L., EP588
Malea T., EP955
Maleta L., EP561
Malhan H., EP1220
Malherbe J. L. R., EP585
Malhotra P., EP331
Malik S., EP1083
Malika C., EP683
Malishevskaya I., EP1321
Mallano S., PB1461
Mallek R., PB1527
Mallikarjuna V., S283
Mallouri D., EP1232, EP1254, EP1256, PB1583
Malloy R., EP1010
Maloisel F., EP1176
Maloney D. G., S213, EP508, EP731, EP791
Malpica L., EP881
Maluquer C., EP329, EP350
Maly J., S135, EP1163
Mamedov I., EP333
Mamedova A., EP772
Mammadova L., S225
Mammali I., EP777
Mamolo C., EP1025, EP1033, EP1175, PB1665, PB1667, PB1668
Manaças M., PB1732
Manara R., EP348, EP1201, EP1310
Mancini C., EP949
Mancini M., EP419
Mancini V., PB1387
Manco L., EP700
Mandac Smoljanovic I., EP932
Maneikis K., EP486
Manel B., PB1371, PB1373, PB1374
Manel M., EP817, EP831, PB1586
Manfredi A., S279, EP722
Manfredi F., EP719
Manfroni C., EP658
Mangasarova Y., EP558
Manghisi B., EP658
Mangi M., EP1135
Manhart G., EP373, EP389
Maniar H., EP465
Manier S., EP984, PB1653
Mańko J., EP1280
Mann C., S183
Mann S., EP699
Mannelli F., S158
Mannering N., S296
Manni M., PB1575
Manni S., EP855, PB1633
Mannina D., EP651
Manninen R.-L., EP1192
Mannis G., EP442
Manola K., EP763
Manolova V., EP1204
Manser A., EP326
Mansilla-Soto J., S250
Mansour H., PB1563
Mansouri L., S143
Mansouri R., PB1423, PB1556, PB1585, PB1749
Mansvetova C., PB1465
Mant T., S263
Mantere T., EP616
Manting E., EP403
Mantoan B., EP860
Mantovani E., EP915, EP920
Mantzourani M., EP1153
Mañú A., EP411
Mañú Pereira M. D. M., EP686
Manuguid F., PB1390
Manzke O., PB1572
Manzoni D., EP407
Mao Q., EP911
Mapar P., EP856
Mapara M. Y., S261, EP736
Mapp S., EP783
Mar B. G., S201
Maran E., PB1746
Maranda E. L., EP480
Marango J., EP452, EP643, PB1391
Marasca R., EP612, EP617
Marasco V., EP744
Marcatili P., EP609
Marceau-Renaut A., EP906
Marchante Cepillo I., PB1407
Marcher C., S134
Marchesani S., EP1203, PB1765
Marcheselli R., EP543
Marchesi F., EP491, EP793, EP883
Marchesi G., S292
Marchesini M., S108

Marchetti M., S292
Marchetti M., EP645, EP1074
Marchica V., EP949
Marco De Lucas F., PB1526
Marcolin R., EP459
Marcon C., S289, EP815
Marcos-Gragera R., EP612
Marcucci G., EP345, EP351
Marculescu R., EP461
Marcus R., EP783
Mardaraz C., EP625
Marei M., PB1609
Margariti M. I., EP763
Margiotta G., EP1184
Margiotta Casaluci G., EP603
Margolskee E., EP1104
Margotto L., PB1390
Maria Serafina Anna S., PB1461
Maria Wagner-Drouet E., S232
Mariani R., EP1307
Mariano L., EP818
Mariano R., EP659, EP663, EP665
Marie M., PB1479
Mariem A., PB1371
Mariglia P., EP624
Marín A., PB1679
Marin C., EP1196
Marin C., PB1746
Marin-Oto M., EP809
Marín-Quilez A., EP1131
Marin-Rubio J. L., PB1385
Marin Sanchez A., EP1089
Marinakis T., EP774
Marinello P., EP764
Marini S., EP630
Marino J., EP990
Marino M. R., S114
Marino M., EP883
Marinoni M., EP1155, EP1158
Marion S., EP986
Maris M., EP541
Mariz J., S278
Mariz M., EP975
Marjanović M., PB1605
Markala D., EP1044
Marke R., S110
Marković D., EP759
Markelov V., EP544, EP822
Markovic U., EP1004
Marks D., EP353, EP371
Marks H., PB1702
Marktel S., S249, S268, S269, EP741
Markwood C., EP859
Marolleau J.-P., S180
Maroto-Martín E., EP721
Marott J. L., EP359
Marquart H., EP359
Marques A. C. B., PB1732
Marques A. I., PB1789
Marques B., EP1102, EP1114, EP1121
Marques I., EP488
Marques L., EP488
Marques O., S100, S275
Marquet J., EP631
Marquet Palomanes J., EP489
Márquez J. A., PB1526
Márquez M. E., EP625
Márquez-Gómez I., EP1324
Marquez Villegas F. G., EP1156
Marr C., EP896
Marr H., EP797
Marra A., S227
Marra R., S276, EP688
Marrero C., PB1679
Marschalek R., S105
Marshall D. A., S313
Martell B., PB1408
Martell R., EP390
Martella E., EP949
Martella F., S308
Martelli M. P., S227
Martens A. W. J., S141, EP608, EP873
Martianez Canales T., EP400
Martín A. Á., EP1234
Martin A., PB1393
Martín B., EP413
Martin C., EP927
Martin C., EP1231
Martin C., PB1406
Martin H., S232, EP968
Martin J., S185, EP1012
Martin J.-E., EP1058
Martin K., EP1210, EP1215
Martin M. P., EP1346
Martin M., EP933
Martin P., EP530, EP785, EP798
Martin S., EP708
Martin S., EP767
Martin T., EP964, EP977, EP980, EP981, EP986, EP1006
Martin T., EP978, EP990, EP1049
Martín-Antonio B., EP721, PB1642
Martín Calvo C., PB1788
Martin-Consuegra Ramos S., EP578, EP1139, EP1331, PB1821
Martín-Escudero V., EP1167
Martín-Fernández M., S293
Martín Izquierdo M., EP893, EP907
Martin Lopez A., EP1253
Martín Moro F., EP489
Martín-Ramos M. L., EP1021
Martin-Regueira P., EP457, EP465
Martín Rojas R., EP870
Martín-Sánchez E., EP809
Martín Sánchez J., EP1237
Martín-Subero J. I., EP858
Martín-Téllez S., EP1324
Martina M. P., PB1684
Martina Z., EP615, EP623
Martinelli G., S125, EP438, EP448, EP455, EP827, EP1034, PB1581, PB1678, PB1695
Martinelli S., EP617
Martinez A., EP363, EP824
Martínez C., EP479
Martínez C., EP1335
Martínez C., S237
Martínez C., EP413
Martinez E., S165
Martinez G., EP980, EP981
Martinez G. A., EP1039
Martinez L., PB1526
Martinez P., EP408
Martínez M., PB1793
Martínez M., EP479
Martínez-Botía P., EP812
Martínez-Caballeira D., EP812
Martinez-Calle N., EP514, EP532, EP649, EP765, EP797
Martínez Carreño M. J., EP1168
Martínez-Cibrián N., S237
Martinez-Cordero H., PB1675
Martinez-Cuadron D., EP447
Martínez de Castro E., EP1320
Martínez-Francés A., EP889
Martínez-Galán J., EP1320
Martinez Hellin A., PB1599
Martínez-Laperche C., EP726, EP870, EP1132
Martínez-López J., S143, S152, S185, S210, EP329, EP374, EP408, EP412, EP708, EP721, EP952, EP986, EP1012, EP1021, PB1653, PB1689, PB1793
Martinez-Martinez R., S185
Martínez Morgado N., EP336
Martinez Murillo C., EP363
Martinez-Nahharo A., EP1000, PB1644
Martínez Nieto J., EP712
Martínez-Paz P., S293
Martinez-Prieto M., EP510, EP516
Martínez Revuelta E., EP1345
Martinez-Roca A., EP472, EP481
Martinez Rolón J., EP665
Martínez Sánchez M. D. P., PB1407
Martínez-Sánchez P., EP329, EP350, EP352, EP447
Martínez Tobar L., PB1518
Martínez Vázquez C., EP1327
Martínez-Valiente C., S160
Martinho A., EP809
Martinkov V., PB1650
Martino B., EP651, EP1079, EP1106
Martino M., EP729
Martino R., EP546
Martino Bofarull R., EP587
Martins C., PB1449
Martins G., S278
Martins G., EP848
Martins H., EP354, EP1032
Martins M., PB1726
Martins S., S278
Martins Rocha Ribeiro A. P., PB1538
Martone S., EP688
Martorelli C., EP1170
Marturano E., EP1211, EP1219, EP1222, PB1762
Martynkevich I., PB1491
Maruta M., EP937
Maruyama D., S218
Marvaki A., EP1254
Marwa B., PB1371, PB1373, PB1374
Marziali M., EP1307
Marzolini M., EP788
Marzuttini F., EP1288
Masana Flores E., PB1704
Masarova L., S136, S167, EP471, EP1096
Mascarenhas J., S203, EP1077, EP1080, EP1085, PB1711
Mascaro R., S245
Mascerenhas J., EP1106
Maschan A., EP590
Maschan M., EP333
Masciopinto P., EP1188
Masciulli A., S158, EP1089
Mascolo C., EP1127, EP1140
Mashkina E., PB1548
Masiejczyk M., S164
Masih-Khan E., EP989, EP1038, PB1643
Mašlejová S., EP631
Maslikova U., EP1260
Maslyak Z., PB1459
Masmanidou M., EP1232, EP1256
Mason B., EP1175
Mason C., S150
Mason J., S263
Mason J., EP432
Mason-Blanche P., EP975
Masouleh B. K., S117, EP341
Massa A., EP1307
Massariello P., EP741
Masselli E., EP1061
Masszi A., EP768
Masszi T., EP963, PB1641
Mastaglio S., EP719
Masud A. A., EP1078
Mata Martínez G., EP374
Matasar M. J., S211, EP519, PB1434
Mateos M. C., EP350, EP492, EP546
Mateos M.-V., S184, S185, S191, S193, EP973, EP974, EP987, EP994, EP1003, EP1012, EP1021, EP1031, PB1653, PB1655
Materna C., EP758, EP839
Mathas S., EP767
Matheakakis A., EP1153, PB1516
Mathot R., EP569
Matias J. S., PB1732
Matías-Martín J., EP1131
Matilla-Garcia A., EP1343
Matis S., EP906
Matlan V., PB1353
Mato A., S145, EP500, EP524, EP633, EP635, PB1504
Matos J., EP1191
Matous J. V., EP782, EP784, EP1019
Mátrai Z., S143
Matson D. R., EP378
Matsouka C., PB1516
Matsuda A., PB1455
Matsue K., S226
Matsumura I., EP667, EP668, EP914, EP1101, EP1105
Matta Hanna B. M. H., PB1818
Mattar B., EP541
Mattar M., EP1195, PB1813
Matte' A., EP695
Mattei D., EP463
Mattlener J., S225
Mattlin H., EP606
Mattos É. R., EP1039
Mattsson J., EP1261
Mattsson M., S143
Matturro A., PB1460
Maugeri C., PB1409
Maung S., PB1413
Maurer A., S196, S197, EP1063
Maurer B., EP752
Mauri M., EP658
Maurier F., EP697
Mauro E., PB1409
Mauro F. R., EP624, EP645
Mauro M. J., S153, EP677
Mauro R., PB1397
Mavroudi I., EP588
Maximov V., PB1512, PB1611
Maximova N., EP1291
May A. M., EP467
Mayberry K., S265
Mayer J., S142, S152, S299, EP473, EP1063, EP1076, EP1081
Maynadié M., EP705, EP1143
Mayor-Bastida C., EP631
Mazan M., S164
Maze D., EP362, EP1082, EP1083, EP1093, PB1753
Maziarz R., EP508, EP510
Mazor R. D., EP330
Mazumder A., EP973
Mazza D., EP1067
Mazzoleni S., S259
Mbow M., EP938
McBride E., PB1377

McCarthy H., EP636
McCarthy N., EP432
McCarty H., EP1292
McCloskey J., S135, S153, EP462
McClune B., EP743
McClure B., EP321
McCord R., EP503
McCormack E., EP383, EP396, EP403
McCourt O., EP1189
McCrae K., S103, EP703
McCurdy A., EP989, EP1038, PB1643
McDonald A., EP439, EP585
Mcdonald L., PB1412, PB1413
McDonald V., S299, EP566
McEllligott A. M., EP628
McFadden I., EP982
McGee B., EP691
McGeehan G., EP379, EP382
McGraw K., EP899
McGuire C., EP711
McGuirk J., EP516
McHugh J., EP806
McIntosh J., EP745
McIver A., EP1010
McKay P., EP504
McKay P., EP765, EP783, EP797
McKerrell T., EP555
McKinney M., EP503
McLeroy J., EP495
McLornan D., S202, EP738, PB1719
McMenamin M., EP1292
McMillan A., EP498, EP514, EP765
Mcmillan I., PB1747
McMullin M. F., EP1058
Mcnamara C., EP1082, EP1083, EP1093
McNulty J., EP1339
McQuilten Z., S282
McSweeney P. A., EP495, EP787
Mdhaffar M., PB1363
Mead A., EP682, EP1058, EP1074, EP1085
Mebarki M., EP1282
Meckl A., PB1658
Mecott A., PB1438
Mecucci C., S108
Meddeb B., PB1373, PB1420, PB1423, PB1556, PB1585, PB1731, PB1749
Medeiros J., EP354
Medeiros L. J., EP882, EP1104
Medeiros N., EP839, EP840
Medhaffar M., PB1562, PB1564, PB1690
Medhaffer M., PB1527
Medina F., EP1346
Medina Martinez J. S., S133
Medinger M., EP1242
Medinger T., EP979
Mediwake H., EP1289
Meduri E., S129
Meehan B., S305
Meenaghan T., PB1545
Meeuwes F. O., S220
Megalakaki A., EP919, EP1153
Meggendorfer M., S143, S175, EP373, EP892, PB1514
Megías Vázquez D., EP374
Megido M., EP893
Mehalhal N., EP1159
Mehdid F., EP1255, PB1629
Mehovic R., EP859
Mehr R., EP502
Mehra A., S211
Mehra M., EP977
Mehra V., S283, EP738, EP1276, EP1279
Mehta A., S222, S224
Mei C., EP891, EP923
Mei J., PB1712
Meignin V., S295
Meijer E., S233
Meijer K., S256, EP567
Meijerink J. P., S107, EP335, EP538
Meinhardt A., EP436
Meissner J., EP767
Mekinian A., EP906
Mekni S., EP1285
Mela Osorio M. J., EP663, EP665, PB1380
Melana S., EP904
Melchardt T., EP971
Melear J. M., EP643, EP969
Melero C., EP606, EP616
Melero Valentín P., PB1734
Melhem Bertrandt A., EP1046
Meli E., EP1184, PB1442
Melikyan A., EP1071
Melillo L., EP491
Melissinidis G., PB1681
Mellenthin L., EP887
Mellerick L., EP1292
Mellgård B., PB1768
Mellinghoff S., PB1504
Mellink C., S149, EP599
Mellios Z., EP551, PB1515, PB1516
Melnichenko V., EP772, EP1190
Melnikov I., EP1328, PB1638
Melnyk U., PB1508, PB1691
Melo J., PB1449
Meloni A., EP1309, EP1313, EP1314, PB1602, PB1770, PB1771, PB1810
Melotti D., EP649
Memon K., PB1833
Memon T., PB1833
Mena A., EP563
Mena M. P., PB1642
Mena Santano A. M., EP1324
Menarguez J., EP870
Mende N., EP751
Mendeleeva L., EP1270
Mendes W., EP439
Mendes Pires C., PB1538
Méndez-Ferrer S., EP1058
Mendizabal A., PB1526
Mendonca D., EP1039
Mendoza I., EP824
Menendez M., EP1346, PB1819
Meneses Ferreira A., EP1251
Menezes D., S131
Meng L., EP1300
Meng N., PB1636
Meng X., S106
Mengarelli A., EP883
Mengel E., EP694
Mengge G., EP454
Menna G., EP1155
Menne T., EP498, EP506, EP539, EP765, PB1444
Menon K. N., S103
Menon R., EP444
Menshikova I., PB1465, PB1822
Menzel S., EP410
Menzies T., EP1259
Merabet F., EP652
Meral A., PB1755
Meral Güneş A., PB1372
Mercadal S., EP329, EP546
Merchan B., PB1666
Merchan B., EP479
Merchán B., EP890
Merchán Muñoz B., PB1425, PB1450, PB1692, PB1787
Mercier G., PB1742
Mercier-Ross J., PB1760
Merelli I., S249, S269, EP1067
Meriem A., PB1374
Merino Vega D., PB1753
Meriranta L., EP856
Merli M., EP543, EP860
Merlini G., S189, EP1011, EP1036
Mertz J., EP1080
Merz H., EP853
Merz M., EP972
Mesa M. C., PB1679
Mesa R., S201, S202, S203, EP1074, EP1078, EP1080, EP1081, PB1702
Mesa Morales Z., EP823, EP1250
Mesguich C., EP497
Mesini N., EP617
Mesli N., EP1159
Messaoudi N., PB1598
Messerich N.-M., PB1708
Messina G., PB1810
Messina M., S112, S114
Messiou C., S181
Metafuni E., EP394, EP1233
Mettivier L., EP1170
Metzeler K., S121, S128, S161, EP896
Metzner M., S128
Meuleman N., S180, EP739, PB1657
Meunier M., S156
Meyer C., S105
Meyer E., EP1224
Meyerhöfer M., S129
Meyers G., S238
Mi H., EP548
Miah K., EP968
Miakova N., EP358
Mian H., EP989, EP1038, PB1643
Miano M., EP1158, EP1307
Mianulli A. M., S114
Miao H., EP506, EP769
Miao X., EP967
Miao Y., EP601, EP618, EP801, PB1497, PB1576
Micallef F., PB1682
Miccolis R., PB1461
Miceli R., EP729
Michail M., EP551
Michailidou C., PB1608
Michallet A.-S., EP646
Michalopoulou A., PB1829
Michalova K., EP948
Michaltsova E., EP1241
Michel E., S121
Michel M., S291, S295, EP689, EP1147, EP1150
Michelis F., EP1261
Michelutti A., EP477
Micheva I., EP1123, PB1686
Michos A., PB1829
Michot J.-M., PB1626
Micklem D., EP463
Middeke J. M., EP436
Mielcarek M., S238
Mielke S., S242
Miesbach W., S256, EP730
Miettinen J., EP424, PB1383
Migeon M., EP451
Miggiano M. C., S154, EP673
Migkou M., EP993, EP1014, EP1016, EP1041
Migliavacca M., S258, EP741
Miglietta S., S102
Miglino M., EP459
Migone De Amicis M., EP1307
Miguel García C., EP893, EP1131
Mihai F., EP828
Mihaljevic B., S307, EP629, EP631, EP1043
Mihaylov G., EP1134
Mikala G., EP980, EP981, PB1641
Mikdame M., PB1551
Mikecin Drazic A.-M., S246
Mikhael J., EP986
Mikhail D., EP1241
Mikhailova E., PB1467
Mikhailova N., EP544, EP556, EP771, EP1190
Mikhalev M., EP647, EP1110
Mikhaleva M., PB1491
Mikhaltsova E., EP1260
Mikhaylova N., EP770, PB1456
Miki H., EP942
Mikkelsen E., EP1107
Miklos D., S235, EP787, EP1224
Mikula M., S164
Mikulić M., EP826, EP1263, EP1287, PB1539
Milani G., S292
Milani P., EP1011
Milani R., EP741
Miles D., EP444, EP632
Miles G., PB1463
Miles R. R., S221
Miljak A., PB1575
Millacoy P., EP574
Miller A., S261
Miller J., EP326
Miller J., EP797
Milletti F., S117
Milliken S., EP1186
Millot F., EP343
Mills K., S143, PB1384
Mills R., PB1671
Milne P., S105
Milner G., PB1654, PB1694
Milner S. G., S227
Milojkovic D., EP671, EP682, EP1058
Miloš M., EP573
Milosevic I., EP631, EP1326
Milosevic M., EP932
Milošević M., EP759
Milosevic Feenstra J., S198
Milsom M., S195, S246
Milunovic V., PB1494
Min C.-K., S184, EP1006, EP1029
Mina R., S182
Minaev M., PB1432, PB1446
Minaeva N., PB1549
Minami Y., EP667, EP668
Miñano A., S303
Minard-Colin V., S221
Minardi V., EP651
Minařík J., S186, EP816, EP954, EP1028, EP1042, PB1637, PB1640
MIncheff M., PB1792
Minchillo M. L., S108
Minden M., EP1082
Minelli O., EP1288
Mineo G., EP651
Minetto P., EP459
Minga E., EP631
Minnella G., EP394
Minnema M., S189, S191, EP495, EP796, EP804, EP1011, EP1020, EP1036, PB1698

Minniti C., S314, EP1206, PB1762
Minoia C., EP1184, PB1550, PB1737
Minoldo D., EP997
Minullina R., EP1190
Miranda A., PB1732
Miranda R., EP881
Mirandola P., EP1061
Miras F., S143, EP631
Mirasol A., PB1600
Mirolyubova Y., PB1402
Miron Y., PB1528
Mironov K., PB1700
Mironov O., EP1190
Miroshnichenkova A., EP333
Mischnik M., EP1210
Misidou C., EP919, PB1436, PB1681
Miskin H., EP638
Misleh J., EP642
Missere M., EP1314, PB1602
Mistrik M., EP1042
Mistry J., S179
Misurina A., EP884, PB1574
Misyurin V., EP564
Misyurina A., EP564
Misyurina E., EP1190
Mital A., S201
Mitani K., EP914
Mitchell S., S229
Mitev L., PB1530
Miteva D., S101, EP915, EP920, EP1304, EP1306
Miteva V., PB1686
Mitina T., EP1048, PB1500
Mitola G., EP753
Mitrovic M., EP1043
Mitrovic M., EP833, EP1326
Mitrovic O., EP629
Mitsura E., EP1321
Mittelman M., S288
Mitterbauer-Hohendanner G., EP461
Miyakawa Y., S312, EP566, EP689
Miyake K., S300
Miyamoto T., EP507, EP667, EP668, EP914
Miyano S., EP914
Miyazaki Y., EP667, EP668, EP909
Miyoshi H., S226
Mkwizu E., PB1514
Mlayah Z., PB1427
Mnif S., PB1752
Mnif T., EP1191
Mo H., EP1104
Mo X., EP847, EP1246
Mo X.-D., S234, EP1226, EP1252, PB1591
Mobasher M., S149
Mochkin N., EP772, EP1190
Modemann F., EP825
Mody-Patel N., PB1485
Moerland P. D., S141
Moertl B., PB1748
Mohamed H., S138
Mohamed O., EP1220
Mohamed S., PB1710
Mohamed Adnene L., PB1427
Mohammed A., PB1466, PB1597
Mohammed A., S168
Mohan M., EP559
Mohan S., EP924, PB1713
Mohandas N., EP695
Mohi G., PB1712
Mohr F., S124
Mohty M., S216, S232, S233, S236, S242, EP431, EP1228, EP1238, PB1653
Mohyuddin G. R., EP743
Moia R., S143, EP603, EP624, EP631
Moiraghi B., S153, EP659, EP663, EP665
Moiseev I., EP544, EP770, EP771, PB1612, PB1617
Mojsilović S., EP759
Mokatrin A., S235
Mokhtari S., EP345, EP351
Molano E., EP809
Molero A., EP450, EP907
Molero-Labarta T., PB1495
Moles-Moreau M.-P., EP1176
Molica S., EP624, EP645, EP651
Molina L., EP652
Molina-Arrebola M. A., EP1183, PB1607
Molina Hurtado J. R., PB1788
Molinos-Quintana A., S116
Moliterno A., EP1100
Mollee P., S189
Möller S., PB1740
Møller C. T., EP392
Møller M. B., EP851
Møller P., S134
Møller T., S134
Møller-Palacino N. A., S159
Molnar Z., EP768
Mologni L., EP658
Molteni R., EP1067
Moluçon Chabrot C., S157
Momčilović S., EP759
Momotow J., EP767, EP779
Mompel O., EP563
Monaldi C., EP419
Monesmith T., S251
Monfrini C., EP723
Mongay Soler L., S211
Monge I., EP472
Mongiorgi S., EP753
Monia Z., EP714, EP817, EP831, PB1586
Moñiz Díez A., EP612
Monnet T., EP938
Monsalvo S., EP726, PB1696
Monsef I., EP1187, PB1430
Montalban-Bravo G., S132, S167, EP430, EP1104
Montanaro A., S108
Montañés Gracia Á., PB1821
Montaño A., EP1324
Montaño-Figueroa E., S172
Monteiro A., EP418, PB1767
Monteiro L. P., PB1745, PB1823
Monteiro P., EP488
Monteith B. E., PB1662
Montermini L., S305
Montero G., PB1724
Montes de Oca R., PB1698
Montes de Oca V., EP665
Montesinos P., S131, S138, S311, EP329, EP350, EP352, EP413, EP428, EP438, EP439, EP445, EP447, EP448, EP450, EP455, EP457, EP465, EP546, PB1407
Montez M., EP444
Montillo M., EP650
Montini E., S258, EP1067
Montoro J., EP587, EP1231
Montoro J., EP889
Montoro-Lorite M., EP734, PB1642
Monzón Manzano E., EP1072
Moore J., S179
Moore R., S128
Moorman A., S111, EP317
Moppett J., S111
Mora B., S158
Mora E., EP413, EP670
Mora M. A., EP1346
Mora M., PB1666
Mora Argumánez M., PB1425, PB1450
Morado M., EP712
Morado Arias M., S270, EP692
Moraki M., EP1311
Moraleda J.-M., EP1012
Morales D., PB1692, PB1787
Morales M. D., EP350
Morales M. L., EP408, EP412, EP952
Morales M., S285
Morales Curbelo A., PB1561, PB1798
Morales Sanz D., PB1425, PB1450
Moran S., EP685, EP706
Morando J., S236
Moratalla L., EP612
Moratalla Lopez L., EP823, EP1250
Morawska M., EP631
Mordini N., S243
Mordoh J., EP663
Moreau P., S180, S186, EP963, EP975, EP980, EP981, EP986, EP987, EP988, EP1006, EP1009, EP1031, EP1046
Moreaux J., EP950
Moreira A., EP579, PB1693
Moreno C., S147, EP636
Moreno C., EP809
Moreno D. F., EP1021, PB1642
Moreno D., PB1493
Moreno L., EP408
Moreno R., PB1449
Moreno V., EP612
Moreno Carbonell M., EP578, EP1139, EP1331, PB1821
Moreno Carrasco G., PB1651
Moreno Jiménez G., EP489
Moreno-Jimenez M. G., EP1338
Moreno Vega M., EP670
Morente Constantín E., PB1826
Morgades M., EP329, EP350, EP352
Morgado M., EP837
Morgan G., EP739, EP1259
Morgan K., EP1052, EP1192
Morgan L., PB1753
Mori A., EP668
Mori T., EP1101, EP1105
Morić Perić M., EP819
Morici N., EP1113
Möricke A., EP325, EP342
Morin F., EP540
Morineau N., S212, EP511
Morishia T., EP522
Morishima S., S218
Morisse M. C., S210
Morita Y., EP914
Moritz L., EP736
Morley N., EP523
Moro D., EP665
Moro M., EP616
Morokawa H., S254
Morote M., EP413
Moroz L., EP1349
Morozova E., PB1612, PB1617
Morris D. K., EP1289
Morrison R., EP370
Morrissey C. O., S282
Morschhauser F., S212, S216, EP501, EP506, EP511, EP766, PB1565
Morsink L., EP1284
Mortoglou M., PB1384
Mosa C., EP1155
Moschogianni M., EP774
Moschogiannis M., EP808, EP1272, PB1577
Mosevoll K. A., EP1296
Moshe Y., EP487
Moshkovich O., PB1769
Moskowitz A. J., S208
Moskowitz C. H., S208, EP528
Mosteo L., S278
Mota A., PB1457
Motabi I., PB1609
Motabi I., EP554
Motais B., EP724
Motalkina M., EP1264
Motllo C., PB1649
Motlova E., EP661
Motorin D., PB1402
Motta I., S268, EP843, EP1307
Motta M., EP634, EP650, EP793
Motta M., EP1155, EP1158
Motwani V., S176
Motyko E., PB1491
Motzfeldt I. K. F., EP383, EP399, EP417
Moudiou T., PB1378
Mouhayar E., EP480
Mould D., EP928
Moulis G., EP1125
Moumni I., PB1752
Mouna M., PB1466, PB1597
Mounier M., EP705, EP1143
Moura A., EP1286
Moura P., EP760
Mourad Z., PB1410
Mourafiq O., PB1598
Mous R., EP499
Mozas P., EP872, PB1567, PB1568
Mozessohn L., EP931
Mpatsis I., EP1256
Mpogatsa E., PB1681
Mraz M., S142
Mtvarelidze Z., PB1537
Muckenthaler L., S100
Muckenthaler M., S100, S275
Müdder K., S275
Mueller A. M., EP717, EP748
Mueller L., EP545
Muffly L., EP1224
Mufti G., EP738
Muftuoglu M., EP430
Mughal T., EP427
Múgica-Muñagorri I., EP492, EP574
Muhammad J., EP1046
Muiña B., EP889
Mujeebuddin A., EP594
Mulè A., PB1397
Mulet Lazaro R., S123, EP378
Mullai R., EP815
Müller F., EP887
Müller H., S307, EP764
Müller L., EP409
Müller N., EP547
Müller P., EP1059
Müller-Tidow C., EP436, EP467, EP1245
Mulligan S., EP631
Mullighan C., S106
Mulroney C., EP1235
Munaretto V., EP1201, PB1746
Munder M., S183, EP968

Munger M., EP652
Munir M., S148
Munir T., EP592, EP644, EP649, PB1480
Muniz L. B., EP1039
Muñíz P., EP726, EP870
Muñoz A. J., EP1320
Muñoz J., S205, S213, EP495, EP787
Muñoz Ballester J., EP1250
Muñoz-López D. F., EP1324
Muñoz-Pérez M. I., EP1324
Munshi L., EP485
Munshi N., EP984, EP1009
Munshi P. N., S213
Muntión Olave S., EP907
Munugalavadla V., S148
Munzer M., EP343
Mura R., EP348
Murakhovskaya I., EP685, EP706, EP713
Murali I., EP614
Murciano T., EP336
Murillo L., EP336
Murphy C., EP806
Murphy P., PB1413
Murphy R., PB1769
Murphy T., EP362, EP1082
Murray D., EP1341
Murray J., EP317
Murray M., PB1545
Murru R., EP624, EP645
Murthy V., EP439
Murty S., PB1390
Musat M., EP1025, EP1033
Muscat J., PB1595
Muschick K., EP1209
Musiek A., PB1428
Musso M., EP445, EP651
Mustjoki S., S152, EP580, EP611
Musto P., S182, EP651, EP1188
Musuraca G., EP827, EP1034, PB1581, PB1678, PB1695
Mutahar E., PB1664
Mutez V., S121
Mutlu Y. G., PB1458, PB1699
Mutsaers P. G., S220
Mutvar A., S304
Muus P., EP592
Muzi C., PB1442
Myers J., EP508
Mykhalska L., EP776, PB1691
Myklebust T. Å., EP1022
Mykytiv V., PB1413
Mylin A. K., PB1740
Myllymäki M., EP925
Mylvaganam G., S177
Nadal N., EP898
Nadarajah N., S310
Nadeem O., EP973
Nadeu F., S143, EP858, EP872, PB1567, PB1568
Nadia S., EP817
Nadjet S. A., PB1559, EP683
Nador G., PB1671
Nadwan E., PB1410
Nafady H., EP1118
Nagalla S., EP1337
Naganuma M., EP635
Nagao T., EP667
Nagar S. P., EP992
Nagarajan C., PB1660
Nagle S., EP508
Nagler A., S232, S233, S242, EP431, EP502, EP526, EP716, EP1228
Nagui Rizk D., EP1185
Nagumantry S. K., EP765
Nagy A., EP572
Nagy Z., EP1081
Nagy Jr. B., EP572
Nahi H., S193, EP1237
Nai A., S277, S279, EP1302
Naidu P., S168
Nair B., EP500, EP524, EP633
Nair R., EP881
Nair S., EP977
Najda J., EP1028
Nakagawa M., EP852
Nakamae M., EP1101, EP1105
Nakamura H., EP875
Nakamura R., EP965
Nakamura R., S238, EP345, EP351
Nakamura S., EP942
Nakao S., S171, EP580, PB1476
Nakaseko C., EP667, EP668
Nakayama M., S226
Nakazawa H., EP580
Nakazawa Y., S254
Nakjang S., S105, EP876
Naldini L., S102, S252, S258, S259, EP1298
Naldini M. M., S259
Nallet E., EP938
Nan F.-J., EP1030
Nanaa A., S169, EP908
Nanayakkara S. N., PB1525
Nangia N., S241
Nanni J., EP405
Nannya Y., EP914
Nantel S., EP365
Napier E., EP800
Nappi D., EP1034, PB1581, PB1678, PB1695
Naqvi K., S135, EP909, EP917, EP926
Narancic M., EP826
Narang M., EP969
Narasimha K., EP940
Narayan R., S168
Narayanan S., EP1058
Narayanan S., EP365
Narbaitz M., EP927, PB1534
Narbutas Š., EP1196
Nardelli C., EP1188
Nardi F., EP622
Narkhede M., S224
Narula S., EP1010
Nascimento Costa J. M., EP421, PB1350, PB1630
Naseem S., EP331
Nashwan A., PB1710
Nasone J., EP1282
Nasserinejad K., S149
Nassi L., PB1550
Nasta S., EP800
Nastouli E., EP983
Nastoupil L., PB1565
Natalia M., EP1273
Natalia M., EP781
Natalie Oliva E., S311
Nataraj S., S250
Natesirinilkul R., EP1330
Nath C., EP342
Nath U. K., EP631
Nathan R., EP758
Natsoulis G., EP1074, EP1086
Naumann R., S247
Nava W., PB1438
Navada S. C., EP904
Navajas Laguna C., PB1426
Navarrete M., EP336
Navarro A., EP858, EP872
Navarro R., EP701
Navarro W., EP1074
Navarro Aguadero M. Á., EP374
Navarro-Bailón A., EP631, EP1253, PB1575
Navas Elorza B., EP1089
Naveiras O., EP750
Navickas A., PB1380
Nay D., PB1573
Nazarova E., EP584, EP1112
Nazha A., EP455, EP480
Nazir J., EP1191
Neale A., S299, PB1733
Nebenführ S., EP422
Nedeva A., PB1530
Neelapu S. S., S213, EP791
Negoro E., EP522
Negri Aranguren P., EP659
Negricea R., S222
Negrin R., S253
Nehab A., PB1563
Nehme A., S305
Neil R., EP754
Neill L., EP498
Néji S., PB1592
Neldeborg S., EP392
Nelsen L., EP1171
Nemchenko I., EP674, EP680, EP681
Nemets A., S255
Nemkov T., EP1067
Nerlov C., EP373, EP377
Nero A., EP1206
Nesheiwat T., S190, EP972, EP977, EP978, EP987, EP1049
Nesrine B., EP714, EP817, EP831, PB1586
Nesterova E., EP799
Netea M. G., EP612, EP1067
Nethe M., S163
Neto J. L., S106
Neto Da Rocha M., EP720
Netto Chaer L., EP1251
Neubauer A., EP436, EP438, EP467, EP968
Neuhof A., EP1025, EP1033, PB1665, PB1667, PB1668
Neumann M., EP318, EP375
Neumann T., EP381
Neumeister P., EP521
Neutiyal J., EP463
Neves A., PB1727
Nevill T., EP365, EP931
Newman B., EP470
Newrick F., EP1189
Neziri B., S139
Ng A. S., EP857
Ng A. P., EP433, EP1057
Ng C., S238
Ng M., S120, EP398
Ng S.-B., EP882
Ngan K. W., PB1489
Ngo A., EP608
Nguyen B., PB1639
Nguyen P., PB1354, PB1355, PB1356
Nguyen P., S169, EP908
Nguyen S., EP841
Nguyen T., S226
Nguyen T. V., S187
Nguyen-Khac F., S143, EP898
Nguyen-Quoc S., S243
Ni B., EP520
Ni B.-W., PB1531
Ni J., EP339
Ni Loingsigh S., PB1545
Niazi Y., EP612
Nibourel O., EP385
Nicanor J., EP1286
Nichele I., EP1124, EP1129
Nicholson G., EP1193
Nicod C., EP720
Nicolas Virelizier E., S212, EP511
Nicolau-Travers M.-L., EP416
Nicolay J. P., EP509
Nicolini F. E., S152
Nicolosi M., EP1184
Nidamarthy P. K., S173
Nie D., EP356
Niederwieser D., S236, EP435, EP1106
Nielsen L., EP654
Nielsen L. K., PB1740
Nielsen O. J., EP359
Niemann C. U., S143, EP602
Niemann D., EP436
Niemeier B., EP979
Niemeyer C. M., S199
Nieminen O., EP580
Nierkens S., EP324, EP727
Nieto J. M., PB1819
Nieto M., EP952
Nieto Vázquez A., PB1462, PB1464, PB1794
Nieuwenhuis E., S274, EP582
Nieuwenhuizen L., EP567
Nievas M. V., EP485
Nifenecker M., EP1182
Nihed E., EP714, EP817
Nihel E., EP831, PB1586
Niittyvuopio R., S242, S243, EP1228
Nijhof I., EP1027
Nijland M., S220, EP766, PB1575
Nikiforova A., EP681
Nikiforova K., EP361, EP1241
Nikiforow S., PB1415
Nikitin E., EP631
Nikitin I., EP641, EP653, PB1524
Nikitina T., EP1190
Nikolaev I., EP822
Nikolaeva N., EP762
Nikolaidou B., EP1232
Nikolay M., EP781
Nikolou E., PB1515
Nikulina E., EP558, EP884, EP1071
Nikulina T., PB1402
Nilam J., PB1817
Nilsson J., PB1634
Nilsson L., PB1634
Ning J., EP440
Ninomoto J., S147
Niprapan P., EP1330
Nishihori T., EP536, EP739
Nishikawa H., EP580
Nishikii H., S226
Nishimori H., S174, PB1471, PB1477
Nishimura J.-I., S291, EP594, PB1480
Nissrine J., PB1466
Nitsa E., EP1311
Niu H., EP894
Nixdorf D., EP725
Nizard S., EP1095
NIzzoli M. E., EP793
Nnamani M., S261
Nocentini G., EP1127
Noël N., S215
Noguera N., EP420
Nokhrina E., EP358
Nolan J., EP806
Nolde M., EP896
Nolte M., S163
Nomdedeu J., EP329

Nonell L., EP606
Noni M., PB1829
Nonis A., S219
Nooka A., EP1026, PB1698
Noon K., EP539
Noor S., PB1535
Norasetthada L., EP1330, PB1437, PB1751
Nørgaard M., EP1126
Norin S., EP970
Norman J., EP498
Norman S., PB1759
Normant E., EP638
Nørskov K., S134
Nosaka K., S218
Nösslinger T., EP648
Notarangelo L., EP1158
Notarfranchi L., EP949
Notario C., PB1679
Nour B. A., EP1285
Novak J., EP439, EP473
Novakova Z., EP473
Novaković S., PB1610
Novelli S., EP1231
Noviello M., EP719
Novikov M., EP776
Novikova I., EP1321
Novo A., EP329, EP546
Novo M., PB1448
Novoa A., EP880
Novosad O., EP776, PB1691
Novotny W., S207, EP639, EP789
Nowak D., EP917, EP926
Nowakowski G. S., EP496, EP553, PB1441, PB1451
Nowek K., EP748
Noya Pereira M. S., EP1091
Ntanasis-Stathopoulos I., S280, S287, EP959, EP993, EP1041
Nückel H., EP979
Nuevo I., PB1666
Nuevo López M. I., PB1425, PB1450, PB1692, PB1787
Numerof R., EP1130
Nunes T. D. A., PB1745, PB1823
Nunez Y., PB1545
Nuñez-Torron C., EP1338
Núñez-Torrón Stock C., EP489
Nupponen N. N., EP424
Nuqui P. B., PB1758
Nur E., S314, EP1197, EP1221, PB1762
Nur M., PB1412, PB1580
Nürnberg P., S225
Nurra C., EP459
Nwagha T., EP1344
Nyamutswa L., EP786
Nyegaard M., EP392
Nyffenegger N., EP1204
Nyvold C. G., EP851
Nzouakou R., EP1212
O'Brien D., EP628, EP806, EP885
O'Brien S., S145
OConnell C. L., EP913, EP1075, EP1078
O'Connell N. M., S256
O'Connor O. A., EP506, EP638
O'Doherty R., PB1413, PB1545
O'Donohoe P., EP1258
O'Dwyer K., S117, EP452
O'Dwyer M., EP941, PB1545
O'Hara L., PB1753
O'Hear C., S222, EP503, EP545, PB1565
O'Keeffe D., PB1413
O'Leary H., EP628
O'Mahony D., EP765, EP806
O'Reilly M., EP788
O'Reilly S., EP806
O'Shea D., EP806
O'Sullivan J., PB1719
Oarbeascoa G., EP726, EP1168, PB1696
Oates M., EP610
Oates T., EP760
Obacz M., S164
Obeidat K., PB1710
Oberic L., EP786, EP790
Obermüller J., EP970
Obernauerova J., EP816
Obr A., PB1444
Obuchova T., EP799
Obukhova T., EP357, EP360, EP564, PB1352
Ocheni S., PB1756
Ochi T., EP937
Ochirova O., S286
Ochoa P., EP880, PB1675
Ocio E. M., EP970, PB1655
Oda A., EP942
Oda T., S226
Odaman Al I., EP704
Odchimar-Reissig R., EP904
Oddolo D., S182
Odenike O., EP917, EP926, EP1106
Odero M. D., EP492
Odilov A., EP1325
Oelke M., EP740
Oerlemans S., EP1162
Oeser A., PB1430
Offidani M., EP793
Offner F., S180, EP501, EP530, EP636, EP654
Ofiteru G., EP828
Ofori-Asenso R., EP596
Ofran Y., EP487
Ogata H., PB1703
Ogawa M., S301, EP586, EP590, EP594
Ogawa S., EP580, EP914
Ogbonnaya A., EP934, PB1390
Oggier A., EP750
Oh S., S201, S202, EP1075, EP1080, PB1713
Ohanian M., EP440, EP452, EP464, EP466, EP471
Ohler A., EP786
Ohshima K., S226
Ohta T., EP507, EP1229
Ohtake S., EP667, EP668
Oiwa K., EP522
Ojeras P., PB1415
Okabe M., EP1229
Okabe S., EP903
Okamura D., PB1455
Oki Y., S222, EP519
Okić Đorđević I., EP759
Okoye H., EP1344
Oksenberg D., EP1198
Oksenhendler E., EP1147
Okur Acar S., PB1820
Oláh Z., S303
Olalla Saad S. T., EP1213
Olarte I., EP363, EP824
Olave M. T., EP329
Olave M., EP447
Oleinik Y., EP1264
Olejnik J., EP788
Olesen G., EP359
Olgun N., PB1834
Olid M., EP809
Oliinichenko O., EP776
Oliva E. N., EP566, EP1187
Oliva S., PB1550
Oliva Ramirez A., EP1165
Olivari V., S277
Olivas I., S150
Oliveira A. C., EP631
Oliveira F., EP579, PB1693
Oliveira I. L. O. D., PB1745
Oliveira J., EP579, PB1693
Oliveira M. L., S106
Oliveira M., S278
Oliveira N., EP665
Oliver R., EP514
Oliver-Caldes A., EP734, PB1642
Olivi A., S259
Olivi M., S308, EP474
Olivier C., EP893
Olivier P., EP497
Olivieri J., S289, EP631, EP795, EP815
Olivieri S., S306, EP1152
Olkhovik T., EP1110
Olkhovskiy I., EP647, EP1110
Ols M., S177
Olschok K., S196
Olshan A. S., PB1743
Olshanskaya Y., EP333, EP358
Olszewski A., EP503, EP545
Oltolini C., EP744
Oluwole O. O., S117, S213, EP495
Oluyadi A., S271
Olyslager Y., EP964, EP972, EP1003
Omarova F., EP1260
Omel J., EP985
Omer M., EP828
Ommen H., EP457
Oña R., EP889
Ondrisova L., S142
Onen Goktepe S., EP355, PB1523
Ong C.-K., EP857
Ong D. M., EP429
Onida F., S243
Onizuka M., EP507, EP1229
Ono T., EP667, EP668
Onodera K., S270
Onofre de Oliveira I. L., PB1823
Onofrillo D., EP348
Onozawa M., EP438, EP441
Ons C., PB1371
Ooi M., EP961
Oostendorp R., S247, EP761
Oostvogels R., S220
Opalinska J., EP1001, EP1026
Opat S., S147, EP525, EP783
Opinto G., PB1737
Oppelt Raab A. T., PB1823
Oppezzo P., EP625
Oran B., EP464, EP468
Orchard K., PB1384
Ordentlich P., EP379
Oreglia J., EP1113
Ören H., EP1138, EP1342, PB1372, PB1834
Orero M. T., EP563
Orfanidis I., EP1031
Orfao A., S185, EP329, EP352
Oriol A., S185, S187, S191, S193, S311, EP973, EP980, EP981, EP984, EP988, EP1009, EP1012, EP1021, EP1031
Orlando E., S168
Orlov P., PB1512
Ørntoft A. K., S134
Orozco Colon R. E., PB1651
Orsel J., EP324
Orsini-Piocelle F., S180
Ørskov A. D., EP913
Orsucci L., S219, EP793
Ortan G., EP355
Ortega C., EP625
Ortega L., EP1320
Ortega M., EP336
Ortemann-Renon C., EP694
Ortin X., EP546
Ortiz M., PB1493
Ortiz S., EP665
Ortiz Maldonado V., EP734, PB1642
Ortiz-Ruiz A., EP412
Ortiz Tanchez J., EP318
Ortu La Barbera E., EP491
Ortuño F. J., EP889
Oruc O., PB1705
Osaki H., S129
Osawa Y., PB1703
Osborne W., EP498, EP765
Oscier D., S143, EP631
Osipov I., EP1190
Osman M., PB1454
Osorio S., EP1089, PB1493
Ospedalieri P., EP491
Ossenkoppele G., EP400
Österborg A., EP882
Ostojic A., EP826, PB1539
Ostojic-Kolonic S., EP932, PB1494
Ostrovsky O., EP716
Osunkwo I., S314, EP1206, PB1762
Otaolea L., PB1526
Otasevic V., S307, EP629
Otoukesh S., EP345, EP351
Ottaviani E., S125, EP1079
Ottema S., S123, EP378
Ottesen J. T., S159
Ottmann A., EP318
Ottmann O., S133, S168
Ottone T., EP420
Ouandji S., EP697
Oura M., EP942
Ovsepyan V., EP1112
Owada Y., S226
Owatthanapanich W., PB1419
Owen C., EP599, EP636
Owen R., S181, EP1259
Oymak Y., EP704, EP1316, PB1372, PB1755, PB1820
Ozawa Y., EP668
Özcan A., EP1216, EP1218, EP1316, PB1372
Özcan M., S137, S211
Özdemir G. N., PB1372
Ozdemir H., EP1317
Özdoğu H., EP1216, EP1218, PB1755
Özmen F., EP1244
Oztiz-Romero P., PB1439
Öztürk A., EP1342
Öztürk N., EP1283
Pabst T., EP1242
Pacchiardi K., S126
Pace N., EP545
Pachón V., EP1320
Paciello M. L., EP721
Paciello Coronel M. L., PB1689
Pack R., PB1723
Packman K., EP869
Padayatty J., EP555, EP559
Padilha I., S262
Padron E., PB1394
Pagani A., S277, S279, EP1302
Pagani I. S., S151, EP332
Pagano L., EP394, EP491, EP793
Pagel J. M., S148, S214, EP500, EP633, PB1566
Pagliaro L., S108

Pagliuca A., S283, EP738, EP1276, EP1279
Pagnano K., EP672
Pagoni M., S287, PB1515, PB1516
Paik J., EP861
Paiva A., EP809, PB1616
Paiva B., S184, S185, EP809, EP971, EP1012
Paka P., EP1026
Pakulska U., S164
Palabougiouki M., PB1376, PB1378
Palacio Garcia C., EP336
Palacios F., EP659
Palandri F., EP1079, EP1085, EP1089, EP1092, EP1106, PB1713
Palaska V., EP1044
Palassopoulou M., EP551, EP774
Paley C., EP1092
Palladini G., S189, EP1011, EP1036
Pallini R., S259
Pallotta A., EP571, EP1319
Palma-Barqueros V., EP1131
Palmas A., S182
Palmeira L., PB1483
Palmer J., S202
Palmér L., PB1655
Palmieri S., EP1034
Paloma-Mora M. J., EP574
Palomba M. L., EP500, EP782
Palombi F., EP883
Palomera L., EP1012, EP1021
Palomino L., EP733
Palomino Mendoza D., EP1253
Palomo L., EP889
Palomo-Antequera C., EP812
PalomoLopez N., EP1135
Palumbo A., EP1001
Palumbo G., EP651
Palumbo G. A., EP1021, EP1079, EP1127, EP1140, EP1203, PB1409, PB1765
Pan J., S115, S119, EP1223, EP1294
Pan L., EP639
Pan X., PB1478
Pan X., PB1648
Pan Y.-Y., PB1552
Panagiota V., EP757
Panagiotidis P., EP631, EP773, EP774, PB1560
Panarelli A., EP688
Panayiotakopoulos G., S287
Panayiotidis P., S152, EP439, EP919, EP1153
Panchal A., S146, EP632
Pancham S., S263
Pandya B., PB1405
Pane F., S114, EP651, EP685, EP706, EP827, EP1034, EP1166, PB1581, PB1678, PB1695
Paneesha S., PB1572
Paner A., EP973
Pang A., PB1781
Pangalis G., EP631, EP774, EP808, EP1272, PB1577
Panigada M., EP1067
Panina E., EP376, EP402, EP423
Panitsas F., EP1272, PB1560, PB1681
Panitz N., EP364
Panizo A., PB1534
Pannen K., S196, S197
Pannikodu E., EP1339
Panovska A., S142
Pansa A., PB1357
Panse J., S174, S201, S219, EP595, EP1191
Pantelia D., EP763
Panteliadou A., EP1256
Panter C., PB1753
Pantic N., EP833, EP1326
Pantin J., S238
Paola B., S121
Paola G., EP1089
Paoli C., S158
Papa E., EP883
Papadaki E., EP551, PB1681
Papadaki H., EP588, EP1153
Papadakis S.G., EP588, PB1681
Papadopoulos P., EP1089
Papadopoulos V., EP919
Papadopoulou H., PB1772, PB1812
Papadopoulou V., EP688
Papaemmanouil E., S133
Papageorgiou S. G., EP551, EP774, EP919, PB1516
Papageorgiou T., PB1376, PB1378
Papaioannou D., EP1299
Papaioannou G., PB1368, PB1697, PB1721
Papaioannou M., EP631, EP1153, PB1681
Papajík T., EP552, EP631, EP802
Papakonstantinou E., PB1368
Papakonstantinou I., EP955
Papalexandri A., EP1254, PB1368, PB1378, PB1697, PB1721
Papanagnou E.-D., S280
Papanikolaou A., EP1044
Papanikolaou E., EP939
Papanikolaou X., EP983, EP1047
Papanota A.-M., EP959
Papassotiriou I., S280
Papathanasiou K., EP955
Papathanasiou M., EP1254, PB1697
Papayan L., EP1332, EP1333
Papayannidis C., EP364, EP457
Papayannopoulos V., EP813
Papazian N., EP943
Papoudou-Bai A., EP955
Papoutselis M., EP919, PB1436
Pappa V., S287, EP919, PB1516, PB1681
Parambil J., S103
Paramor M., EP1058
Parasole R., EP348
Pardalis V., EP773, EP774, PB1560
Pardanani A., S169
Pardieu B., S126
Pardo C., EP1167
Pardo Vela A., PB1704
Pardo-Saganta A., EP411
Paredes-Muñoz Y., EP1343
Parekh S., EP936, EP1003
Pareto A. E., EP827, EP1034, PB1581, PB1678, PB1695
Parfenenkova A., PB1612, PB1617
Parini R., S102
Parisi C., EP741
Parisi L., EP785, EP798
Parisi M. S., PB1409
Park C.-J., EP918
Park H.-S., EP918, PB1417
Park J., S250
Park J. E., EP786
Park J.-H., EP918, PB1417
Park S., EP1029
Parker C., EP539, EP1165, EP1169
Parker H., S143
Parmentier A., EP931
Parody R., EP1231
Parovichnikova E., S286, EP357, EP360, EP361, EP756, EP1241, EP1260, PB1785
Parquet N., EP540
Parreira H., EP820
Parreira J., EP807
Parrish J., EP881
Parviz M., EP602
Parys W., EP566
Pasanen A., EP856
Pasanisi J., S126
Pascal M., EP734, PB1642
Pascale S. P., PB1460
Paschka P., EP463
Pasciolla C., EP491
Pascual Izquierdo C., EP1132
Pasi K. J., S256
Pasin F. M., EP1313
Pasquale R., EP1099
Pasqualin D., EP550
Pasricha S.-R., EP1057
Passamonti F., S158, EP1085, PB1702
Passannante M., EP459
Passweg J., EP748, EP1228, EP1242
Pastoors D., EP378
Pastushenko I., EP776
Pastushenko Y., EP557, PB1691
Pasvolsky O., EP1247, PB1528
Patanè M., S259
Patel A., EP498
Patel A. R., PB1571
Patel A., EP1136
Patel B., S167, EP596
Patel F., EP904
Patel K., EP1210
Patel K., EP464, EP468, EP1104
Patel K., PB1566
Patel K., PB1463
Patel M. R., EP500, EP633
Patel N., PB1671
Patel N., S168
Patel P., S290, S291, S312, EP689, EP709, EP1180
Patel P., EP984, EP1009
Patel P., S145, S148
Pater J., PB1662
Paterra R., S259
Paterson N., EP1199
Patkar N., EP958
Patnaik M., S169, EP910, EP1106
Patón C., PB1369
Patra-Kneuer M., EP879
Patriarca A., EP603, EP685, EP706, EP1077, EP1085, EP1089
Patriarca F., S182, EP1237
Patricia A. M., EP701
Patrinoiu O., EP828
Patrinos A., EP1153
Patte C., S221
Patten P., EP649
Patti C., EP651, PB1397
Pattipaka T., EP1222
Paul D., EP1133
Paulos Mesquita I., EP1032
Paulsson B., EP1107
Paulus A. C., EP896
Paumard E., EP546
Paumard Rodríguez E., PB1788
Pavão C., EP579, PB1693
Pavlakis G. N., S287
Pavletic S., S239
Pavlicek P., EP1042
Pavlisa G., EP826
Pavlistova L., EP948
Pavlovsky A., EP625
Pavlovsky C., S153, EP663, EP665
Pavlovsky M., EP625, EP663, EP665
Pawarode A., EP1235
Pawlyn C., EP1259
Paz Coll A., EP670
Pazzaglia M., S125
Peceny R., S183
Peczynski C., EP431
Pedersen P. T., PB1740
Pedersen R. K., S159
Pederson D., S103
Pedro C., PB1383
Pedrosa C., PB1457
Peerlinck K., S256
Peffault de Latour R., S157, S172, S174, S301, EP594, PB1471, PB1476, PB1477, PB1481
Peggs K., EP788
Pêgo A., EP848
Pegtel D. M., S225
Pei F., EP1303
Pei L., S193
Pei X., EP728, PB1803
Peixeiro R., PB1399, PB1457
Peixoto M., S248
Pejsa V., EP886, PB1494
Pelagiadis I., EP1146, PB1351, PB1468
Peleteiro Raíndo A., PB1734
Pellacani A., EP455
Pellegrini C., EP543
Pellegrino R. M., EP384
Peloquin F., PB1753
Pelosi E., EP420
Pelouchová J., EP1196
Peluso T., EP988
Pelzing M., EP1210
Pemmaraju N., S113, S200, EP427, EP430, EP464, EP468, EP1078, EP1096
Peña C., PB1675
Peña E., PB1370
Peña M., EP659
Peña Muñoz F., EP1253
Penack O., S241
Penalva M. J., EP546
Peñarrubia M. J., S293
Pender E., EP1292
Peng C., EP548
Peng J., S297
Peng W., EP787
Peng X., EP1223
Peng X., EP565
Peng Y.-L., EP922
Penka M., PB1677
Penneroux J., S126
Pennese E., S219
Pensato V., EP753
Penta De Vera D'Aragona R., EP478
Pentidou A., PB1436
Pepe A., EP1309, EP1313, EP1314, PB1602, PB1770, PB1771, PB1810
Peppe J., EP1074, EP1086
Pepper C., EP644
Peppercorn D., PB1671
Pepperell D., S282
Pequeño Luevano M. P., PB1438
Peragine N., EP624
Perales M.-A., S241
Perdibon M., PB1746
Perego R., EP658
Pereira A., EP630
Pereira C., PB1671
Pereira J., EP818
Pereira M., PB1616

Pereira S., EP820
Pereira V., PB1727
Pereira-Reis J., S278
Perek S., EP475
Perekhrestenko T., PB1508
Perera K., EP628, PB1413
Perera M., EP806
Perera R., EP711
Perera T., PB1596
Perera Alvarez M., EP1116, PB1798
Perera Alvarez M. A., EP1116, PB1495
Perez A., EP450
Perez A., EP1231
Perez C., EP809
Pérez E., EP1234
Perez J., EP1161
Perez J. J., S185
Perez M., EP665
Pérez P., EP563
Pérez-Amill L., PB1642
Perez-Callejo D., EP501
Pérez-Corral A., EP726
Pérez Encinas M. M., EP670, EP1091, PB1734
Pérez-Galán P., EP872, PB1567
Pérez-Gómez A., EP1324
Perez Gonzalez J. A., PB1599
Pérez González S., S293
Pérez-Jacobo F., EP832
Perez-Lamas L., EP1338
Pérez -León S., EP1149
Perez Lopez E., EP1253
Perez Lopez R., EP670
Pérez Martínez C., S293
Pérez Martínez M., EP374
Pérez-Moyano R., EP1183
Pérez Persona E., EP496
Pérez-Raya M., EP1324
Perez Rus G., EP1132
Pérez-Simón J. A., S237, EP447, EP450, EP1237, PB1407
Pérez-Warnisher T., EP809
Pergantou H., PB1829
Peric Z., EP826, EP1263, EP1287
Perifanis V., PB1807
Perini G., EP550
Peris I., EP492
Periša V., PB1684
Periselineris J., S283
Peritore G., EP1314
Perkins A., PB1723
Perkins P., EP508
Perl A. E., S135, EP437, EP438, EP441, EP443, EP448
Perolla A., PB1502, PB1628
Peron M., EP1176
Perotta E., EP634
Perro M., EP938
Perrone V., PB1766
Perrot A., S180, S186, EP987, EP995, EP999
Perrotta S., S101, EP1307, EP1310, EP1158
Perruccio K., EP1238
Perry C., S255, S284, S285, EP502
Persky D., S214
Persson E., EP1191
Pertine B., EP665
Perusini A., EP927
Pesce E. A., EP543
Peshnyak J., EP1349
Pessach I., EP774
Peter B., S198, EP902, EP1066, EP1068, EP1070
Peter J., S175
Peter R., EP1242
Peter W., EP853
Peterlin P., S138, EP917, EP926
Peters F. S., S141, EP608
Petersen S. L., EP359
Petinati N., EP756
Petiti J., EP661
Petkova N., PB1530
Petrenko A., S286
Petrocca F., EP1009
Petrone A., EP1158
Petrone A., EP1155
Petrone M., EP1203
Petrov A., PB1402
Petrov S., PB1491
Petrova A., EP674, EP680, EP681
Petrova T., EP1190
Petrucci L., EP1184
Petruzzellis G., EP815
Petsa P., EP1272
Pettersson H., S158
Pettikiriarachchi A., EP1057
Pettinato M., S277, EP1302
Pettine L., EP1099
Pettirossi V., S227
Pettit K. M., S201, EP1074, PB1408
Pettitt A. R., EP610
Petzer A., EP971
Peulen J., S170
Peyre M., EP790
Pezzella L., EP622
Pezzetti L., PB1442
Pezzullo F., EP1314
Pezzullo L., EP1170
Pfeilstöcker M., S198
Pfirrmann M., S152
Pham S., S222, PB1565
Philippar U., EP869
Philippe L., S215
Philippet P., EP343, EP1208
Phinyo P., EP1330
Phipps A., EP610
Phua C., PB1662
Phuoc V., EP536
Pianese J., EP1127
Piasecki J., EP747
Piatek C., S301
Piazza F., EP645, EP795, EP855, EP1053, PB1633
Picardi M., S205, EP491, EP1166
Piccini M., S114
Piccione E., EP501
Piccone C., S260
Pichler P., EP496
Piciocchi A., EP624, EP793
Pickles T., PB1554
Picton L., S253
Pidala J. A., S238
Piechotta V., S281, EP1045, EP1187, PB1756
Piedimonte M., EP491
Piepenbroek B., S243
Pierce A., EP388
Pierce S., EP464, EP468, EP676
Pierdomenico F., EP445
Pierie C., EP631
Pierini A., EP1288
Pierres M., EP995, EP999
Pieters R., EP538
Pietra D., EP1098
Pietrangelo A., EP1305
Pietrasanta D., EP645, EP650
Piette C., EP343
Piga A., S101, EP1304, EP1305, EP1306, EP1307, EP1312, PB1808
Pigaditou A., PB1516
Pigneux A., S138, EP451, EP456, EP457, EP482, EP909
Pika T., EP986, EP1042
Pike A., EP592
Pike A., EP430
Pileri S., EP543
Pilheden M., EP406
Pillai R., EP351
Pillarisetti K., EP967
Pillon M., S221
Pilz F., S245
Pilz V., EP764
Pimenta J., EP1274, EP1290
Piñana J. L., EP350, EP1231
Pineda I., EP809
Pinegina O., EP822
Ping J., EP782
Pinho Peixeiro R., EP1281
Pinho Vaz C., EP1274, EP1281, EP1290, PB1789
Pinilla J., EP536
Pinilla-Ibarz J., S145
Pinter-Brown L., EP509
Pinto A. L., EP488
Pinto R., EP488, PB1474
Pinto V., EP688, EP1307
Pinto-do-Ó P., S248
Pinzón Mariño S. F., EP1139, EP1331, PB1821
Piolatto A., PB1808
Pioltelli M. L., PB1442
Piontek M., EP389
Piontek T., EP1026
Piovan E., EP316
Pipe S., S256, EP730
Piperidou A., EP1272
Piperno A., EP1307
Piras F., EP1067
Piriyakhuntorn P., EP1330, PB1437, PB1751
Pirotte M., EP844
Pirroni S., EP1298
Piršić M., PB1684
Pirvu C., EP828
Pisani F., S219
Piskac Zivkovic N., S304
Pistoia L., EP1313, EP1314, PB1602, PB1770, PB1771, PB1810
Pita M., S314, PB1762
Pitkänen E., EP856
Pitrolo L., EP1307
Pittrow D., EP1340
Pivonello R., EP1166
Pizzano U., S289
Pizzi M., EP1124, EP1129
Pizzi S., S258
Pizzolo G., EP645
Pizzuti M., S154, PB1460
Plaks V., S213, EP791
Plantaz D., EP343
Plantinga M., EP727
Plaschkes H., EP514
Plat G., EP343
Plata E., EP551, EP773, EP774, EP808, EP1272, PB1560, PB1577
Plate A., EP1192
Plattel W. J., EP766
Platzbecker U., S161, S165, S202, S243, EP431, EP435, EP436, EP458, EP896, EP897, EP910, EP915, EP917, EP920, EP926, EP1081, EP1106, PB1619
Plekhanova O., EP358
Plesa A., EP407, EP432, EP1262
Pluess M., EP938
Pluetschow A., S209, EP767
Pochard C., EP701, EP950
Pocock C., S311, EP428, EP445
Pocock R., EP797
Pócsi M., EP572
Podar K., EP971
Podoll T., EP1073
Podoltsev N. A., EP437, EP438, EP448
Poh C., EP731
Poh Z. S., EP857
Pohlkamp C., S310
Poinsot G., EP1095
Pokala S., EP807
Polackova P., PB1677
Polese F., EP1108
Poletaev A., EP576
Poliatskin I., EP1264
Polimeno A., EP405
Polinder S., EP567
Politi L., S219
Politou M., S287, EP773
Poll A., EP327
Pollo B., S259
Pollyea D. A., EP429
Polo B., PB1449
Polu K., S238
Polverelli N., EP1079
Polyanskaya O., S138
Polzer A., EP879
Pomares H., EP889
Pomilio A., EP695
Pönisch W., EP971
Ponomareva N., EP358
Pontesilli S., S102
Ponticorvo S., EP1310
Pontikoglou C., EP588, EP919, EP1153
Ponzoni M., S219, S249
Poon Z., EP905
Poort V., EP335
Popa M. L., EP383, EP396, EP403
Popat R., S187, EP983, EP1001, EP1026, EP1046, EP1047, PB1661
Popat U., EP464, EP468
Popescu M., EP828
Poponina E., EP1347, PB1496, PB1836
Popov A., EP333, EP358
Popov V. M., EP631, EP828
Popova B., EP788
Popova M., S286, EP556, EP822
Popova N., EP1260, PB1785
Popplewell L., S210
Popradi G., EP353
Poquioma E., PB1362
Porcu P., S218
Porfirieva N., EP1190
Porkka K., S168, EP396, EP428
Porrino-Herrera C., PB1607
Porro Camarero A., EP1345
Porse B. T., EP373
Portell C., EP783
Portell-Rigo I. M., PB1607
Porter J. B., S101, S257, S266, S271, EP692, EP1301, EP1304, EP1306
Porter R., EP642
Porto G., S278
Portugal R., EP837
Posch F., EP521
Positano V., EP1313, EP1314, PB1770, PB1771
Pospelova T., EP778, PB1389, PB1512, PB1611
Pospisil Z., EP473

Pospisilova S., S142, S143
Pospíšilová D., EP691
Pospíšilová Š., EP631
Posthuma E. F., S155, EP637, EP640, EP796, EP803, EP804, EP1020, EP1162
Posthuma W., S149, EP434
Postma M., PB1676
Potamianou A., EP987
Potenza A., S252
Potenza L., EP612, EP617
Potluri J., S137, EP444, EP909, EP1078
Potluri R., S311
Potluri S., S122
Pottegård A., S296
Potter V., S283, EP738, EP1276, EP1279
Potthoff K., EP979
Potuckova E., EP320
Poudel G., EP332
Pouleau B., EP938
Pouli A., EP919
Pour L., EP816, EP954, EP963, EP970, EP974, EP976, EP1028, EP1042, PB1655
Powell Jr. D. J., EP721
Power M., EP365
Poyser J., EP717
Poza M., EP708
Pozas M., EP408
Poziopoulos C., EP774
Pozzi G., EP1061
Pradat Y., S133
Prader F., PB1777
Prahladan M., EP555, EP559
Pramod P., PB1541
Prasad V., EP743
Prasannan P., EP857
Prassolov V., EP426
Prassopoulos V., EP774, PB1560
Pratt G., S181
Pratz K. W., S137, EP437, EP444, EP909
Pravato S., EP645
Pravdic Z., EP833, EP1326
Pregno P., S154, EP673
Preisinger C., EP387
Prejzner W., EP1077, EP1081
Preložnik Zupan I., EP1109
Prem S., EP1261
Premji S., EP881
Premoli E., PB1766
Premuzic V., EP561
Prenovitz R., S177
Presa M., EP1167
Preudhomme C., S128, EP385, EP407, EP906
Prezioso L., EP491
Prideaux S., EP797
Priego V., EP643
Prikhodko O., PB1465, PB1822
Prince H. M., S186
Prinjha R. K., S129
Prior T., S191
Pro B., EP506
Prochazka K., EP521
Procházka V., EP552, EP802
Prodel M., EP995
Proell J., EP897
Proenca-Modena J. L., EP1213
Proietti M., EP843
Prósper F., EP411
Prósper Cardoso F., EP907
Protopappa M., EP1153
Prouty A., EP861
Prugova V., EP1110
Prymak S., PB1353
Psaltopoulou T., S280
Psyllaki M., PB1515
Ptáček J., EP552, EP802 Ptasinska A., S105
Pu J., PB1480
Pucciarini A., S227
Puccio G., EP1155, EP1158
Puchol A., PB1799
Puerta Puerta J. M., PB1704
Puertas B., EP1234
Pugacheva J., PB1650
Pugaciute B., EP486
Pugliese G., EP459
Pugliese N., EP1079, EP1166
Puglisi F., EP1004
Puguet G., EP1149
Puhlmann M., EP506
Puig N., S185, EP985, EP1012
Puiggros A., S143, EP606, EP616, EP631
Puissant A., S126
Pujol M., EP665
Pukrop T., S219
Pulanić D., EP573, EP826, EP1263, PB1539, PB1605
Pulczynski E., S219
Pule M., EP788
Pulikkottil A. J., S124
Pullarkat V., S137, EP345, EP351, EP442, EP909
Pullon H., S282
Pulluqi P., PB1502, PB1628
Pulsoni A., EP793, EP860
Punatar S., EP958
Punwani N., PB1706, PB1717
Punzalan R., EP590
Purcell S., EP371, EP671, EP672, EP684
Purev E., PB1565
Purmessur R., EP1164
Purtill D., PB1393
Pushkareva T., EP762
Pushkaryova T., PB1366
Putti M. C., EP348, EP1307
Puzzovivo A., PB1550
Pylypenko H., EP974, EP976, EP1076
Pyne N., S106
Pyne S., S106
Qayum N., EP503
Qazilbash M., EP1235
Qi K., EP977, EP785, EP798, EP969
Qi M., EP969, EP1024
Qi R., EP877
Qian C., PB1593
Qiannan S., EP1300
Qiao W., EP440
Qin L., EP1120
Qin X., S189
Qin Y., EP518
Qin Y., EP669
Qin Y.-Z., EP347, EP656, EP1226
Qiu J., EP548
Qiu L., EP560
Qiu L., EP792
Qiu L., EP742
Qiu L., S194, EP792, PB1670
Qiu Y., EP1031
Qiuling W., EP951
Quach H., EP976, PB1660, PB1698
Quaglia F. M., EP645
Quaglino P., PB1428
Quaini F., S108
Quaresima M., EP1307
Quarta A., PB1770, PB1810
Quehenberger P., S302
Queipo de Llano M.-P., EP329, EP352, EP546
Queiroz S., EP1054, PB1631
Quek R. G. W., EP1163
Quéré S., EP1171
Quick D., EP1019
Quijada-Alamo M., S140
Quinn F., EP628, EP806, EP885, PB1579
Quinn J., EP806, EP1292
Quinquenel A., EP652
Quintana L. F., PB1642
Quintanar T., EP1320
Quintanilla-Martinez L., S124
Quintarelli C., EP1203
Quintela M., S278, EP1281
Quirós C., EP809
Quiroz Cervantes K. S., EP1089
Qun Wu J., EP599
Quon D., S256
Quota A., EP1307, PB1810
Quotti Tubi L., EP855, PB1633
Qureishi M., EP830
Ra S., EP731
Raab A. T. O., PB1745
Raab M., EP968
Raab M.-S., S190
Raanani P., S288, EP655, EP1060, EP1247, PB1528
Rab M., S274
Rabe A., EP1090
Rabin K., EP317
Rabin N., EP983, EP1047, EP1189
Rabuñal Martinez M. J., PB1734
Racetin A., PB1605
Rachid K., PB1374
Rachid M. M., EP604
Rácil Z., S281, EP473
Radford J., S205, EP518, EP539
Radford-Weiss I., EP898
Radhachandran A., EP911
Radhika R., PB1484
Radia D., S201
Radić Krišto D., EP932, PB1684
Radici V., EP815
Radman I., EP561, PB1539, PB1605
Radocha J., EP816, EP1042
Radová L., EP954
Radujkovic A., S243, EP1245
Raetz E., EP317
Raffoux E., S126
Raffy L., EP497
Ragaini S., EP860
Raggi L., S249, S268
Raguideau F., EP999, EP1095, EP1207
Rahhal M., PB1380
Rahmoune N., EP1255, PB1629
Rai R., EP904
Raihane B. L., PB1373, PB1374
Raimondi A., S176, EP859
Raj K., EP738
Rajak J., S199
Rajala H., EP580
Rajangam K., PB1415
Raje N., S192, EP984
Rajeeve S., EP570
Rajic J., EP833
Rajkovic-Hooley O., S314, PB1762
Rajkumar S. V., EP975
Rajnics P., PB1641
Raju A., EP934
Rak J., S305
Rakhit C., EP711
Ram R., S255, S284, S285
Ramachandran A., EP731
Ramakrishnan A., S239
Ramakrishnan P., EP1173
Ramasamy K., EP994, PB1653, PB1671
Ramassone A., EP604
Rambaldi A., S112, S114, S158, S240, S241, EP1009, EP1089
Ramchandren R., S205
Ramenghi U., EP1158
Ramírez A., PB1675
Ramírez J., PB1675
Ramirez M. J., EP670
Ramírez M., PB1369
Ramírez López A., PB1518
Ramírez-Maldonado V., EP1131
Ramírez Páyer Á., PB1507
Ramos C., EP363, EP824, EP1335
Ramos F., EP447, EP889, EP893
Ramos R., EP1172
Ramos T., S253
Ramos-Arrieta M., EP832
Ramos-Campoy S., EP616
Ramos Castro C., EP1072
Rampal R., EP1075, EP1077, EP1080, EP1085
Rampi N., EP744
Rampotas A., EP649, EP797
Rana P., EP331
Ranchon F., PB1546
Rand V., EP876
Randi M. L., EP1108, PB1601
Rane L., EP417
Rangel D., PB1445
Ranghetti P., EP634
Rani L., S143
Ranjan S., S311
Rank C. U., EP359
Rao N., EP869
Rao S. S., EP642
Raos M., PB1539
Raoudha M., PB1373
Raoutha M., PB1374
Rapado I., S143, EP408
Rapezzi D., S154
Raponi S., EP624
Raposo B., S106
Raposo J., EP354, EP1032, PB1449
Raposo Puglia J. Á., PB1584
Raptis A., EP973
Rasche L., S175
Rasheed H., PB1410
Rasheed W., EP1276
Rashid K., PB1827
Rasi S., EP603
Raskin S., EP502
Rasko J. E., S257
Rasouli M., EP382
Rassenti L. Z., S140
Rassi A. B., PB1745
Rassidakis G., EP882
Rassmussen S., PB1709
Rastgoo N., EP452, EP643, PB1391
Ratjen K., EP853
Rattanathammethee T., EP1330, PB1437, PB1751
Rattarittamrong E., EP1330, PB1437, PB1751
Räty R., EP863
Rauh J., EP979
Rauner M., EP896
Rausch C., EP440, EP466
Rausch T., EP853
Raut M., EP764
Rauthan A., PB1469
Ravandi F., S113, S132, S136, S167, EP367, EP428, EP430, EP440,

EP445, EP455, EP464, EP466, EP468, EP471, EP676
Ravano E., PB1442
Ravasio G., S292
Ravelli E., PB1442
Ravichandran S., EP1000, EP1011, PB1644
Ravindranath Y., EP696, EP1194
Raviwong J., EP1017, EP1018
Ravn Landtblom A., EP1088
Rawat V., S124
Rawi R., PB1813
Rawicki M., EP1243
Rawstron A., EP644
Rayani S., EP1010
Rayford A., EP463
Rayhane B. L., PB1371
Raynov J., PB1530
Raza A., EP910, EP1106
Razakariasa F., EP1145
Razzak A., EP835
Rchid K., PB1373
Re A., EP449, EP543
Re F., EP463
Reagan P. M., EP787
Rebelo A., EP820
Recasens Flores M. D. V., PB1821
Recchiuti A., EP695
Récher C., S137, EP416, EP438, EP456, EP482, EP909
Recht M., S256, EP730
Reda G., EP631, EP634, EP645, EP1099
Redder L., PB1740
Reddy E. P., EP904
Reddy N., S214
Redfearn J., EP1052
Redman M., EP731
Redondo P. C., EP1161
Redondo-Izal A. M., EP492, EP574
Reece D., EP989, EP1009, EP1019, EP1038, PB1643, PB1662
Rees D., EP711
Reeves B., PB1720
Regadas L., PB1399, PB1457
Regalado-Artamendi I., PB1696
Regazzo G., EP883
Rege-Cambrin G., S154
Regenyi E., S120, EP328, EP398
Reger R., PB1543
Reggiani G., EP1201, PB1746
Regnault A., EP1171
Rêgo D. D. F. B., PB1745
Reguera-Iglesias J. M., EP1324
Reguera-Ortega J. L., S237
Rehn J., EP321
Reid E., EP643
Reig G., PB1799
Reikvam H., EP1296, PB1606
Reiman A., EP986, EP989, EP1038, PB1643
Reinhardt C., EP431, EP1228
Reinhardt D., EP398
Reinhardt H. C., S183, S242, S243
Reinikainen K., EP940
Reinke S., S225
Reinoso Segura M., EP1237
Reiser M., EP1157
Reitan J., EP786
Reiter A., S201, S203, EP1065, EP1070, EP1087, EP1106, PB1723
Rejeski K., EP547
Rejtő L., PB1641
Relf J., EP501
Relvas L., EP700
Remaggi G., PB1675
Remberger M., EP1261
Remedi V., EP625
Reményi P., S233
Ren J., PB1786, PB1795
Ren K., EP985
Ren S., S228, EP334, EP862, EP864, EP865, EP866, EP868, EP874
Ren X., EP581
Ren X., EP377
Ren Y., EP891, EP923
Ren Y., EP1271, EP1303
Renaberg T., S134
Renault M., EP1262
Rener K., EP575
Renne S., PB1602, PB1770
Repchenko E., EP1321
Requena G., EP1122
Requirand G., EP950
Resar L., EP1100
Reshef R., S213
Restaino G., EP1313
Restivo G. A., EP1158
Restrepo P., EP936
Restuccia F., EP491
Retiere C., S162
Reusing S., EP326
Reuter C., EP689
Revicki D. A., EP1182
Revilla N., EP1131
Reyes-Montecillo M. P., PB1600
Reyes-Palomares A., EP412
Reynaud C.-A., S295
Reynolds J., S282, EP433
Rezende M. J. D. A., PB1745
Rezo Vranjes V., EP826
Rezvani A., EP1224
Riaz I., EP1015
Ribadeneira M., EP1202
Ribakovsky E., S255, EP502
Ribeiro D., S106
Ribeiro M. L., EP700
Ribeiro P., EP418, EP820, PB1726
Ribera J., EP329, EP352, EP546
Ribera J. M., EP329, EP350, EP352, EP546
Ribersani M., EP1307
Ribourtout B., EP898
Ribrag V., EP790, PB1569
Ricart A., EP638
Riccardi V., EP695
Ricchi P., EP1305, EP1307, EP1309, EP1314, PB1810
Rice W., EP452, EP643, PB1391
Richard S., EP936
Richards M. K., EP341, EP590
Richardson A., S258
Richardson H., PB1662
Richardson P., S186, S187, EP963, EP970, EP973, EP974, EP975, EP976, EP988, PB1655, PB1698
Richter D., S127
Richter J., S152
Richter J., EP936
Richter K., EP318, EP375
Rico L., S293
Rider D., EP846
Ridgeway J. A., EP909
Riedel A., S175
Riedell P. A., S210, EP516
Riedl J. M., EP521
Rieger K., EP717
Rienhoff H., EP1074, EP1086
Riera T. V., S176
Ries-Fecourt C., EP938
Rietveld J., EP608, EP873
Rieu J.-B., EP456
Rifkin R., EP969, EP985
Rifkin-Zenenberg S., S261
Rigano P., PB1810
Riger T., EP358
Righi R., PB1602, PB1771
Rigoli L., PB1771
Rigolin G. M., S143, EP624, EP631, EP645
Říhová L., EP954, PB1677
Riley K., EP592
Rim J., PB1371
Rinčić G., PB1684
Rincón C., EP809
Ringeleviciute U., EP486
Rinne M., S168
Río P., EP721
Rio-Machin A., PB1383
Ríos O., PB1675
Ríos R., S185, EP1012
Rios Rodelo M. R., PB1438
Rios Rull P., PB1679
Rioufol C., PB1546
Risbo N., EP1126
Risinskaya N., EP558, EP884, PB1352, PB1414
Risitano A., S174, EP585, EP589, EP651, PB1476, PB1477, PB1480, PB1481
Risse M.-L., EP980, EP981, EP986, EP1006
Risueño A., S131
Risueño R. M., EP415
Ritchie D., S236, EP1243
Ritchie E., S135, EP1078
Ritgen M., S146, EP632
Riu G., EP472
Riva A., EP1313, PB1602
Riva E., PB1675
Riva M., EP795, EP1053
Riva M. E., EP665
Riva M., PB1627
Rivas S., PB1724
Rivas-Delgado A., EP872, PB1567, PB1568, PB1575
Rivas Pollmar M. I., EP1072
Rivera J., EP1131
Rivero A., EP872, PB1567, PB1568
Rives S., S116, EP734
Riviere E., S295
Rivière I., S250
Rivière J., EP761, EP896
Rivis S., EP1298
Rivolti E., EP1016
Rizio A. A., EP1179, EP1219
Rizo A., EP910, EP1106
Rizzari C., EP342, EP348
Rizzi L., EP997
Rizzieri D., EP427
Rizzo L., PB1627
Rizzo M. G., EP883
Rizzo O., PB1657
Roa M., PB1675
Robaina Sanchez E., EP1116
Robak P., EP988
Robak T., S145, EP636, PB1504
Robbins A., EP1147
Robert H., EP1069
Robert N., EP950
Roberti D., EP1307
Roberts J., EP1058
Roberts K., S106
Robin M., S243
Robinson A., EP555
Robinson N. J., PB1405
Robinson S., PB1719
Roboz G., S131, S167, EP428, EP443, EP445
Robrecht S., S144, S146, EP632
Robu M., PB1582
Roccaro A., EP449
Rocco S., EP1034
Rocha I., EP820
Rocha V., EP818, EP1251
Rocha Silva P., EP488
Rochate D., EP579, PB1693
Rocino A., EP651
Rockich K., PB1706, PB1717
Roddie C., EP498, EP788
Rodgers C., PB1671
Rodrigo J., EP365
Rodrigues C., EP1274, EP1290
Rodrigues-Lima F., S162
Rodríguez A., PB1828
Rodríguez Á., EP1234
Rodriguez G., PB1675
Rodriguez G., EP1231
Rodríguez J., EP606
Rodriguez P., EP606
Rodríguez-Alén A., EP1131
Rodríguez-Arbolí E., S237
Rodríguez Barquero P. A., EP1327
Rodriguez-Calvillo M., EP574
Rodríguez-García A., EP408, EP412
Rodriguez Gil M. A., EP823, EP889
Rodríguez González M., PB1651
Rodríguez Gutiérrez J. I., PB1526
Rodriguez-Gutierrez-Macias J. I., EP447
Rodríguez Lefler C., EP578, EP1139, EP1331, PB1821
Rodriguez-Lobato L. G., EP734, PB1642
Rodríguez Macías G., EP1168
Rodriguez-Medina C., EP447, EP546, PB1407
Rodriguez-Meira A., EP1058
Rodriguez-Otero P., S185, S187, S191, EP973, EP984, EP1001, EP1009, PB1698
Rodríguez-Rivera M., EP606, EP616
Rodriguez-Santiago B., EP606
Rodríguez-Sevilla J. J., S303, EP612
Rodríguez-Torres N., S237
Rodríguez Veiga R., PB1407
Rodriguez-Veira R., EP450
Rodríguez-Vicente A. E., S143
Rodríguez-Vigil C., PB1821
Rodríguez Villa A., PB1788
Rodstrom J., PB1709
Rodts U., PB1742
Roeder N., EP846
Roeker L., EP633, EP643
Roeloffzen W., EP1011
Roemer M., S225
Rogacheva Y., EP556, EP822
Rogozhkina D., PB1785
Rohrlich P., EP343
Roig M., EP563
Rojas S. V., EP757
Rojas Contreras R., PB1788
Rojo-Vidal C., EP1343
Rolfs C., S161
Roliński J., EP1280
Röllig C., EP375, EP436, EP448
Román L. G., EP1234
Roman Molano L. G., EP1253
Romanenko N., EP836
Romano A., EP1004
Romano F., EP1158
Romano L. G., EP567
Romano Gargarella L., EP645
Romanova M., PB1421
Romanus D., PB1639

Romashevskaya I., EP1321
Romeo D., S292
Romeralo-Calvo L., EP1343
Romero A., EP612
Romero Aguilar A., EP823
Romero Gónzalez M. D. M., PB1722
Romero Maciel M. A., EP665
Romero Marquez S., S247
Romić I., PB1684
Romito F., PB1737
Rompietti C., S108, EP620
Ron N., EP1060
Ronan R., EP784
Roncevic P., EP561, EP826, EP1263, PB1539
Ronchi Corrêa J., S106
Roncon S., EP1281, PB1789
Ronconi S., EP860, EP1034, PB1581, PB1678, PB1695
Rondelli D., EP736
Rondogianni P., EP774
Rondogianni P., PB1560
Rönnstrand L., EP406
Roos Weil D., EP652
Roost Clausen M., EP499
Ropero P., PB1819, PB1821
Roque A., EP1102, EP1114, EP1121
Roque D., EP421, EP630, PB1350, PB1630
Rosas E., EP1335
Rosati E., EP620
Rosati M., S287
Rosato B. E., S276, EP688
Rose S., S203
Rosell A., EP670
Rosen J.-P., EP509, PB1428
Rosenberg E., EP716
Rosenhain M., EP927
Rosenquist R., S143
Rosenwald A., S175
Rosenzweig M., S189
Rosin V., PB1431, PB1432, PB1446, PB1447
Rosiñol L., S185, S193, EP980, EP981, EP1012, EP1021, PB1642
Rosko C., PB1780
Ross D. M., S151, EP1074, EP1086, PB1723
Ross T., S177
Rossetti J., EP1074, EP1086
Rossi A., S188, EP1002, EP1008
Rossi C., S215, EP705, EP1143
Rossi C., S269
Rossi D., S143, EP603, EP648, EP650
Rossi F. G., EP1099
Rossi G., S295
Rossi G., EP449, EP506, EP1089
Rossi M., EP651
Rossi M., EP394
Rossignol J., EP1095
Rosso R., EP1307, PB1810
Rosta A., EP768
Rosti G., S153, S154, EP673
Roth A., EP896
Röth A., S174, S219, S290, S291, S301, S312, EP595, EP689, EP1179, PB1480
Rothenberg-Thurley M., EP896
Rothman J. A., S270
Rothman J., S238
Roti G., S108
Rotondo F., EP1184
Rotta M., S239, PB1415
Rottek J., EP768
Roubakis C., PB1681
Rouce R., EP341
Roufosse F., EP1087
Rouhi A., S178
Roumiantsev A., EP358
Roumier C., EP407, EP432
Roussel M., S180
Roussel X., EP720
Rousselot P. H., S153, EP679
Roussou M., EP1016, EP1041
Routbort M., EP1104
Routledge D., PB1698
Rovere-Querini P., S279
Rovers J., EP458
Rovira M., EP587
Rovira M., S232, S233
Rovó A., S243
Rowe E., EP984
Rowe J., EP462
Roy K., S229
Roy N. B., EP1199
Roy-Peau F., EP933
Royston M., EP1337
Rozario N., PB1364
Rozema J., EP811
Rozenberg I., S173
Rozova A., PB1760
Rozovski U., EP1060
Rrakli V., EP424, EP871, EP945
Ru K., PB1473
Rua M., EP809
Ruan G.-R., EP460, EP484
Ruan Y., EP1271, EP1303
Ruane M., PB1588
Rubboli A., EP1113
Rubinacci A., S268
Rubio A., S150
Rubio J., EP1320
Rubio M.-T., S216, EP497
Rubio Lopes-García L., EP489
Ruchlemer R., EP631
Ruckdeschel A., S175
Rücker F. G., EP376, EP402, EP423
Ruckser R., EP971
Rudan D., S304
Rudge J. F., EP765
Rudilosso L., S258
Rudiuk T., EP776
Rueter M., EP1125
Ruffo G. B., EP1307
Rufián L., EP408
Ruggeri L., EP1288
Ruggeri M., S114, EP1089
Ruggiero E., S252, EP719
Ruhnke L., EP436
Rui H., EP869
Ruiz K., EP1318
Ruiz M., EP1320
Ruiz M. S., PB1509, PB1511
Ruiz-Cara J., EP1183
Rukavitsyn O., EP1190
Rülicke T., S198
Rumi E., S158, EP1074, EP1089, EP1098
Rummel M., S219
Rummelt C., EP467
Rungjirajittranon T., PB1419
Rus A., EP828
Rusconi C., EP1184
Rushworth S., S179
Russell J. S., S191, EP967
Russell K., S147
Russell L., EP317
Russell N., S130, S133, PB1753
Russell-Smith A., EP370, EP1175
Russell-Smith T. A., PB1520
Russo C., S259
Russo D., EP1267
Russo G., EP1155, EP1158
Russo L., S292
Russo M. F., EP927
Russo R., S276, EP688, EP695
Russo S., S154, EP673
Rustan N., EP1263
Rusznyák Á., EP572
Rutella S., S125
Rutgers L., EP1308
Ruthsatz T., EP1210, EP1215
Rutten A., EP400
Rutten C., EP1197
Ruvolo V., EP430
Ruzicka M., EP547
Ryan J., EP682
Ryan J., S239
Ryan M., EP944
Ryan R. J., EP1238
Ryan S., EP317
Rybolovleva T., EP1112
Rymko M., EP1028
Ryu H., PB1513
Rzepa E., EP373
Rzymski T., S164, EP480
Saad H., EP1159
Saari M., EP940
Saas P., EP697
Sabatini L., EP1203, PB1765
Sabattini E., EP1124, EP1129
Saber E. S., PB1479
Saber W., EP353
Sabhan A., EP834, PB1589, PB1729
Sabir M., EP383, EP417
Sabitova R., PB1783, PB1784, PB1779
Sabljic N., EP833, EP1326
Sabloff M., EP931
Sabrine M., PB1374
Saburova O., EP1328, PB1638
Sacchi De Camargo Correia G., EP570
Sacco A., EP1113
Sacha T., S153
Sachanas S., EP808, PB1516, PB1577
Sachanas S., EP774
Sachchithanantham S., EP1000, PB1644, PB1654, PB1694
Sachdeva M. U. S., EP331
Sackmann F., EP665
Sacma M., EP761
Sadeghi D. F., EP1323
Sadek I., PB1625
Sadelain M., S250
Sadhik M., EP746
Sadie R., S181
Sadiq A. A., EP643
Sadovnik I., S198
Sadullah S., EP555
Sáenz de Tejada I. M., S184
Saez B., EP411
Saez M. I., EP1346
Saez Marín A. J., EP489
Sáez Perdomo M. N., EP662
Safae F., PB1597
Safah H., EP445
Safar V., PB1546
Saffar S., PB1814
Safin R., EP1190
Safra I., PB1752
Sagakyants A., EP762
Sagiraju S., EP603
Saglio G., S154, EP661, EP673, EP677
Saguem I., PB1452
Sagüés M., EP670
Sagues Serrano M., EP1089
Sahakyan L., EP1056
Sahbudak Bal Z., EP355
Sahib S., PB1589
Şahin A., EP1216, EP1218
Sahin F., EP586
Sahraoui L., PB1563
Saidi D., EP1159
Saidi E. I., PB1443, PB1585
Saidi M. H., EP1159
Sainati L., EP1201, PB1746
Saini L., S313
Saini M., S259
Saint-Martin J.-R., EP530
Sainz J., EP425, EP612
Saito A., EP1101, EP1105
Saito S., S254
Saito T., EP1101, EP1105
Saitou T., EP937
Saja K. F., EP559
Sakabedoyan C., EP972, EP987
Sakai T., PB1587
Sakaida E., S244, EP668
Sakamoto T., S226
Sakata-Yanagimoto M., S226
Sakellari I., EP1232, EP1254, EP1256, PB1583, PB1804
Sakellariou K., EP551
Salah M., PB1813
Salai G., PB1539
Salama M., EP821
Salama M., S169, EP1080
Salama M., EP821, PB1367
Salama P., EP546
Salamero O., EP450, EP457, EP587
Salamoon M., EP775, EP1055
Salar A., EP606, EP890, PB1572
Salas E., EP1320
Salas Q., EP1231
Salas Camacho G., PB1826
Saldi S., EP1288
Saleem A., EP717
Saleh M. F. M., EP715
Salek S., EP1187
Salem A. H., EP444
Salemme A., EP1166
Salgado M., EP1320
Salhotra A., EP345, EP351
Salido E., EP889
Salido M., EP606, EP616, EP890
Salih H. R., EP376, EP467
Salimi T., EP916
Salinero M. M., EP1234
Saliu F., S279
Salles G., S213, EP529, EP530, EP553, EP785, EP786, EP791, EP798, PB1444, PB1546
Sallman D. A., PB1394, PB1624
Salma K., PB1371
Salman H., S214
Salmon M., EP660
Salomon-Perzynski A., EP829
Saloua L., EP1285
Salson M., EP385
Salvatore S., EP1158
Salvestrini V., EP753
Salvetti F., S292
Salvino M., EP1054, EP1286, PB1631
Salwender H., S183, EP376, EP968, EP1046
Samani S., EP1339
Samaniego F., EP643
Samaras C. J., EP1019
Samarina S., PB1431, PB1446, PB1447

Sambani C., EP763
Samedli V., PB1809
Samedli V., EP1317
Sami B., PB1597
Samir M., PB1818
Sammarelli G., EP949
Samoilova A., EP1190
Samoylova A., EP772
Sampaio-Marques B., EP425, EP612
Sampol A., EP1021, EP1231
Samson M., EP697
Samuelsson J., EP1088
San José S., EP612
San Miguel J., EP988, EP1012, EP1021
Sancetta R., S154, EP634
Sanches M., PB1449
Sánchez A., S293
Sánchez A., PB1679
Sánchez B., EP606
Sánchez E., PB1369
Sanchez E., EP983
Sanchez I., PB1719
Sanchez I., PB1654, PB1694
Sanchez M. B., EP663, PB1509, PB1511
Sánchez R., EP412
Sanchez Avalos J. C., EP663, EP880
Sánchez Blanco J. J., PB1575
Sánchez del Real J., EP893
Sanchez-Godoy P., EP621
Sanchez-Guijo F., EP670
Sánchez-Guijo Martín F., EP907, EP1253
Sánchez-Iglesias J. M., EP492, EP574
Sanchez-Maldonado J. M., EP425, EP612
Sánchez-Pina J., EP952
Sánchez Pina J. M., PB1689, PB1793
Sánchez Prieto I., EP1327
Sánchez-Sánchez M. J., EP350, EP352
Sánchez Sosa S., EP662
Sancho J. M., EP546, EP786, PB1791
Sanchorawala V., S189
Sanderson R., EP498
Sandhu I., EP963
Sandhu K., EP345, EP351
Sandnes M., PB1606
Sandrine C., EP1278
Sanford D., EP365
Sanga E., S292
Sangarappillai C., EP1212
Sanhes L., S156
SanJuan A., EP413
Sanjuan-Pla A., S160
San-Miguel J. F., S185, S186, S193, EP975, EP1009
Sanoja-Flores L., S185
Sant'Antonio E., EP1098
Santamaria Lopez A., PB1604, PB1794
Santana C., S156
Santana Santana G., EP1116
Santarsieri A., EP765
Santeramo T. M., PB1461
Santi A., S227
Santi L., EP1298
Santiago M., EP889
Santiago Balsera M., EP413
Santini V., EP910, EP915, EP920, EP1106, PB1619
Santomasso B., EP1003
Santoro A., S114
Santoro A., EP455, EP729
Santoro C., S306, EP571, EP1152, EP1319
Santoro M., EP1091
Santos A., EP1054, EP1286, PB1631
Santos A. B., PB1666, PB1692, PB1787
Santos A. L., PB1616
Santos H., EP1054, EP1286, PB1631
Santos J., PB1727
Santos J., EP1054, EP1286, PB1631
Santos J. D. A., EP1039
Santos M., EP1054, EP1286, PB1631
Santos R., S248
Santos W. O., PB1745, PB1823
Santos Mínguez S., EP893, EP1131
Santos Montero A. B., PB1425, PB1450
Santos Silva C., PB1538
Sanz G., EP413, EP889
Sanz J., S233
Sanz M. Á., EP413
Sanz Caballer J., EP587
Sanz Rekalde L., PB1651
Sanz-Villanueva L., EP870
Sapra S., EP1171
Sapunarova K., S211
Sara B., PB1427
Saracco P., EP1155, EP1158
Saraf S., EP1202
Saragoussi D., PB1639
Saraiva F., EP820, PB1767
Sarbeji F. K., PB1562, PB1564, PB1690
Sarda S. P., EP595, EP1191, PB1485
Sargas C., EP413
Sargent J., EP806
Sargın G., PB1778
Sarid N., S288
Sarkis R., EP750
Sarmento L., EP418
Sarmento-Ribeiro A. B., EP421, EP630, PB1350, PB1616, PB1630
Sarouei K., EP503, PB1565
Sarper N., EP1316
Sarpova M., PB1431
Sarry A., EP456, EP482
Sarsor Z., EP1060
Sartor C., EP364
Sartori R., EP795
Sarvide S., EP809
Sarzana M., S102
Sasaki K., S113, S167, EP440, EP676
Sasanakul W., EP850
Sasca D., S129
Sasse E., EP1172, PB1743
Sasse S., EP779
Sato N., S300
Sats N., EP756
Sauer M. G., S257, S266, EP1301
Saumell S., EP336
Saunders C., EP820, PB1726, PB1767
Saunders V. A., S151
Saussele S., S152, EP660
Savage K. J., S205, EP506, EP769, PB1554
Savani B. N., S233, S242, EP431
Savchenko V., S286, EP360, EP756, EP799, EP1241, EP1260, EP1270, PB1785
Saveliev L., EP358
Savill K., EP737
Savona M. R., EP1182
Sawa M., EP507
Sawyer E. K., S256, EP730
Saxena K., EP676
Sayapina I., PB1465, PB1822
Sayar H., EP445
Sayas M. J., EP447
Saydam G., S211
Sayinalp N., EP1316
Sbaraglia M., EP1124, EP1129
Sborov D., EP743, EP1026
Scala S., EP1298
Scalzulli P., EP651
Scandura J., EP1085
Scapinello G., EP795, EP1053
Scaramuzza S., S269
Scarano E., EP634
Scarfo L., S143, EP631, EP634, EP645, EP650
Scarisbrick J., EP509
Scarpa M., EP694
Schaap N., S232
Schaap-Johansen A.-L., EP609
Schachter J., EP716
Schachter L., EP508
Schaeper U., EP1057
Schäfer-Eckart K., S242, EP436
Schaible B., S290, S291
Schaich M., EP436
Schanzer J., EP879
Schaub A., EP1200
Schaub V., EP767
Schecter J., S190, EP972, EP977, EP978, EP987, EP990, EP1049
Scheid C., S190, EP968, EP1045
Scheinberg P., S172, PB1476
Schell B., EP906
Schemionek-Reinders M., EP387, EP657
Scherle P., EP861
Schettini L., EP1203
Schewe D. M., EP375
Schiano de Colella J. M., S212, EP511
Schiattone L., EP634
Schiavoni G., S227, EP611
Schiby G., EP502
Schieck M., EP325
Schieppati F., S292
Schild B., EP342
Schill M., EP1157
Schiller G. J., S117, S135, S188, EP437, EP438, EP443, EP1002, EP1008, EP1019, EP1075, EP1077
Schilling C., PB1412
Schimmer A., EP362, EP1082
Schipani M., EP603
Schipperus M., EP1348
Schiroli G., EP1298
Schittenhelm M. M., EP467
Schjesvold F., S186, EP975, EP988
Schjødt I., EP359
Schlammadinger A., S303
Schlee C., EP318
Schlegelberger B., S139, EP325, EP402
Schlenk R. F., EP376, EP467
Schliemann C., EP436
Schlums H., PB1543
Schmalbrock L. K., EP376
Schmalzbauer B., EP422
Schmelmer V., EP1224
Schmid C., EP431, EP1228
Schmidt A., PB1517
Schmidt A., EP1095
Schmidt B., EP979
Schmidt B., EP648
Schmidt C., EP547, EP725, PB1748
Schmidt L., EP373
Schmidt M., S261
Schmidt P., S273
Schmidt-Hieber M., EP436, EP1239
Schmitt A., EP1176
Schmitt C., EP971
Schmitt T., EP1245
Schmoellerl J., EP380, EP381
Schmolke A.-S., EP897
Schmoll H. J., S219
Schmöllerl J., EP389
Schmoor C., EP467
Schneeweiß-Gleixner M., EP902, EP1065, EP1068
Schneider C., S144
Schneider M., S161, EP896
Schneider T., EP768
Schneider V., EP386
Schöberl F., EP547
Schöder H., S208
Schoefs E., EP1192
Schoel W., PB1748
Schoenland S. O., EP1245
Schoergenhofer C., S302
Scholl S., S168, EP436, EP467
Schöllkopf C., S134
Scholz C. W., PB1565, PB1572
Schönland S., S189, EP1011
Schorb E., S219
Schou K., S134
Schoumans J., EP606, EP616
Schrade A., EP376
Schrappe M., EP325, EP342
Schreck C., S247, EP761
Schreder M., EP971
Schreurs J., S149
Schrezenmeier H., EP386
Schrezenmeier J. F., EP402
Schrimpf C., EP757
Schroader B. K., EP934, PB1390
Schroeder M., S238
Schroeder P., EP1202
Schroeder T., EP376
Schroers R., EP968
Schruef A.-K., EP1070
Schu D., EP1210, EP1215
Schubert B., S129
Schuh A. C., S137, EP362, EP457, EP465, EP909, EP1082
Schuh A., EP649
Schüler H. M., S196
Schulthess P., EP846
Schultz H., EP433
Schulz E., EP521
Schulz H., EP979
Schulz J., EP435
Schulz L., S197
Schulze M., EP979
Schulze zur Wiesch J., EP410
Schumacher L., EP754
Schuppert A., EP1063
Schuringa J. J., EP399
Schuschel K., EP328
Schuster M., EP530
Schuster M. B., EP373
Schuster S. J., S210, EP510, EP633, EP800
Schutgens R. E. G., PB1730
Schütte L. M., EP567
Schutz C., EP321

Schutz N., PB1675
Schwaab J., EP1065, EP1070
Schwab C., EP317
Schwab S., EP980
Schwaenen C., EP467
Schwaner I., EP648
Schwarz T., EP521
Schwarzer A., S120
Schwiertz V., PB1546
Schwind S., EP435
Schyrr F., EP750
Sciabolacci S., S227
Sciannameo V., PB1808
Sciumè M., EP449
Sciumè M., PB1357
Scolnick J., EP961
Scondotto S., EP1309
Scordo M., S241, EP1235
Scorilas A., EP959
Scortechini A. R., S154, EP673
Scot-Smith C., PB1521
Scott B. L., EP1106, EP1182
Scott D., PB1554
Scott Callander N., EP1002
Scuron M., EP693
Seabra P., PB1457
Seal C., PB1390
Sebag M., S188, S192, EP989, EP1002, EP1008, EP1019, EP1038, PB1643
Sébert M., EP906
Secreto C., S308, EP474
Seda V., S142
Sedarati F., PB1407
Sędek L., EP322
Sedinic M., S304
See W., S131
Seedhouse C., PB1381
Seefat M., EP1027
Seehaus C., PB1675
Seehra J., EP758, EP839, EP840, EP842
Seesaghur A., EP1126, EP1157
Seet C., EP1019
Seftel M., EP365
Segerberg F., EP718, PB1543
Seggewiss-Bernhardt R., EP436
Segman Y., S255
Segui E., EP1320
Segura de la Torre L., PB1649
Segura Diaz A., EP662
Seguy F., PB1626, PB1713
Sehgal A. R., S213, EP791
Sehgal L., EP861
Sehn L. H., PB1434
Sehn L., PB1554, PB1572
Seidalin N., EP838
Seidel L., EP844
Seifeddine N., EP714
Seitz P., PB1517
Seixas F., PB1701
Sekerel B., PB1365
Sekeres M. A., S166, S167, EP928, EP1182
Sekhar M., EP1058
Sekiya M., S300
Sellam G., EP503, EP545
Selleri C., EP651, EP1170
Selleslag D., EP445, EP909
Sellink E., S294
Selma K., PB1374
Selmi Y., PB1731
Selvaratnam V., PB1489
Semenova N., PB1447, PB1800
Semenzato G., EP611, EP810, EP855, PB1633
Semerad L., EP473
Semiglazova T., EP1264
Semochkin S., EP457, PB1638
Sen A., EP591
Sen J., S201
Şen T., EP1283
Sen'kova A., PB1389
Senates E., EP694
Senent L., S160, EP889
Sengar M., EP958
Sengeløv H., EP359
Senin A., PB1649
Senina A., S150
Senra J., EP1039
Seo J., PB1398
Septans A.-L., EP1176
Sequy F., PB1572
Seraj L., PB1487
Serbest G., S218
Seregina E., EP576
Seres Y., PB1649
Sergeev P., EP424
Sergentanis T. N., S287
Sergey S., EP1264
Serio B., EP1170
Serpanou A., EP955
Serra M., EP1313
Serramito-Gómez I., EP1131
Serrano J., EP447, EP546
Serrano L., EP670
Serrano Lopez J., PB1407, PB1788
Serrao A., S306, EP1319
Serras Pereira R., PB1767
Sersch M., EP962
Sertic D., EP826, EP1263
Serve H., EP436
Serventi Seiwerth R., EP1263, EP1287
Sesques P., S216, PB1546
Sevastoudi A., EP1044
Ševčíková S., EP954, PB1677
Ševčíková T., EP724, EP1297
Sever M., EP1109
Severina N., EP799, PB1490
Severinsen M., S134, EP1107
Severn C., EP760
Sevil F., EP1329
Sevindik G., EP631
Sevindik Ö. G., PB1458, PB1699
Sexl V., EP422, EP752
Seyffert S., EP784
Seymour F., EP854
Seymour J. F., S145, EP599
Sha Y., EP548, PB1497
Shacham S., S188, EP530, EP924, EP966, EP1002, EP1008
Shacham-Abulafia A., EP655, EP1060, PB1528
Shadman M., EP508, EP642, EP731
Shaengkhamnang B., EP1330
Shafer F., S290, S291, S312, EP689, EP709, EP1179
Shah A., PB1671
Shah B., S117, EP536, PB1364, PB1735
Shah F., EP1304, EP1306
Shah J., S188, EP530, EP924, EP966, EP974, EP976, EP1002, EP1008
Shah M. V., S313, PB1390, PB1405
Shah M., S169
Shah N., EP496
Shah N., EP523, EP765, EP797
Shah N., EP984, EP1009
Shah N. N., EP500, EP524, EP535, EP633
Shah R., EP353, EP370
Shah R., PB1738
Shah S., EP958
Shah S., PB1639
Shah V., S129
Shahda M., PB1422
Shaheen I., PB1818
Shaheen M., EP1276
Shaheen N., EP1322
Shahswar R., S139
Shakirova A., PB1612, PB1617
Shalay O., PB1358
Shalay O., PB1353
Shamsili S., EP455, EP480
Shamy A., EP931
Shanbhag N., EP733, EP736
Shang A., EP596, PB1486
Shao J., EP1077, EP1085
Shao Y., EP581, PB1492
Shao Y., PB1478
Shao Z., EP894
Sharf G., PB1759
Shargian L., EP1247
Shariatpanahi A., S178
Sharma A., EP736
Sharma A., EP733
Sharma M., EP1163
Sharma R., EP899
Sharma S., EP958
Sharma S., S142
Sharma V., PB1475
Sharman J., S148, EP541, EP635, EP642
Sharplin K., EP498
Shasha D., S284, S285
Shatilova A., PB1402
Shatokhin Y., PB1548
Shaughnessy P., EP541, EP747
Shaw J. W., EP1178
Shaya S., PB1659
Shazly M., PB1774
Shchetsova O., PB1785
Shebunyaeva J., EP778
Shefer G., S285
Shegani I., EP859
Sheldon K., EP1164
Shelekhova T., EP1190
Shemirani A., EP1323
Shem-Tov N., EP526
Shen H., PB1497
Shen L., EP962
Shen L., PB1542
Shen L.-J., EP1030
Shen R., EP787
Shen T., S117, PB1735
Shen Y., EP631
Shenton G., S116
Shepard R., PB1418
Shepherd L., PB1662
Sheppard S., EP1217
Sherf Y., S288
Sheridan W. P., EP585, EP589
Sherif Damadoglou A., PB1681
Sherman L., EP910, EP1106
Sherry M., PB1662
Sherstnev P., PB1836
Sherstnev D., EP1190
Sherstnev F., EP1347
Shestopalova I., PB1465
Sheth S., EP733, EP1312, PB1805
Sheth V., EP738
Shetty J. K., S101, EP1304, EP1305, EP1306, PB1702
Shewade A., EP545
Shi D., EP1120
Shi D.-Y., EP1240
Shi H., EP669, EP1120
Shi H., S217, EP505, PB1435
Shi J., EP1275, EP1277, PB1361
Shi L., EP1050, PB1685
Shi L., EP710
Shi P., EP356
Shi S., EP710
Shi X., EP601, EP618, EP801, PB1576
Shi X., PB1416
Shi Y., S211
Shi Y., EP1257
Shi Y., EP1082
Shi Y., EP327
Shi Z., S225
Shibata T., S300
Shibayama H., EP914
Shikata S., S300
Shilling C., PB1580
Shilova E., EP836
Shimano H., S300
Shimoda K., S202, EP1101, EP1105
Shimoni A., EP526, EP716
Shimono J., EP852
Shimony S., EP487, EP1247
Shin D.-Y., EP1029
Shin N., EP693
Shipounova I., EP756, PB1467
Shiraz P., EP1224
Shizuru J., EP717, EP1224
Shmidt D., EP771
Shochat T., S309
Shomron N., EP330
Shorikov E., EP358
Short N., S113, S132, S167, EP367, EP430, EP440, EP464, EP466, EP468, EP471, EP676
Shortt J., EP1074, EP1086
Shouval R., EP526
Shpilberg O., EP330
Shragai T., EP1023
Shudrak N., EP776
Shuey D., EP693
Shukhov O., EP674, EP680, EP681, EP756
Shulgina O., EP762
Shustik C., EP782
Shuvaev V., S286
Shvidel L., S288
Siakantari M., EP774
Siakantaris M., EP551, EP773, EP808, EP1272, PB1560, PB1577
Siala N., PB1690
Sianidou K., EP1299
Sibai H., EP362, EP1082, EP1083, EP1093
Siblany G., PB1763
Sica S., S114, EP394, EP1233
Sicre de Fontbrune F., S157
Sidana S., EP1224
Siddaiahgari S., PB1469
Siddani S., S135
Siddiq N., EP1093
Siddiqi R., EP1015
Siddiqi R., EP786
Siddiqi T., S147
Siddiqui M., EP466
Siddiqui M., EP931
Siddiqui M., EP446
Sidhu G., EP1189
Sidi Y., PB1407
Sidi Mansour N., EP1159
Sidi Mohamed El Amine B., EP683, PB1558, PB1559
Sidira C., PB1812
Sidorova J., EP1333
Sidorova Z., PB1783, PB1784
Sidorova Z., PB1618, PB1635
Siefkas A., EP911

Siegel D. S., S187, EP984, EP1019
Siegmund L., EP749
Sieriedin V., PB1691
Sierra J., EP423, EP438, PB1405
Sierra M., EP893
Sighinolfi S., S249
Şık N., EP1342
Sikirica S., EP370, EP1175, PB1520
Silbermann M., EP1027
Silipigni R., PB1357
Sillar J., EP485
Silowsky J., EP1017, EP1018
Silva A., S278
Silva J. P. A., PB1745
Silva M., PB1767
Silva M., S264
Silva P., EP375
Silva Andrade Costa C., PB1538
Silva Barcelos E. C., EP620
Silva Coelho P., EP1281
Silva De Tena P., EP1132
Silva Martins A., PB1449
Silva-Pinto A. C., EP1211
Silvani P., EP741
Silvennoinen R., EP1192
Silverman L. R., EP904
Silvestri D., EP348
Silvestri L., S277, S279, EP1302
Silzle T., PB1708
Simashova P., EP1190
Simenone R., EP1273
Simental-Legarda L., EP832
Simeone E., EP477
Simeone R., EP1291
Simeonidis S., PB1812, PB1816
Simeonova K., PB1652
Šimíček M., EP724
Šimkovič M., EP631
Simoens S., EP1192
Simões A. T., EP1102, PB1616
Simón Pilo I., PB1426
Simonetti G., S125
Simoni L., EP994
Simonova M., EP974, EP976
Simpauco J. J., EP849
Simpson D., EP525, EP636
Sims K., S260
Sims R. B., PB1441
Singh E., EP992
Singh M., EP317, EP876
Singh P., EP586
Singh S., PB1711
Sinha A., S124
Sinha D. K., EP976
Siniaev A., S286
Sinkó J., S281
Sinnige H., EP1027
Sirachainan N., EP850
Siragusa S., EP651
Siriwardena P., S283
Sirvent N., EP343
Siska B., EP542
Sivakumaran M., PB1525
Sivashangar A., PB1596
Sivcheva L., EP1076
Sive J., EP983, EP1047
Skaftason A., S143
Skambraks S., EP376, EP423
Skånland S. S., EP614
Skarbnik A., S148, S235
Škerl P., PB1610
Skikne B., S131, S311, EP428, EP445, EP446
Sklirou A. D., S280
Skoetz N., S281, EP779, EP1045, EP1187, PB1430, PB1756
Skopec B., EP1134
Skoura A., S192
Skoura E., PB1560
Skov V., S159
Skrypets T., EP557
Slama B., S156
Slatter J. G., EP1073
Slavnitsch K., S198
Slavutsky I., EP625
Sletta K., EP383, EP417
Slipicevic A., EP424, EP871, EP945
Sliwa T., S198
Sloan S., EP861
Smedby K., S143
Smeenk L., S123, EP378
Smeets M. W., EP324
Smelyanskaiya M., EP1110
Smesny Trtkova K., PB1637, PB1640
Smet A., EP654
Smetanina N., EP699
Smirnova A., EP333
Smirnova A., PB1612
Smirnova E., EP1190
Smirnova L., PB1650
Smirnova S., EP631
Smisek P., EP342
Smit J., EP967
Smit L., EP400
Smith C. C., S135, EP443, EP448
Smith E., EP1082, EP1093
Smith J., S219
Smith J., PB1711
Smith L. M., PB1698
Smith L., PB1744
Smith M., S130
Smith P., EP693
Smith S., S136
Smith S., EP559
Smith S., EP530
Smith S., EP731
Smith Y., PB1780
Smith-Whitley K., S260
Smolarczyk R., EP724
Smolej L., EP631
Smolewski P., S205
Smol'yaninova A., PB1785
Smucler A., PB1493
Smykova O., EP544, EP770
Smyth L., EP885
Smyth L., PB1413
Snauwaert S., EP654
Snider J., PB1571
Sninska Z., EP1134
Snyder M., PB1588
Soares Almeida L., PB1449
Soares-Da-Silva F., S248
Sobas M. A., EP1089, EP1091
Sobesky S., S225
Sobieraj-Teague M., EP783
Sobolov S., EP1017, EP1018
Sobotka J., EP724
Sobrinho Simões M., EP488, PB1474
Socie G., S235, S236
Sockel K., S161, S243, EP896
Socoro N., EP472
Sodaro G., S126
Sodhi L., EP555
Soe Z., EP644
Soefje S., EP1051
Soekojo C., EP961
Sofer O., S288
Sofocleous C., PB1468
Sogabe K., EP942
Sogbe M., EP809
Sohn B. S., EP1029
Sohn S. K., S235, EP445
Sohoni S., S145
Sokal A., S295
Söker M., EP1216, EP1218, EP1316, PB1755
Sokol L., EP509
Sokolov A., EP357, EP360, EP361
Sol Reis C., EP488, PB1474
Solán L., PB1696
Solano F., PB1793
Soldatenkov V., EP1332, EP1333
Solé F., EP889
Solem C., PB1735
Solh M., S192, EP518
Solheim M., EP1296
Soliman D.S., EP631, PB1377
Söling U., EP979
Solodovnikov A., EP358
Sologuren-Sanchez-Ferragut A. M., EP1343
Solomon S., EP455, EP480
Solovev M., EP1270
Solovey M., EP896
Soloviev M., EP693
Somervaille T., EP450, EP1077, EP1078, EP1085
Sommavilla R., PB1517
Sommer Kristensen L., EP888
Sommet A., EP1125
Sonam P., EP331
Sønderskov Gørløv J., S219
Song F., EP961
Song I.-C., PB1513
Song K., S178, EP365, EP989, EP1019, EP1038, PB1643, PB1698
Song L., PB1542
Song W., S115, S119
Song X., PB1542
Song X., EP1277
Song Y., S313
Song Y., EP1024
Song Y., EP1223, EP1294
Song Y., S194
Song Y., S206, S207, EP789, EP792, PB1555
Sonia M., PB1824
Sonneveld E., EP319
Sonneveld P., S180, EP943, EP1011, EP1027, EP1031, EP1036, PB1655
Sonntag C., S180
Sonnveld P., EP1020
Sood S., S245
Sorà F., S154, EP394, EP1233, PB1506
Sorasio R., S240
Soraya B., PB1558
Sorcini D., EP620
Sørensen H. T., EP1126
Sørensen J. F., EP392
Soret J., EP595
Soria B., EP352
Soria J. M., EP1320
Soriano F., EP1113
Soriano M., EP1212
Sorkee H. P., PB1438
Sormann S., EP971
Soroka V., EP1332, EP1333
Sorrentino F., PB1770
Sorror M., EP508
Soscia R., EP624
Sostelly A., PB1480
Sotiropoulos D., EP1256, EP1299, PB1583
Soto I., EP812
Sotomayor Duque G., PB1438
Soubortseva I., EP1071
Soukayna H., PB1597
Soulières D., S262, PB1760
Soumerai J. D., S214
Soundarajan R., PB1671
Souravla A., PB1516
Sousa H., EP425
Sousa P., S251
Sousa Santos P., EP820, PB1726
Souza C., EP1286
Souza E. M. B. D., PB1745
Sovena G., PB1357
Soverini S., EP419
Soyer N., EP1216, EP1218, EP1316
Spaargaren M., EP608
Špaček M., EP631
Spackman R., EP555
Spadano A., S182
Spadini S., EP348
Spadola V., PB1602
Spain V., EP1052
Span B., EP1284
Span L., S201
Spanholtz J., EP748
Spanoudakis E., EP774, PB1436, PB1681
Spanswick V., EP788
Sparksman D., EP523
Spasiano A., EP1307, PB1810
Spassov B., PB1421, PB1503
Spector M., EP1017, EP1018
Spectre G., S309
Spectre G., EP1060
Speker M., S303
Speletas M., EP1340
Spencer A., EP965, EP975, EP985
Sperotto A., S289, EP815
Sperr W. R., S198, EP461, EP664, EP897, EP902, EP1065, EP1068, EP1070
Špička I., S184, S186, EP816, EP948, EP974, EP975, EP976, EP980, EP981, EP1028, PB1652
Spiekermann K., EP896
Spielmann M., EP375
Spina M., PB1448
Spina V., EP603
Spinelli C., S305
Spinelli M., EP1155, EP1158
Spinelli O., S114
Spinello Z., EP855, PB1633
Spinet B., EP612
Spinozzi G., S258
Spirin P., EP426
Spivak J., EP1100
Spolzino A., EP793
Sporchia A., PB1451
Sportoletti P., S108, S154, S227, EP620, EP631, EP645, EP651
Spoulou V., PB1829
Sprecher D., S103
Spyridis N., PB1583
Spyridonidis A., S233, S242, EP431
Srbova D., EP661
Sreckovic S., EP596, PB1480
Sretenovic A., EP1043
Srichairatanakool S., EP1330
Sripakdeevong P., EP733, EP736
Sriram H., EP958
Srivastava S., S153
Sriwichai M., EP1330
Srour S., EP881
Staber P. B., EP897
Stadler M., S139, EP1228
Stadtmauer E., S187
Stafford G., EP765
Stagakis E., EP600
Stagno F., S154

Staib P., S183
Stakiw J., EP989, EP1038, PB1643
Stalpers F., EP324
Stamatopoulos K., S143, EP609, EP631
Stambouli H., PB1443
Stancioaica M. C., PB1379
Stanganelli C., EP625
Stanulla M., EP325
Stanzel S. F., PB1480
Starikova O., EP1260
Starklint J., EP1107
Starkova J., EP320
Starodub H., EP935
Stary J., EP320
Stas L., PB1404
Stasi L., EP719
Stathis A., EP518
Stauder R., PB1777
Stavrogianni N., EP631
Stavroulaki E., EP1153
Stavroyianni N., EP609, PB1583
Steede T., PB1545
Steegmann-Olmedillas J. L., EP670
Steel C., EP876
Stefanelli T., PB1780
Stefanoni D., EP1067
Stefanzl G., S198, EP461, EP902, EP1065, EP1066, EP1068, EP1070
Steffen B., EP436
Steffensen M. S., PB1740
Stefka A., EP1010
Stege C.A., EP1027
Stegmaier K., S108, S126
Steidl S., EP879
Steimle T., EP790
Stein A., EP345, EP351, EP427
Stein E., EP465
Stein J., PB1753
Steinberg M. H., EP736
Steinemann D., EP325
Steinfeld J., EP1087, EP1122
Steinhäuser S., EP318, EP375
Steininger M., EP381
Stejskal L., EP816
Stelitano C., EP651, EP793
Stella A., EP620
Stella R., S289
Stellas D., S287
Stellato P., EP348
Stelljes M., S242, EP353
Stelmakh L., EP544
Stelter M., EP325
Stemler J., S281
Stenehjem D., PB1625
Stenke L., EP684
Stenling A., EP1107
Stentoft J., EP1107
Stepanishyna Y., EP557
Stepchenkova E., PB1779
Stephenson T., S193, EP967
Sternberg A., EP765
Stevens D., EP439, EP541, EP969, EP976
Stevens H., EP1192
Stevenson A., EP1178
Stevenson W., EP433, EP1074, EP1086
Steventon L., EP1047
Stewart F., EP345, EP351
Stewart M., EP1164
Steyn R., EP1164
St-Hilaire E., EP931
Stiakaki E., EP1146, PB1351, PB1468, PB1516
Stiehl T.-P., S159
Stiff P., EP495
Stilgenbauer S., S144, S145, S146, S219, EP632, EP786
Stivel M., EP665
Stocchi R., S289, EP815
Stoilova B., S136
Stojanova V., PB1522
Stojkov I., PB1777
Stoker-Postier C., EP1209
Stolyar M., EP647, EP1110
Stölzel F., EP436
Stoma I., PB1590
Stoppa A.-M., S180, EP963
Storck S., S295
Storek M., EP709
Štork M., EP954, PB1677
Storring J., EP931
Storti P., EP949
Storti S., EP793
Storto M., S249, S268, S269
Stouffs M., PB1715
Stougaard M., EP392
Stovin C., S283
Stoychov-Yaguronoska M., PB1421
Sträng J. E., EP402
Stratienko V., EP776
Stratigaki M., PB1468
Straub J., EP948, EP1042
Straus D. J., S205, EP769
Streetly M., EP994, PB1654, PB1694
Strefford J. C., S143
Streneva O., EP358
Strickland S., EP438, EP442, EP455
Strijdhorst A., EP1221
Strobbe L., EP1027
Strocchio L., S258
Stroobants S., EP517
Strouse B., S202
Struemper H., PB1698
Strulev V., EP987
Strutt S., EP1198
Stuckey R., EP662, EP1091, EP1116, PB1495
Stull D. M., EP985
Sturesson H., EP406
Sturgess K., EP765
Stussi G., EP1242
Stutz C., EP938
Styles L., S235
Su A., S126
Su H., EP792
Su H., EP1103
Su J., S312, EP689, EP709, EP1179, EP1193
Su L., S253
Su L., EP493, EP469, PB1416
Su N., EP512, EP537, EP549
Su W., EP1194
Su W., EP1120
Su X.-T., EP957
Su Y., S104, S231, EP1295
Su Y., EP1225
Suarez L., EP740
Suárez S., EP546
Suárez Cabrera A., EP1116, PB1495, PB1561
Suárez-González J., EP870
Suarez-Varela S., EP670
Subach R. A., EP443
Subash C., PB1687
Subbotina T., PB1700
Subirá D., PB1692, PB1787
Subira Perez D., PB1425, PB1450
Subklewe M., EP547, EP725, EP749
Subramanian S., EP958
Such E., EP329, EP413, EP889
Suciu S., EP343
Sudarikov A., EP558, EP626, EP681, EP799, EP884, EP1071, EP1325, PB1352, PB1414, PB1490, PB1785
Sudhindra A., PB1571
Suehara Y., S226
Sueoka E., EP875
Suere P., EP938
Suero B., PB1395
Suessner S., EP897
Sugimoto Y., EP1101, EP1105
Sugiura I., PB1587
Suijk L., EP1197
Sujobert P., EP451
Sukhareva A., S286
Sullivan L., PB1405
Sultana E., PB1682
Sumitani R., EP942
Sumiyoshi T., EP965
Sun B. J., PB1513
Sun D., S177
Sun F., PB1648
Sun J., EP877
Sun J., EP356
Sun J., EP469, EP493
Sun K., S204
Sun L., EP910, EP1106
Sun M., EP783
Sun Q.-Y., EP460, EP484
Sun R., EP1248
Sun R.-J., EP1230
Sun W., EP1050, PB1685
Sun X., EP605, PB1499
Sun X., EP792
Sun X., PB1648
Sun X.-Y., S231, S298, EP1295
Sun Y., EP847
Sun Y.-Q., S234, EP1240, PB1591
Sun Z., PB1648
Sundaram S., PB1498
Sundaresan S., PB1485
Suñe G., EP721
Suo P., EP847
Sureda A., S185, EP501, EP587, EP1012, EP1167
Sureda Balari A., EP499, EP975
Surinach A., EP596
Suriu C., S288, PB1663
Surleaux D., EP417
Surleraux D., EP383
Surve S., PB1501
Suryanarayan K., S184
Sushil S., EP1186
Susman D., PB1573
Sutherland H., S188, EP365, EP1002, EP1008
Sutton L.-A., S143
Sutton L., PB1412, PB1580
Sutton R., EP321
Suvajdzic Vukovic N., EP833, EP1326
Suzuki K., S189, EP1006
Suzuki R., EP507
Suzuki T., EP443
Suzuki Y., PB1587
Svanberg E. R., EP613
Sveshnikova Y., S286
Svingel L., EP1107
Svitina S., EP1333, PB1618, PB1635
Svoboda J., EP800
Svobodova K., EP948
Swallow E., PB1768
Swanink R., EP677
Swanton S., PB1383
Swartz N., PB1485
Sweeney J., S138
Sweet K., EP427, PB1394
Swords R., EP928
Sy O., EP677
Sychevskaya K., EP564, PB1574
Sydvander M., EP970
Syed H., EP958
Syed I., EP913
Sykora M., EP816
Symeonidis A., EP551, EP919, EP1014, EP1016, EP1028, EP1031, EP1153
Symeonidou M., PB1436
Symington E., S256
Syrigou A., EP1153, EP1254
Szafer-Glusman E., S147
Szakacs G., EP389
Szaleczky E., EP768
Szarzyńska B., EP322
Szczepański T., EP322
Szegezdi E., PB1545
Szendrei T., PB1641
Szer J., S236
Szer J., S174, EP586, EP595, PB1471
Szita V. R., PB1641
Szoke A., EP636
Szoltysek K., S105, EP382
Szomor Á., S211
Szotkowski T., EP473
Szukalski L., EP1091
Szydlo R. M., EP1133
Szymańska A., EP1280
Szymczyk A., EP1280
Tabares Carrasco S., PB1788
Tabata R., S226
Tabita M., EP700
Taborsak T., EP1287
Tabouret-Viaud C., EP497
Tachynopoulou V., EP1254
Tadmor T., S255, S288, EP631, EP1023, PB1759
Tafuri A., S154
Tafuri M. A., EP867
Tagara S., PB1697
Taha R., PB1454
Taher A. T., S101, EP1220, EP1304, EP1306, PB1805
Taherinasab A., S114
Tahri S., EP943
Tai F., EP692, EP696
Tailor I., PB1609
Takahashi K., S136, S167, EP367, EP440, EP466, EP471
Takahashi N., PB1455
Takahashi N., EP667, EP668
Takahashi S., EP1229
Takahashi Y., PB1780
Takamatsu H., S171
Takeda R., S300
Takenaka K., EP937, EP1101, EP1105
Takeuchi K., EP914
Talati C., S165, PB1394
Talaulikar D., PB1433
Talbi A., PB1629
Talotta D., EP603
Talpaz M., EP1074, EP1077, EP1080, EP1085
Tam C., S147, EP525, EP631, EP633, EP638, EP782
Tamayo-Velasco A., S293
Tambaro F. P., EP478, PB1392, PB1790
Tan A., PB1624
Tan L., S174

Tan M., PB1625
Tan P., EP433
Tan S. M., PB1489
Tan S., PB1542
Tan S. H., EP857
Tan T.-D., PB1552
Tan W., EP1303
Tan X. N., EP500
Tan Y., EP469, EP493, PB1416
Tan Y., S115
Tan Z., S142
Tanabe M., S171
Tanae K., PB1455
Tanaka H., EP914
Tanaka J., EP1006
Tanaka M., EP1229
Tanaka M., S254
Tanaka T., EP1101, EP1105
Tanaka Y., EP903
Tanchanco C. A., PB1600, PB1754
Tandon M., S144, S146, EP632
Tang B., EP805, EP1174
Tang C., S176, EP859
Tang D., EP915, EP920, EP1306
Tang F., EP847
Tang F.-F., S234
Tang G., EP1120
Tang J., EP528
Tang J.-P., EP638
Tang J.-L., EP483
Tang K., S119
Tang M. W., EP1197, EP1221
Tang S.-Q., S230
Tang T., EP1198
Tang W., EP784
Tang W., EP510
Tani M., EP543
Tanimoto K., EP937
Tankersley C., EP783
Tantawy A., EP1220
Tantiworawit A., EP1330, PB1437, PB1751
Tantravahi S. K., EP1078, PB1625
Tao L., PB1434
Tao W., EP379
Taparkou A., PB1772
Tapia Torres M., EP1116
Tapper W., EP1064
Tarabeh K., PB1663
Tarantini G., EP651, PB1461
Tarantino M. D., PB1733
Tarantolo S., S165
Tarasev M., PB1761
Tarek B. O., EP1285
Tarjan D., EP1051
Tartaglia M., S258
Tartaglione I., EP1305, EP1307, EP1310
Tartari C. J., S292
Tartas N., EP880
Tarte K., S212
Taskén K., EP614
Tasselli L., S227
Tassi I., EP955
Tast B., EP725
Tatarczuch M., EP1074
Tatarnikova S., PB1785
Tatiana G., EP781
Tatiana I., EP781
Tatic A., PB1379
Tausch E., S144, S146, EP632
Taussig D., S138
Taveras A., EP784
Tavitian S., EP456, EP482
Tawana K., EP470
Tawfik N., PB1813
Tawil N., S305
Taylor A., PB1521, PB1661
Taylor J., EP854
Taylor J., EP633
Tayo B., EP1214
Tazi Y., S133
Tazón-Vega B., S143, EP336
Tchaicha J., S177
Tchan M., EP694
Tchuxina J., EP1048, PB1500
Tcvetkov N., PB1612, PB1617
Tecchio C., EP1267
Tedeschi A., S147, EP636, EP650, EP782, EP783, EP793
Tedesco L., PB1771
Tedone E., EP459
Tee T. M., S107
Tefferi A., S169
Teich K., S128
Teichman J., EP931
Teipel R., S184
Teixeira L., EP550
Teixeira S., S251
Telen M., EP1202, PB1764
Telerman A., EP655
Teles M., S278
Telfer P., EP1212
Teli A., PB1376, PB1772, PB1807, PB1812, PB1816
Tembhare P., EP958
Tempra P., EP880
Teng C.-L. J., PB1552
Tengesdal I., EP1067
Tenorio P., PB1679
Tenorio-Nuñez M., EP1338
Tenshin H., EP942
Teo W., EP597
Ter Borg M., S170
Ter Horst P., PB1676
Ter Horst R., EP612
Ter Meulen J., S177
Teramachi J., EP942
Teramo A., EP611
Terao T., S226
Terenzi A., EP1288
Terfay A., PB1598
Terol M. J., S143, EP546, PB1493
Terpos E., S280, S287, EP551, EP939, EP959, EP985, EP993, EP994, EP1001, EP1014, EP1016, EP1031, EP1041, EP1044
Terpstra W., S149
Terradas Terradas M., EP754
Terrenato I., EP883
Terriou L., S157, EP685, EP706
Teruel A. I., EP1021
Teruel-Montoya R., EP889
Tervonen T., PB1398
Terzi Di Bergamo L., EP603
Teshima T., S235, EP852
Tesio N., PB1808
Tessler S., EP462
Testa T., PB1721
Testa U., EP420
Testi A. M., S306
Thabet M., EP1118
Thadani Mulero M., EP599
Thakurta A., EP1062
Than H., EP905
Thankachan J., S113
Thayer M., EP452, EP643, PB1391
Thayur N., EP559
Thebault M., EP697
Theis F., EP376
Theobald M., S129
Theocharides A., S196
Theodorakakou F., EP993, EP1036, EP1041
Theodoridou S., PB1608
Theodoropoulos J., EP611
Theorell J., PB1543
Thépot S., S157, EP910, EP1106
Theurich S., PB1756
Thieblemont C., S210, S212, S215, S216, EP495, EP497, EP530, EP540, EP783, EP786, EP790
Thiede C., S128, S161, EP436
Thiel M., S294
Thirman M. J., S137, EP909
Thol F., S128, S131, S139, EP376, EP402, EP423, EP457, EP467, EP757
Tholouli E., EP498
Thomaidou E., PB1376, PB1378
Thomalla J., EP968
Thomas A., S130
Thomas A., EP377
Thomas B., EP1278
Thomas D., S151
Thomas D., S238, S299
Thomas I., S130, S133
Thomas M., EP1058
Thomas S., EP784
Thomas X., S138, EP407, EP451, EP457, EP494, EP1262
Thomenius M. J., S176
Thompson A., PB1381
Thompson A., S101, S257, S261, S266, EP1301
Thompson G., PB1395, PB1406
Thompson M. C., EP524
Thompson M. A., EP985
Thornton D., S177
Thornton P., S143
Thorvaldsdottir B., S143
Thrasher A. J., S257, S266, EP1301
Thulasi P., EP1026
Thuresson M., EP973
Thuret I., S257, S266, EP1301
Thurner L., S219
Tiab M., S180
Tiacci E., S227, EP611, EP793
Tian H., EP978, EP990, EP1049
Tian M., EP895, EP900
Tian X., EP512, EP537, EP549
Tian X., EP1117
Tian Y., EP1050, PB1685
Tian Z., PB1542
Tian Z., EP627, PB1544
Tiboni F., S269
Tichenor M., EP869
Tichy D., S183
Tick L., S149
Tick L., EP1162
Tiedemann R., PB1662
Tieghi A., EP1079
Tien H.-F., EP922
Tietze-Bürger C., EP1239
Tiftik N., EP1216, EP1218, PB1755
Till B., EP731
Tillman H., S265
Tillmann S., S197, EP387
Tillmanns S., PB1451
Tilly H., S212, EP511, EP530
Tim E., EP797
Timmerman K., S103
Timmerman J. M., EP495, EP787
Timmers G.-J., EP1027
Timofeev V., PB1691
Tinchon C., EP971
Tingting L., EP951
Tiong I. S., EP429
Tippett G., S136
Tiribelli M., S154, EP477, EP673, EP1079
Tirtakusuma R., S105
Tisdale J. F., S261
Tisi M. C., EP543, EP729, EP795
Tislevoll B., EP399
Tiu R. V., S135, EP437, EP438, EP441, EP448
Tjoa M. L., EP703
Tjønnfjord G. E., EP614
Tkachenko O., PB1691
To I., S222
Tobias K. K., PB1754
Tobinai K., S218, EP506
Todorovic Balint M., EP833, EP1043
Toft N., EP359
Tokgoz H., EP1316, PB1755
Toledo-Hernandez E., EP1343
Toloza M. J., EP659
Tolu T., PB1683
Tomacinschii V., PB1582
Tomaiuolo G., EP688
Tomarchio V., EP867, EP883
Tomasian V., EP351
Tomasso A., PB1506
Tomasson M., S192
Tomazos I., EP1337
Tomic K., S307, EP629, EP631
Tomiczek M., EP807
Tomin D., EP833
Tomita A., EP1101, EP1105
Tomkinson B., PB1408
Tomlinson B., PB1391
Tomlinson E., PB1756
Tommasso A., EP604
Tonda M., S260
Tondeur S., EP898
Tonelli D., PB1445
Tonev I., PB1792
Tong B., S267, PB1805
Tong C., EP346
Tong H., EP891, EP923, EP1120, PB1613
Tong S., EP687
Tonino R., EP1348
Tonino S., S149, EP766, EP803, EP873, PB1575
Tonks A., EP388, EP393
Tonon L., S121
Topp M. S., S117, S175, EP787
Toptas T., PB1683, PB1705
Torelli L., EP1291
Torka P., PB1498
Tormo M., EP329, EP350, EP352, EP447, EP546, EP889, EP893
Tormo Díaz M. D. M., PB1407
Tornesello A., EP1155, EP1158
Toropova I., S286
Torrado Chedas T., PB1794
Torrebadell M., EP734
Torregrosa-Díaz J. M., S156, EP933
Torrent A., EP329, EP350, EP352, EP546
Torres A., PB1631
Torres D., EP625
Torres-López A., EP492
Torres Ochando M. K., PB1798
Toscani D., EP949, PB1633
Tosello V., EP316
Tosti M. E., EP793
Tóth A., EP572
Totman J., S176
Toubert A., S162, EP906
Touloumenidou T., EP1254, PB1368, PB1721
Toumi N., PB1564

Tourjeman L., EP631
Touw I., S170
Touzeau C., S180, EP963, EP973, EP995, EP999
Tovar N., S168, PB1642
Townsend W., EP498, EP539
Toye A., EP760
Tozatto Maio K., EP818
Toze C., EP365
Trabelsi H., PB1592
Trachana M., PB1816
Tracy M., EP485
Trad R., EP720
Træden D., PB1615
Traer E., S168
Tragiannidis A., PB1368, PB1376, PB1378
Trakada G., EP993
Tran K., S177
Tran N., S189
Tran Q., S299
Tran T., PB1354, PB1355, PB1356
Trandafir M., PB1369
Tranekaer S., EP690
Trede N., EP541
Treglazova S., EP1071
Tregubova Y., EP1112
Treiner E., EP416
Treliński J., S202
Tremante E., EP883
Tremblay G., EP1025, EP1033
Trenina N., EP1190
Trentin L., S147, EP624, EP631, EP645, EP793, EP810, EP855, EP1053, EP1124, EP1129, PB1633
Treon S. P., EP782, EP784
Trestman S., EP1023
Tretiak N., EP935
Trevisanutto P., PB1357
Triantafyllou E.-F., EP773, EP808, EP1272, PB1560, PB1577
Triantafyllou T., EP1044
Tricarico S., EP1288
Tricta F., EP1312, PB1760
Trifonova E., PB1500
Trigo F., S278, EP488, PB1474
Triguero A., S158, S237, EP1084
Trimnell C., S314, PB1762
Trimoreau F., EP898
Tripodo C., S125, S249
Trithiphen S., EP845
Trivedi J., EP1173
Trka J., EP320
Trněny M., EP631, PB1451
Troester S., EP380
Troisi D., EP1310
Troitskaya V., S286, EP357, EP360, EP361
Trojer P., EP1080
Trojok P., EP853
Trombetta E., EP921
Tromp B., S189
Trompeter S., S260
Trost M., PB1385
Trotman J., S282, EP782, EP783
Trotti C., EP1098
Trougakos I. P., S280
Troussard X., EP646
Trudel S., S192, EP965, EP1001, PB1698
Truelove E., EP854
Truger M., S175
Trümper L., EP506, PB1738
Trumpp M., S161
Truppel-Hartmann A., EP984
Tsaftaridis P., EP773, EP808, EP1272, PB1560, PB1577
Tsai C.-H., EP922
Tsai D., EP515
Tsai D. E., EP500, EP524, EP633
Tsaknakis G., EP588
Tsao-Wei D., EP913
Tsapas A., PB1804
Tsaur G., EP358
Tsavdaridou V., PB1376, PB1378
Tse E., EP631
Tse W., EP445
Tselousova O., EP584
Tsempera E., EP939
Tseng C. C., EP758, EP840, EP842
Tseng M.-H., EP922
Tshernichovski D., S285
Tshneyder T., EP556
Tsiakanikas P.-I., EP959
Tsiarentsyeva M., PB1590
Tsigankov I., EP556
Tsirakis G., EP1153, PB1516
Tsirigotis P., EP551
Tsirkinidis P., EP774, EP808, EP1272, PB1577
Tsirogianni M., EP551
Tsirou K., EP1044
Tsokanas D., EP919
Tsolas E., EP955
Tsompanakou A., PB1721
Tsonis I., PB1515, PB1516
Tsourdi E., EP896
Tsourouflis G., EP808, PB1577
Tsui H., EP1093
Tsuji N., S171
Tsukasaki H., EP522
Tsukasaki K., S218, EP506, PB1455
Tsukurov O., EP928
Tsvetkov N., EP1134
Tsvetkova G., PB1421
Tsvietkova N., PB1366
Tsyba N., EP674, EP680, EP681
Tucci A., S219, EP449
Tucci F., S102, S258, EP741
Tuchman S., S188, EP1002, EP1008
Tucker D., EP797
Tudesq J. J., S216
Tüfekçi Ö., EP1138, EP1342, PB1372, PB1834
Tuglular T., PB1705
Tulstrup M., PB1615
Tung J. S. L., PB1674
Tung M. L., EP597
Turba E., PB1364
Turcatti G., EP750
Turesson I., EP1035
Turgunova L., EP838
Turgutkaya A., PB1778
Turhan A., EP679
Türker M., EP1216, EP1218, EP1316, PB1755
Turki I., PB1363, PB1527
Turkina A. G., EP672, EP674, EP680, EP681, EP756
Türkkan E., EP1316
Turner C., EP523
Turner C., EP1214
Turon F., EP1084
Turrini R., EP938
Turtle C., EP508, EP731
Tuset E., EP889
Tüsüz Önata E., EP1138
Tüzün F., EP1138
Tvedt T. H. A., S290, S312, EP689
Tweardy M., EP1348
Tyster M., EP580
Tytorenko I., EP557
Tzachanis D., S117, EP495
Tzimouli V., PB1816
Tziotziou E., PB1515, PB1516
Tzivelekis S., PB1768
Tzvetkov N., S299, EP1081
Uaprasert N., EP845
Uchida N., S244, EP507, EP1229
Uchida T., S211
Uchiyama H., EP507
Uchiyama M., EP1006
Udomponglukkana R., EP850
Ueda T., EP522
Ueda Y., EP668
Ueda Y., PB1481
Ueda Y., EP709
Ugalde L., EP721
Ugidos M., S131
Ugolkov A., EP390
Ugwu A., EP1344
Uhlig K., S267, PB1805
Uhrberg M., EP326
Uitslager N., EP567
Ulfferts R., EP813
Ullah S., PB1833
Ullrich R., S225
Ullrychova J., EP816
Ultimo S., S227
Ulvik R., PB1606
Umit E., EP577
Ünal E., PB1372
Ünal S., EP1216, EP1218, PB1755
Ünal S., EP1216, EP1218, EP1316, PB1755
Undurraga Sutton M., S153
Ungar D., EP518, PB1440, PB1570
Upasani S., EP635
Uppal K., EP876
Urbaneja-Rodríguez E., EP1131
Urbanelli L., EP384
Urbano-Ispizua A., EP734, PB1642
Urbino I., S308, EP474
Urescu D., PB1582
Ureshino H., EP875
Uriarte J., PB1526
Uribe L., PB1679
Uribe M., EP563
Uroz-de la Iglesia M. L., PB1495
Ursuleac I., EP1119
Urushihara R., S171
Uskudar Teke H., PB1775
Usmani S. Z., S193, EP964, EP977, EP978, EP982, EP985, EP990, EP1049
Uss A., PB1782
Ustariz M., PB1793
Üstkaya Sungur M., EP1138
Usuki K., S174, S226, S301, EP594, EP595, EP1101, EP1105, PB1471
Utoft Niemman C., EP613
Utsunomiya A., S218
Uttenthal B., EP498
Uttenthal B. J., EP765
Uttervall K., PB1698
Uysal Ateş S., PB1834
Uysal-Onganer P., PB1384
Uysal Soyer O., PB1365
Uyttebroeck A., S221, EP343
Uziel O., EP1060
Uzun A., EP1342
Vabishchevich R., PB1402
Vacca M. P., EP1188
Vaccarini S., EP883
Vachhani P., EP1078, PB1720
Vadakekolathu J., S125
Vaddi K., EP861
Vadikolia C., EP1254
Vadikoliou C., PB1697
Vadim B., EP781
Vaganay C., S126
Vagapova E., EP426
Vagge D., S291
Vagia M., PB1516
Vágó E. K., EP1193
Vagos Mata A., EP354
Vahí Sánchez de Medina M., PB1426
Vaide I., PB1725, PB1757
Vaillant J., S246
Vainstein V., S255
Vajnerova R., EP661
Valcárcel D., EP889
Valcárcel Ferreiras D., EP907
Valchuk M., PB1358
Valencia U., EP1335
Valenciano Martínez S., EP1327
Valent J., S189, EP1017, EP1018
Valent P., S198, EP461, EP664, EP752, EP897, EP902, EP1065, EP1066, EP1068, EP1070
Valenti L., EP843
Valentin C., EP1278
Valentino M. S., EP1310
Valeri A., EP721
Valerius T., EP431
Valery S., PB1467
Valk P. J., S128
Valković T., PB1684
Vall-llovera F., EP352, EP546
Valle S., EP872
Valle Aramburu I., EP813
Vallejo A., EP1192
Vallejo C., S172
Vallera D., EP326
Valles M., EP1329
Valletta S., EP377
Vallone A., EP1313, PB1602
Valluri S., EP977, EP978, EP990, EP1049
Valone F., S200
Valsecchi D., PB1766
Valtierra I., S127
Van Beers E. J., S270, S271, S274, EP582, EP691, EP692, EP696
Van Bogaert C., EP654
Van de Brug T., S208
Van de Donk N.W.C.J., S180, S187, S191, S193, EP987, EP1003, EP1020, EP1027, PB1653
Van de Loosdrecht A., S163, EP434, EP458, EP748, EP811
Van de Poll-Franse L. V., EP1162
Van de Velde H., S186, EP981
Van de Ven C., EP324
Van de Wetering G., EP1174
Van de Wiel L., PB1445
Van Delft F., EP327
Van den Akker E., S163, S294, EP1308
Van den Berg A., EP766
Van den Biggelaar M., S294
Van den Enden M., PB1404
Van den Neste E., EP530, EP652
Van der Burg-de Graauw N., EP1027
Van der Deure T., EP400
Van der Garde M., EP896
Van der Hem K., EP1027
Van der Kevie-Kersemaekers A.-M., EP599
Van der Klift M., S149
Van der Kouwe E., EP897
Van der Meer L. T., S107, S110
Van der Meulen S., EP1308

Van der Poel M. W., S220
Van der Reijden B., S128
Van der Spek E., S149, EP1020, EP1027
Van der Straaten H., S149
Van der Straten L., EP637, EP640
Van der Valk P., S256
Van der Windt G. J. W., S141
Van Dijk W. E. M., PB1730
Van Domelen D., S188, EP1002, EP1008
Van Dooijeweert B., S274, EP582
Van Dyke M., EP1122
Van Elssen J., EP458
Van Epps H., EP944
Van Es N., EP1221
Van Es R. J. J., PB1730
Van Eygen K., EP910, EP1106
Van Galen K. P. M., PB1730
Van Gelder M., S149, EP631
Van Gils N., EP400
Van Gorkom G., S232
Van Herk S., S123, EP378
Van Hest R. M., EP567
Van Ingen Schenau D., S107, S110
Van Kampen R., EP1027
Van Klaveren D., S155
Van Leeuwen F. N., S107, S110
Van Meerten T., EP495
Van Mil L., EP608
Van Noesel C., EP608
Van Rhee F., EP985
Van Roon E., EP811
Van Sanden S., EP978, EP1049
Van Solinge W., S274, EP582
Van Stiphout J., EP1194
Van Strien P., S170
Van Til N., EP727
Van Tonder T., S282
Van Tuijn C., EP1197
Van Vlierberghe P., EP316
Van Weissenbruch R., EP1284
Van Wijk B., EP335
Van Wijk R., S274, EP582, EP686
Van Zaanen H., S149
Van Zeeburg H. J., EP458
Vanasse G., S177
Vandebroek M., EP1192
Vandenberghe A., S295
Vandenberghe E., EP628, EP806, EP885, EP1292
Vandenbroucque J., PB1661
Vandendries E., EP353
Vanderfaeillie A., EP1208
Vaneeva E., PB1431, PB1432, PB1446, PB1447
Vanhellemont A., EP1192
Vanni D., S158, EP1098
Vannier C., EP979
Vannini I., EP384
Vannucchi A. M., S158, S201, S203, EP1074, EP1077, EP1080, EP1081, EP1089, EP1106, PB1723
Vanquaethem H., EP1176
Vanquickelberghe V., S180
Vara S., S180
Varady E., EP768
Varda-Bloom N., EP526
Vardaka M., EP1153
Vardanyan R., PB1500
Vardi A., EP609, EP919, EP1232, EP1256
Varela A. I., EP663, EP665
Varela J., EP541, EP740
Varela M. R., EP350, EP1231
Varela M., EP546
Varelas C., EP1256, PB1804
Varettoni M., EP543, EP624, EP634, EP782, EP793
Varga E., S294
Varga G., PB1641
Vargas M., EP893
Vargas S., S264
Varghese S., PB1671
Variami E., EP773, EP774, PB1560
Varley K., S150
Varma N., EP331
Varma S., EP331
Varney M., EP945
Váróczy L., PB1641
Varsi I., PB1790
Varsos H., S190, EP1003
Vasconcellos Nunes I., PB1538
Vasconcelos F., PB1701
Vasconcelos G., EP447
Vasconcelos Cordoba B., EP663
Vasey S., S189
Vasileva A., S286
Vasiliev E., EP1190
Vasilieva V., PB1785
Vasilopoulos J., PB1560
Vasilyeva V., EP1260
Vaskina E., EP584
Vasquez J., PB1362, PB1370, PB1675
Vassal G., S221
Vasseur L., S126
Vassilakopoulos T., EP551, EP631, EP773, EP774, EP777, EP808, EP919, EP1272, PB1560, PB1577
Vassiliou G., PB1674
Vassilopoulos G., EP1153
Vassilopoulos I., EP808, EP1272, PB1577
Vasu S., EP427
Vataire A.-L., EP1005
Vavassori V., S252, EP1298
Vaxman I., PB1528
Vaze A., EP965
Vazquez A., PB1666
Vázquez I., EP411
Vazquez L., EP587
Vázquez Díaz M. S., PB1788
Vazquez Lopez L., EP1253
Vazquez Ramo A., PB1425, PB1450, PB1692, PB1787
Vecchio V., EP1094
Veeger N., EP811
Veelken H., S149
Vega F., EP881
Vega Y., S309
Vegi N., S124
Vekemans M.-C., S180
Vela-Ojeda J., EP985
Velardi A., EP1288
Velasco P., EP336
Velasco-Estévez M., EP374
Velasquez M., EP367
Velders G., S149, EP1027
Velez P., EP670
Velichko A., EP762
Velickovic S., EP588
Vella C., EP723
Vellenga E., EP910, EP1106
Venable J., EP869
Venanzi A., S227
Venegas M. B., EP880
Venglar O., EP1297
Vengoa R., PB1675
Venkatraman S., EP841
Venner C., S188, S189, EP974, EP989, EP1002, EP1008, EP1038, PB1643, PB1662
Ventrici L., EP1200
Ventriglia M. V., EP665
Ventriglia V., EP663
Venugopal S., S132, S167, EP471, EP440
Vera M., EP663
Verameeva V., EP1349
Verbeek M., S242, EP431
Verboom M., EP757
Verboon L., S120
Vercellino L., EP497, EP540
Vercruyssen M., PB1657
Verdon V., EP1200
Vergez F., EP416
Verghese D., PB1424
Vergin R. C., EP704
Verhagen H., S163, EP1308
Verhoeven-Duif N., S274, EP582
Verhoeyen E., EP939
Verhovsek M., S270
Verigou E., EP551
Verma A., S165
Verma S., PB1520
Vermaat J. S., S220, EP530
Vermeeren M. M., EP324
Vermeulen J., S180, S189
Vermeulen M., S123
Vermue E., EP400
Verner E., EP525
Verner J., S142
Verona R., S191, S193, EP608, EP967
Veronese A., EP604
Veronese L., EP652
Veronese S., PB1387
Verri M., EP867
Verrou E., EP1014, EP1044
Verschuur A., S221
Verstovsek S., S200, S202, S203, EP1077, EP1078, EP1080, EP1081, EP1085, EP1096, PB1702, PB1711, PB1713
Vertone D., PB1460
Vervoort B. M. T., S107, S110
Vervoort S., S278
Verzhbitskaya T., EP358
Vestergaard H., S152
Vetoshkin K., EP584, PB1549
Vetro C., PB1409
Vetsiou E., PB1608
Vettenranta K., S116
Vetter V. M., EP755
Vey N., S168
Vezan R., EP341, EP366, PB1735
Vial J.-P., EP652
Viallard J.-F., EP1125
Vianelli N., EP1079, EP1124, EP1129
Vianello F., EP810, EP1124, EP1129
Vianetti N., EP1074, EP1086
Viarengo G., EP741
Viari A., S121
Vibor M., EP932
Vicent A., EP546
Vicente V., S303
Vicenzetto C., EP611
Vichinsky E. P., S267
Vick B., S127
Vidal M.-J., EP352
Vidal Lartitegui L., PB1526
Vidaurre T., PB1362, PB1370
Vidlakova D., EP948
Vidler J., EP649
Vidovic A., EP833
Vidriales M. B., PB1407
Vieira G. C., PB1745, PB1823
Vieira J., EP1032
Vieira L., EP1054
Viero P., S112
Vieyra D., EP967
Vigil C. E., EP463
Viglione V., EP1288
Vignetti M., S112
Vignjević Petrinović S., EP759
Vignoli A., S292
Viguria M. C., EP1231
Vij R., EP987, EP990
Vijnovich Baron A., EP880
Vilariño Lopez M. D., PB1734
Vilas-Zornoza A., EP809, EP907
Villa D., PB1554
Villa I., S268
Villa M., EP658
Villamor N., EP872, PB1567, PB1568
Villarrubia J., EP694
Villasboas J. C., EP643
Villegas A., PB1819
Villegas A. M., EP712
Villemonteix J., S162
Vilmar A., EP786
Vince B., EP768
Vincelette N., PB1394
Vincent L., EP950, PB1742
Vincenzi A., EP1166
Vinci V., PB1771
Viniou N.-A., EP773, EP919, EP1153, PB1560
Vinti L., S258
Viñuelas M. C., EP1320
Violante O., EP1302
Viprakasit V., S101, S271, EP691, EP692, PB1805
Viqueira A., EP671, EP672, EP684
Virijevic M., EP833, EP1326
Visceglie D., EP1314
Visco C., EP795
Visentin A., EP624, EP631, EP645, EP793, EP855, EP1053
Visone R., EP604
Visotskaya L., PB1500
Visser H., S149
Visser L., EP766
Visser O., S155, S220, EP434, EP637, EP640, EP796, EP803, EP804
Viswabandya A., EP1261
Viswanatha D., S169
Visweshwar N., S256
Vita G., PB1460
Vitale A., S112, S114
Vitale C., EP631, EP645, EP650
Vitale M., EP1061
Vitali M., S292
Vitolo U., PB1448, PB1451
Vitrano A., EP1309
Vitriu A., EP880
Vitucci A., EP1307
Viveiros C., EP579, PB1693
Vives S., EP455, EP447
Vives Corrons J.-L., EP691, EP698
Vives Polo S., PB1407
Viviani S., PB1550
Vlachaki E., EP1153, PB1608, PB1804
Vlachová M., EP954
Vladescu C., EP1133
Vladimirova R., PB1503
Vladislav S., EP772
Vlasova J., EP674, PB1612

Vo A. K., EP1296
Vodanovic M., EP561, EP573, EP826, PB1494, PB1539, PB1605
Voermans C., EP1308
Voevoda-Dimenshtein V., EP716
Vogel M., S190, EP977, EP978, EP987, EP1049
Vogel P., EP988, EP1013, EP1019
Vogiatzi F., EP375
Vogrič V., PB1610
Voi V., EP1307
Voitsekhovsky V., PB1465, PB1822
Vojackova E., S142
Volchenkov S., EP1264
Volchkov E., EP333
Volkov A., EP1325
Volkov M., EP1190
Volkov N., EP770
Volkova A., EP822
Volodicheva E., EP1190
Voloshin S., EP836, EP1040, PB1491
Volpe G., EP373
Volpe V. O., PB1394
Volpetti S., S289, EP543, EP793, EP815
Völse K., S109
Von Baumgarten L., EP547
Von Bergwelt M., EP547, EP725, EP749
Von Bergwelt-Baildon M., PB1748
Von Bubnoff N., S236, EP853, EP1081
Von der Heide E., EP318
Von der Weid B., EP750
Von Drygalski A., S256
Von Lindern M., S163, S294
Von Roemeling R., S165, EP390
Von Tresckow B., S225, EP764, EP779
Von Tresckow J., EP631
Vora A., S111
Vora S. M., EP1199
Vorland M., PB1606
Vormoor J., S105, EP876
Vorobyev V., S137, S286
Vorog A., S184
Voropaeva E., PB1512, PB1611
Vorozheikina E., EP807
Vos J., S291, EP796, EP804, EP873
Vose J. M., EP495
Voskaridou E., S101, EP1305
Voso M. T., EP420
Voytko M., EP778
Vrachiolias G., EP631, EP919, PB1681
Vrachiolias G., PB1436
Vrakidou E., EP551
Vrana J., EP1297
Vredenburg M., EP1144, EP1148, EP1151
Vrhovac R., EP1263, EP1287, PB1539
Vucic M., EP833
Vucinic V., EP1239
Vučinić Ljubičić I., EP819
Vukovic V., S307, EP629, EP631
Vuono F., PB1506
Vuoti S., EP940
Vyas P., S128, S136, EP457, EP465, PB1624
Vydra J., S233
Vydyborets S., PB1508
Vyhovska Y., PB1459
Vyniou N.-A., EP774
Vyrla D., EP600
Waage A., EP1022
Wada F., EP1229
Wada H., EP1101, EP1105
Wada M., EP1225
Wade S., EP786
Wadelin F., EP1058
Wafae A., PB1466, PB1597
Wagdy T., EP1220
Wagers S. B., S253
Wagner E., EP458
Wagner T., EP1051
Wagner W., EP657
Wahida A., S310
Wahlin B., PB1572
Wahlstrom J., S235
Waizenegger J., EP463
Wakayama T., S244
Wakita S., EP1101, EP1105
Waksal H., S239
Waldron C., EP628
Waldron D., EP628, EP885
Walek Z., EP724
Walewska R., S148, EP504
Walewski J., S205, EP638
Wålinder G., EP1035
Walker C. J., EP936, EP966
Walker K., S181
Walker P., S148, EP783
Wall D., EP733
Waller E. K., S235, S238, EP516
Walsh A., EP628
Walsh D., PB1412, PB1579
Walsh K., EP800
Walter R., EP455, PB1408, PB1753
Walter W., EP892
Walter-Croneck A., EP1280
Walters M. C., S257, S261, S266, EP1301
Walz B., EP1087
Wambacq S., EP1208
Wan Y., EP910, EP1106
Wan Z., EP929
Wanasundara D., PB1817
Wang X.-L., S204
Wang A., PB1670
Wang A., EP1266
Wang B., S184
Wang C.-C., S298
Wang C.-C., EP460, EP484
Wang C., EP1293
Wang C., PB1416
Wang D., EP372
Wang D., EP524
Wang D., S194
Wang D., EP742
Wang E., EP427, EP438, EP443, EP1075, PB1408
Wang F.-D., EP1117
Wang F., EP847
Wang F.-R., S234, EP1226, EP1252, PB1591
Wang G., EP1249
Wang H., EP1249
Wang H., EP583
Wang H., EP565
Wang H., EP894
Wang H., EP742, EP1230, EP1266
Wang J., PB1398
Wang J.-L., S298
Wang J., EP1024
Wang J., EP439, EP1024
Wang J., S118
Wang J., S301
Wang J., S135, EP460, EP1080
Wang J., EP847
Wang J.-Z., EP1226, EP1252, PB1591
Wang J., EP512, EP537, EP549
Wang J.-N., EP1117
Wang J., S194
Wang L., EP618, PB1497
Wang L., EP337
Wang L., S190
Wang L., PB1594, PB1797
Wang L., EP891, EP923
Wang L., PB1570
Wang M., EP1120
Wang M. L., S256, EP500, EP785, EP787, EP798
Wang M. H., S148
Wang M.-C., S211
Wang Q., EP560
Wang Q., PB1648
Wang Q., S207
Wang S., EP464
Wang S., EP356
Wang T., PB1472
Wang T., EP639, EP792
Wang T., EP339, EP414
Wang T., S238
Wang V., PB1624
Wang W., S223
Wang W.-J., EP916, PB1735
Wang W., S206
Wang W., S194
Wang X., EP794
Wang X., EP1225
Wang X., EP1293
Wang X., PB1648
Wang X., S228, EP334, EP562, EP605, EP627, EP862, EP864, EP865, EP866, EP868, EP874, PB1499, PB1544
Wang X., EP339
Wang X., S250
Wang Y., EP1024
Wang Y., PB1648
Wang Y., S207
Wang Y.-J., EP957
Wang Y., PB1542
Wang Y., S230, S234, EP347, EP356, EP395, EP460, EP805, EP847, EP1174, EP1226, EP1240, EP1252, EP1265, PB1591
Wang Y., PB1702
Wang Y.-F., EP483
Wang Y.-H., EP922
Wang Y.-T., PB1647
Wang Y., EP397
Wang Z., S115
Wang Z., EP548
Wang Z.-D., PB1591
Wang Z.-L., EP460, EP484
Wang Lin S. X., EP967
Wapenaar R., EP654, EP987
Ward R., S262
Warda W., EP720
Wardecki M., S290, S291
Ware S., EP1276, EP1279
Warner S., PB1712
Warren H., EP731
Warushahennadi R., PB1817
Warwick L., EP1177
Wasag B., S128
Wäsch R., EP467
Washington C., S260
Wasserstein M., EP694
Watanabe M., PB1587
Watanabe M., EP1229
Watanabe T., EP875
Waters N., S282
Watson A.-M., EP433
Wattad M., EP968
Wattad M.-A., EP423
Watts J. M., S138, EP1074, PB1720
Waultier Rascalou A., EP652
Wayne A. S., EP341
Weber D., EP376, EP423
Weber D., S130
Webersinke G., EP897
Webster I., PB1764
Wechalekar A., EP1047
Wechalekar A., S189, EP983, EP1000, EP1011, PB1644
Wedge E., EP888
Wegerich S., EP1348
Wehler D., EP1239
Wei A., S131, S138, S168, EP428, EP429, EP433, EP439, EP445, EP457, EP465, EP909, EP917, EP926, PB1624
Wei D., PB1504
Wei H., PB1355
Wei J., PB1781
Wei L., S204
Wei M. C., PB1565
Wei R., EP789
Wei R., EP1240
Wei S., EP685, EP706
Wei Y., PB1670
Wei Z., EP1248, PB1396
Wei Z.-J., EP1230
Weigert K., EP398
Weijers D., EP538
Weill J.-C., S295
Weinbergerova B., EP473, EP1063
Weinkove R., S282
Weirather J., PB1444
Weisel K., S183, S190, EP968, EP977, EP978, EP985, EP987, EP988, EP1009, EP1013, EP1049, PB1653
Weiser Drozdkova D., PB1640
Weiss B., S189
Weiss J., S225
Weiss M., S265
Weissman R., EP330
Weitz I., S174, S290, S291, S312, EP689, EP709, PB1471, PB1475, PB1477
Welch V., EP353, PB1753
Wellard C., S282
Wellbrock J., EP410
Weller S., S295
Wells J., PB1747
Welslau M., EP1157
Weltermann A., EP897
Wen J., EP340
Wen Q., S230
Wen X., EP1223, EP1269
Wendland K., EP887
Wendtner C., S146, EP632
Weng J., PB1670
Weng W.-K., EP1224
Weng Y., PB1786
Wensveen F. M., S141
Wenzel A., EP373
Were J., EP1090
Wermke M., S168
Werner M., EP444
Werner S., EP328
Werner Hansen J., PB1615
Wernicke P., EP665
Wernig G., EP717
Westbrook C., S265
Westerman M., S180, EP1027
Westermann J., EP402
Westerweel P. E., S155, EP666, EP678
Westin J., EP530

Weston H., S282
Wetton W., S310
Wheatley K., S221
Wheeler A. P., S256
Wheeler G., EP788
Whelan C., EP1000, PB1644
Whelan M., EP1010
Whetton A., EP388
Whitaker S., S241
White D., S188, EP988, EP989, EP1002, EP1008, EP1038, PB1643
White D., EP321, EP332
White H., EP660
White J., EP365
Wichmann M., S128, S139, EP402
Wickham N., EP638
Wided M., EP714
Widhopf, II G. F., S140
Wieczorek K., EP1212
Wiegers S. E., EP517
Wienecke C. P., S128, S139
Wierda W., S113, S147, S148, EP524, EP633
Wiesinger A., PB1571
Wiesneth M., EP386
Wiklik K., S164
Wilden H., EP968
Wildes T. M., PB1498
Wilhelmson A. S., EP373
Wilke C., PB1723
Willems L., EP652
Willenbacher W., EP971
William B. M., S213, EP791
Williams D. M., EP1100
Williams J., EP945
Williams J., EP691
Williams M., EP665
Williams P., EP539
Williamson S., EP508
Willis C., PB1625
Willmann M., S198
Wilson A., PB1463
Wilson A. B., EP695
Wilson D., EP965
Wilson M., EP760
Wilson M., EP797
Wilson R., S130
Wilson W., EP514
Wimalachandra M., PB1596
Winckels S., EP748
Winderlich M., EP553
Winer E. S., S165
Winkelmann M., EP547
Winsnes E. A., PB1604, PB1794
Winter G., EP380
Winter S., S161, EP896
Winton E., EP1075, PB1720
Wintrich S., PB1743
Wirths C., S197
Wisniowski B., EP983, EP1047
Witt M., EP322
Witte H. M., EP853
Woei-A-Jin F. S. H., S220
Wojdyla M., EP1144, EP1148, EP1151
Wolach O., EP462, EP487, EP655, EP1247
Wolf J., EP514
Wolf P., S251
Wolf Lundholm B., S134
Wolfe B., EP1010
Wolff D., EP364
Wolff T., EP648
Wolfgang Blau I., EP431
Wöll E., EP971
Wolter M., EP325
Won K. J., EP373
Wondergem M. J., S220, PB1723
Wong E., EP1243
Wong L., S173
Wong R., PB1660
Wong S., S189
Wong S., EP1073
Wongkhut O., PB1751
Woo J. M., PB1417
Wood D. K., S251
Wood E., S282
Wood H., EP813
Wood K., PB1764
Wood L., EP788
Wood S., EP371
Woodard T., S103
Woodley C., PB1719
Woods G., S260
Wook Lee J., EP594
Worel N., EP516
Worthington E., EP1165
Woszczyk D., EP503
Wotherspoon A., S221
Wouters B., S123
Woyach J. A., S148, EP500, EP524, EP633
Woźny T., EP1081
Wrafter A., PB1545
Wright C., EP470
Wright L., PB1480
Wrobel M., EP816
Wróbel T., EP638, EP975, EP1091
Wroclawska M., PB1723
Wu D.-S., S204
Wu E., EP1202, PB1764
Wu H., PB1361
Wu H., EP792
Wu J., PB1542
Wu J., S206
Wu L., PB1614
Wu L.-X., EP460, EP484
Wu M., S194
Wu Q., PB1593
Wu T., EP505, EP1223, EP1269, EP1294
Wu W., EP548, PB1497
Wu W., EP792
Wu X., S190, EP964, EP978, EP1049
Wu X., EP1303
Wu X., EP1266
Wu Y., EP1275
Wu Y., EP1050, PB1647, PB1685
Wu Y., S199
Wu Y.-Y., EP476
Wuillème S., S180
Wulf G., EP376
Würthwein G., EP342
Wysocki M., EP829
Wyssal C., PB1466, PB1597
Xagorari A., EP1299
Xagoraris I., EP882
Xalkiadakis G., EP588
Xanthopoulos V., EP551
Xavier G. A. D. S., PB1745
Xavier L., PB1457
Xhang X., EP374
Xia L., PB1593
Xia M., S163
Xia R.-X., S204
Xia S., EP375
Xia Y., EP512, EP537, EP549, PB1497
Xia Z.-J., PB1647
Xia Z., PB1670
Xia Z., EP423
Xiangyu Z., EP1300
Xiao F., EP1030, PB1531
Xiao H., EP1277
Xiao Y., EP1271
Xiao Z., EP1120
Xiaohui Z., EP454, EP1300
Xiaojun H., EP454, EP1300
Xiaosu Z., EP454, EP1300
Xicoy B., EP587, EP670, EP889
Xicoy Cirici B., EP1089
Xie H., EP1028
Xie Y., EP503
Xie Z., S169
Xilouri I., PB1681
Ximeri M., EP919, PB1516
Xing H., EP490
Xing T., S230
Xingxing Y., EP1300
Xiong H., EP1103
Xiong J., PB1542
Xiong M., EP1230, EP1248, EP1249, PB1396
Xiong Y., S108
Xiong Y., EP1225
Xirou P., EP1044
Xu A.-N., S194
Xu B., PB1648
Xu E., S270, S271
Xu F., PB1614
Xu G., EP891, EP923
Xu J., EP881
Xu J., EP1120
Xu J., PB1624
Xu J., PB1542
Xu J., PB1786
Xu J., S115
Xu J., S236
Xu K., EP983, EP1047
Xu L., EP847
Xu L.-P., S230, S234, EP347, EP395, EP460, EP484, EP1226, EP1240, EP1252, EP1265, PB1591
Xu L., EP1163
Xu N., EP356
Xu S., EP339
Xu W., EP548, EP601, EP618, EP639, EP789, EP801, EP1083, EP1093, PB1497, PB1576
Xu W., PB1542
Xu W., EP891
Xu X., EP742
Xu X., EP490
Xu Y., EP356
Xu Z., EP631
Xuan L., EP356
Xue F., EP533
Xue F., EP1103, EP1111
Xue H., S206
Xuefei L., EP1300
Xun Z., PB1717
Xunhong C., EP1300
Yablokova V., EP1076
Yacoub A., S200, EP1075, PB1715, PB1716
Yadav B., EP580
Yagci M., EP631, EP980, EP981
Yagci N., S294
Yaghmour G., EP913
Yagurinoski M., PB1421
Yaish H., EP696, EP1194
Yakoub-Agha I., S213, S233, S235, S243, EP431, EP1009, EP1228, EP1238
Yamaguchi M., S290, S291
Yamaguchi T. P., EP761
Yamamoto K., S137
Yamamoto K., S300
Yamamoto M., EP668
Yamamoto Y., EP875
Yamauchi N., S218
Yamauchi T., EP439, EP522
Yamazaki H., S171
Yan C., EP847
Yan C.-H., S234, EP1226, EP1240, EP1252, PB1591
Yan D., S150
Yan H., EP346
Yan S., EP1248
Yan Y., EP691
Yan-Li L., EP878
Yancey S. W., EP1087
Yañez E., S211
Yáñez L., S237, EP587, EP631, EP1231
Yang C., EP601, EP618, EP801, PB1576
Yang C., EP593, EP598
Yang C., EP1293
Yang D., PB1781, PB1803
Yang D., EP351
Yang F., EP505
Yang H., S207, EP789
Yang H., S313, EP510
Yang H., PB1712
Yang J., S138, S200, PB1566
Yang J., S228, EP862, EP865, EP866
Yang J., S118
Yang K., EP805, EP1174
Yang L.-P., EP1295
Yang L., PB1542
Yang M., PB1542
Yang M., PB1648
Yang Q., PB1648
Yang R., EP1103, EP1111
Yang S., EP560, EP639
Yang T., EP356, EP397, PB1786, PB1795
Yang T., EP1277
Yang T., EP528
Yang W., EP1120
Yang X., EP764
Yang X., EP1024
Yang Y., EP469
Yang Y., PB1416
Yang Y., EP548
Yang Y., EP792
Yang Y., EP593, EP598
Yang Y., S213, EP791
Yannaki E., S257, S266, EP1301
Yannakou C., EP638
Yannick L. B., EP790
Yano S., S244, EP668
Yao C.-Y., EP922
Yao T., EP951
Yao Y., S265
Yap E. S., S173
Yarali N., EP1316, PB1372, PB1755
Yarchovsky-Dolberg O., EP655
Yared J., S235
Yarza Barrio R., PB1518
Yasenchak C. A., PB1441
Yasmine C., PB1597
Yasmine K., PB1371, PB1373
Yaspo M.-L., S120, EP328, EP398
Yassin M., EP631, PB1710
Yasukawa M., EP937
Yavaşoğlu I., PB1778
Yavrom S., PB1569
Yazhen Q., EP454
Ye B., EP1277
Ye L., EP891, EP923
Ye M., EP397
Ye R.-H., EP476

Ye X., EP891
Ye X., EP962
Ye Y., PB1648
Yeakey A., PB1698
Yebenes Ramírez M., PB1426
Yee C., PB1485
Yee K., S138, EP362, EP931, EP1082
Yeganeh S., S288
Yeh S.-P., S137, EP506
Yeh T.-M., EP964, EP978, EP1049
Yeleswaram S., PB1706, PB1717
Yen H., PB1662
Yen J., S263
Yenerel M., EP586
Yenerel M. N., S145
Yerushalmi R., EP526
Yeshurun M., EP1247
Yeung C., EP731
Yeung D. T., S151, EP321, EP332
Yhim H.-Y., EP1029
Yi J. H., EP1029
Yiannaki E., EP1044
Yildirim Aslan S., EP355
Yılmaz D., PB1683
Yılmaz D., EP1342
Yilmaz F., PB1683, PB1705
Yilmaz H., PB1365
Yilmaz M., S132, EP430, EP440, EP464, EP466, EP468, EP471
Yılmaz S., EP1138, EP1342, PB1372, PB1834
Yilmaz Karapinar D., EP355, PB1523
Yimer H., EP541, EP642, EP969
Yin M., EP500, EP524
Yin Z., PB1499
Yingjun C., EP454, EP1300
Yocoub A., EP1074
Yokoyama H., EP441
Yonezawa T., S300
Yong K., EP977, EP978, EP980, EP981, EP983, EP986, EP1047, EP1049, EP1189
Yoon S.-S., S173, EP438, EP1029, EP1081, PB1660
Yoshida C., S226
Yoshida N., EP875
Yoshioka S., EP507
Yosifov D., S144
Yosr B. A., PB1371, PB1374
Yosra B., EP714, EP817, EP831, PB1586
Youakim N., PB1608
Young A., EP635
Young G., S256
Young K., EP374
Young N., EP580
Young-Min S., EP555
Yousief Ali E., PB1818
Youssef E., PB1818
Youssef M., EP541
Youssef Y., EP861
Yovdiy A., EP1347, PB1496, PB1836
Ypma P. F., EP1020, EP1027
Ysebaert L., S212, EP511, EP646, EP652
Yu B., PB1709
Yu C., EP944
Yu H., EP1050
Yu J., EP590, EP594
Yu J., EP1275, EP1277
Yu J., S107
Yu J., EP909
Yu L., S118
Yu M., EP996
Yu U., EP1293
Yu W., EP454, EP1300
Yu X., PB1594, PB1797
Yu X., EP457
Yu X.-X., EP1265
Yu Z., PB1670
Yuan C., EP527, EP619
Yuan L., EP339, EP414
Yuan L., PB1354, PB1355, PB1356
Yuan Y., EP1198
Yüce D., EP1244
Yucel A., EP1304, EP1306, EP1315
Yucel E., EP1178
Yue C., EP527, EP619
Yue Y., PB1542
Yuen L., PB1654, PB1694
Yuen S., EP506
Yüksel M., EP1283, PB1603
Yun H., S129
Yun H.-J., PB1513
Yun S., EP899, PB1394
Yun X., EP605, PB1499
Yunes J. A., S106
Yuqian S., EP454
Yurekli B., EP1317, PB1809
Yuriev E., EP836
Yuriy K., EP781
Yushkova A., EP558
Yuska B., PB1706, PB1717
Yuste J. R., EP809
Yusuf A., EP982
Zabaleta A., EP809
Zabolotskikh T., PB1465, PB1822
Zach O., EP897
Zadro R., EP573
Zafar S. F., EP642
Zagadailov E., S270, S271, EP710, EP1194, EP1318
Zago M., S183
Zagoridis K., PB1436
Zagrean D., PB1518
Zahia Z., EP683, PB1558, PB1559
Zahra K., EP714, EP817, EP831, PB1586
Zaidi A. U., EP1206
Zaidi S. Z., PB1609
Zaitsev D., PB1402
Zaitseva A., PB1366
Zaja F., EP543, EP1184
Zak P., EP473
Zaka M., EP876
Zakharov S., PB1500
Zakharyan A., PB1411
Zakia M., PB1578
Zakurdaeva K., S286, EP674
Zaliova M., EP320
Zama D., EP491
Zamagni E., S182, EP1016, PB1673
Zamanillo I., EP708
Zamanillo Herreros I., PB1689
Zambelli M., EP741
Zambello R., EP611, PB1633
Zambrano S., EP1067
Zambrano Contreras J. C., PB1538
Zambrano Urbano J. L., PB1728
Zammoeva D., PB1402
Zamora L., EP329
Zamprogna G., EP650
Zanabili J., EP1231
Zancan S., S258
Zanella K. R., EP1039
Zanella L., EP625, PB1380
Zang C., EP1035
Zanni M., S219
Zannier M. E., S289
Zanon D., EP1273, EP1291
Zappasodi P., S114, EP491
Zarifis I., EP1232
Zaritskey A., PB1402
Žárská M., EP954
Zarubina K., EP357, EP360, EP361
Zataraín E., PB1696
Zaucha J. M., EP480
Zaugg B. E., EP1026
Zavidij O., EP1080
Zeballos M., PB1380
Zecca M., EP1158
Zeerleder S., EP1197
Zei T., EP1288
Zeidan A., EP465, EP916
Zeineb H., EP831
Zeiser R., S236
Zekanović I., EP819, PB1684
Zektser M., S255, EP1023
Zelenetz A., S214
Zeljkovic I., PB1494
Zeller C., S127
Zemanova Z., EP948
Zenatti P. P., S106
Zeng L., EP583, PB1472
Zeng Z., S136
Zenhaeusern R., PB1517
Zenke M., S196
Zenkova M., PB1389
Zenz T., S143, EP650
Zerbini M., PB1770
Zerkout S., PB1629
Zervou M., EP1146, PB1351
Zethoven M., S278
Zha J., EP444
Zhai W., PB1781
Zhan L., EP874
Zhang A., PB1723, PB1780
Zhang C., S144, S146, EP632
Zhang D., EP1111
Zhang F., S204
Zhang G., S104
Zhang G.-C., EP1295
Zhang G., EP915, EP1306
Zhang G., EP1257
Zhang H., EP339, EP414
Zhang H., EP452, EP643, PB1391
Zhang H., EP962
Zhang H., S207, EP789, EP794
Zhang H., EP605, PB1499
Zhang J., EP946, EP947
Zhang J., EP1248
Zhang J.-P., EP1230
Zhang J., EP345
Zhang J., S194, EP510
Zhang J., EP957
Zhang J., S265
Zhang J., EP397
Zhang J., S203
Zhang K., S251
Zhang K., S180
Zhang K., PB1648
Zhang L., EP1103, EP1111
Zhang L., EP792
Zhang L., S206
Zhang L., EP899, PB1394
Zhang L., EP931
Zhang M., PB1647
Zhang M., EP534
Zhang M.-M., EP460
Zhang M., EP520
Zhang N., S168
Zhang Q., EP694, PB1542
Zhang Q., S206, S211
Zhang Q., EP414
Zhang Q., EP406
Zhang R., EP1024
Zhang R., EP1257, PB1781
Zhang R.-J., S204
Zhang S., S142
Zhang T., EP794
Zhang W., S223, EP534, EP792, PB1396
Zhang W., EP1120
Zhang X., S194
Zhang X., S118
Zhang X., EP534
Zhang X., S104, EP847
Zhang X.-H., S230, S231, S234, S298, EP347, EP395, EP460, EP484, EP1142, EP1226, EP1240, EP1252, EP1265, EP1295, PB1591
Zhang X., EP1293
Zhang X., EP642
Zhang X., EP1305
Zhang X., EP669
Zhang X., EP372
Zhang X., EP353, EP605, EP627, PB1499, PB1544
Zhang Y., EP605, EP627, PB1499, PB1544
Zhang Y., S223, EP339, EP534
Zhang Y., EP414, EP861
Zhang Y.-M., EP1030
Zhang Y., S204
Zhang Y.-F., EP1030
Zhang Y., PB1542
Zhang Y.-Q., PB1647
Zhang Y., PB1786, PB1795
Zhang Y., EP847
Zhang Y.-Y., S230, EP1252, PB1591
Zhang Y., EP512, EP537, EP549
Zhang Z., EP792
Zhao C., EP1120
Zhao D., EP928
Zhao D., EP346
Zhao F., PB1802, PB1803
Zhao F., EP1312
Zhao H.-Y., S230
Zhao J., EP1037
Zhao L.-P., S162, EP906
Zhao Q., EP805, EP1174
Zhao W., PB1434
Zhao W., EP493
Zhao X., S207
Zhao X., S104
Zhao X.-Y., EP395, EP1142, EP1252, EP1265
Zhao X., EP618
Zhao X., S104
Zhao X.-S., EP347, EP395, EP656, EP1226, EP1265, PB1591
Zhao Y., EP1248
Zhao Y.-L., EP1230
Zhao Y., EP1275, EP1277, PB1361
Zhao Y., EP877
Zhao Y., S206
Zhao Y., EP334, EP862, EP864, EP865, EP866, EP874, EP962
Zharkov P., EP576
Zheleznova V., EP558
Zheljazkov I., PB1522
Zhen J., EP1266
Zheng C., S186
Zheng F., PB1720
Zheng H., S118
Zheng P., S217, PB1435
Zheng Y., EP495
Zheng Y., EP581, PB1492
Zheng Z., PB1795
Zhengli X., EP1300
Zhernjakova A., PB1779, PB1783, PB1784
Zhernyakova A., PB1635, PB1800
Zhong J., S311, EP428, EP445

Zhou C., S147
Zhou D., S223, EP534, EP639
Zhou D.-B., EP1117
Zhou F., EP1075, PB1626, PB1713, PB1715, PB1716
Zhou G., PB1720
Zhou H.-B., PB1647
Zhou H., S204
Zhou H., EP792
Zhou J., S194, S207, EP639, EP789, EP792
Zhou J., EP1248, PB1396
Zhou J.-R., EP1230
Zhou J., EP401
Zhou J.-R., EP1240, PB1591
Zhou K., EP639, EP789, EP792
Zhou L., EP341
Zhou L., EP789
Zhou L., EP1096
Zhou M., S313
Zhou Q., EP877
Zhou S., EP1249
Zhou T., EP460
Zhou T., S188, EP1002, EP1008
Zhou W., EP783
Zhou X., S175
Zhou X., S228, EP334, EP562, EP862, EP864, EP865, EP866, EP868, EP874
Zhou X., EP928
Zhou X., EP1293
Zhou X., EP891, EP923
Zhou Y.-L., EP460, EP484
Zhou Y., EP1269
Zhou Y., S133
Zhou Y., S137, EP917, EP926
Zhou Y., PB1542
Zhou Y.-B., EP1030
Zhou Z.-P., S204
Zhou Z., S118
Zhu A., EP785, EP798
Zhu E. Y., EP524
Zhu H.-L., S204
Zhu H., EP601, EP801, PB1576
Zhu H., EP548, EP618, PB1497
Zhu J., S206, S207, EP789
Zhu J., EP1249
Zhu L., S194
Zhu N., EP931
Zhu P., EP1275
Zhu S., EP1103
Zhu S., PB1613
Zhu S., S302
Zhu W., EP792
Zhu X., S104
Zhu X.-L., S298, EP1142, EP1252
Zhu X., EP877
Zhu Y., PB1614
Zhu Z., PB1646
Zhuang J., EP610
Zhuang J., EP1037, EP1050, EP1120, PB1646, PB1685
Zhuang J.-L., S204, PB1647
Zhuang Z., EP1050, PB1685
Zi J., EP453
Zia A., S210
Zicha D., S142
Zichlin M. L., PB1768
Ziemann F., EP896
Ziga E. D., EP341
Zihala D., EP1297
Ziino O., EP348
Zijlstra J. M., S208, S225, EP517, EP530, EP766
Zikos P., EP551, EP919, EP1153
Zilioli V. R., EP786, PB1442
Zimmerman T., EP805, EP1174
Zimmermann A., EP767
Zimmermann J., EP853
Zimmermann M., EP342
Zimran E., S288
Zinchenko A., EP838
Zinger M., EP1176
Zinger T., S101, EP1306
Zinina E., EP360
Zinzani P. L., S205, S211, EP506, EP509, EP518, EP529, EP543, EP650, EP729, EP769, EP783, EP786, EP793, PB1434, PB1439, PB1569, PB1570
Ziola M., EP1017, EP1018
Ziv E., EP1060
Zivkovic N., EP561
Zizkova H., EP661
Zmajkovicova K., EP784
Zmeeva J., EP607
Zoffoli R., EP920, EP1304
Zoghi B., S239
Zojer N., EP971
Zoletto S., EP1129
Zomas A., EP994
Zonari E., S102
Zonder J. A., EP985, EP1010, EP1017, EP1018, EP1163
Zorina N., PB1549
Zotova O., PB1358
Zou D., S194, S207, EP789
Zou D., EP534, EP1050, PB1685
Zouaoui Z., EP1159
Zoubida T.-M., PB1466, PB1597
Zriba S., PB1443
Zsiros J., S221
Zuazu I., S303
Zuber J., EP378, EP380, EP381
Zubieta M., PB1380
Zucca E., S219
Zucchetti M., EP342
Zucchetto A., EP624
Zucchini P., EP617
Zucenka A., EP486
Zuchnická J., EP631
Zuckerman T., S288, EP462
Zudaire E., EP964, EP1003
Zudaire M., EP587
Zuercher A., EP1200
Zúñiga Á., EP413
Zuo W., EP1265
Zuo Y., EP847
Zupan I. P., EP575
Zupancic Salek S., EP573
Zurko J., EP535
Zuurman M., EP1092
Zvereva M., PB1638
Zverkova A., EP1264
Zvonkov E., PB1785
Zvonkov E., EP360
Zwaan M., EP382, EP569
Zwaginga J. J., EP1348
Zweegman S., S180, S184, EP1020, EP1027
Zwezerijnen G. J., S208, EP517, EP766
Zyuzgin I., EP1264