haematologica
Journal of The Ferrata Storti Foundation

Clinical significance of chromatin-spliceosome acute myeloid leukemia: a report from the Northern Italy Leukemia Group (NILG) randomized trial 02/06

by Chiara Caprioli, Federico Lussana, Silvia Salmoiraghi, Roberta Cavagna, Ksenija Buklijas, Lara Elidi, Pamela Zanghì, Anna Michelato, Federica Delaini, Elena Oldani, Tamara Intermesoli, Anna Grassi, Giacomo Gianfaldoni, Francesco Mannelli, Dario Ferrero, Ernesta Audisio, Elisabetta Terruzzi, Lorella De Paoli, Chiara Cattaneo, Erika Borlenghi, Irene Cavattoni, Monica Tajana, Anna Maria Scattolin, Daniele Mattei, Paolo Corradini, Leonardo Campiotti, Fabio Ciceri, Massimo Bernardi, Elisabetta Todisco, Agostino Cortelezzi, Brunangelo Falini, Chiara Pavoni, Renato Bassan, Orietta Spinelli, and Alessandro Rambaldi

Haematologica 2020 [Epub ahead of print]

Citation: Chiara Caprioli, Federico Lussana, Silvia Salmoiraghi, Roberta Cavagna, Ksenija Buklijas, Lara Elidi, Pamela Zanghì, Anna Michelato, Federica Delaini, Elena Oldani, Tamara Intermesoli, Anna Grassi, Giacomo Gianfaldoni, Francesco Mannelli, Dario Ferrero, Ernesta Audisio, Elisabetta Terruzzi, Lorella De Paoli, Chiara Cattaneo, Erika Borlenghi, Irene Cavattoni, Monica Tajana, Anna Maria Scattolin, Daniele Mattei, Paolo Corradini, Leonardo Campiotti, Fabio Ciceri, Massimo Bernardi, Elisabetta Todisco, Agostino Cortelezzi, Brunangelo Falini, Chiara Pavoni, Renato Bassan, Orietta Spinelli, and Alessandro Rambaldi. Clinical significance of chromatin-spliceosome acute myeloid leukemia: a report from the Northern Italy Leukemia Group (NILG) randomized trial 02/06. Haematologica. 2020; 105:xxx
doi:10.3324/haematol.202.252825

Clinical significance of chromatin-spliceosome acute myeloid leukemia: a report from the Northern Italy Leukemia Group (NILG) randomized trial 02/06

Chiara Caprioli[1], Federico Lussana[1], Silvia Salmoiraghi[1,2], Roberta Cavagna[1], Ksenija Buklijas[1], Lara Elidi[1], Pamela Zanghì[1], Anna Michelato[1], Federica Delaini[1], Elena Oldani[1], Tamara Intermesoli[1], Anna Grassi[1], Giacomo Gianfaldoni[3], Francesco Mannelli[3], Dario Ferrero[4], Ernesta Audisio[4], Elisabetta Terruzzi[5], Lorella De Paoli[6], Chiara Cattaneo[7], Erika Borlenghi[7], Irene Cavattoni[8], Monica Tajana[9], Anna Maria Scattolin[10], Daniele Mattei[11], Paolo Corradini[12,13], Leonardo Campiotti[14], Fabio Ciceri[15], Massimo Bernardi[15], Elisabetta Todisco[16], Agostino Cortelezzi[17], Brunangelo Falini[18], Chiara Pavoni[1], Renato Bassan[10], Orietta Spinelli[1] and Alessandro Rambaldi[1,13]

1 Azienda Socio-Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy;

2 FROM Research Foundation, Ospedale Papa Giovanni XXIII, Bergamo, Italy;

3 Azienda Ospedaliera Universitaria Careggi (AOU), Firenze, Italy;

4 AOU Città della Salute e della Scienza, Torino, Italy;

5 Azienda Ospedaliera San Gerardo, Monza, Italy;

6 Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy;

7 Spedali Civili, Brescia, Italy;

8 Ospedale San Maurizio, Bolzano, Italy;

9 ASST Ospedale di Cremona, Cremona, Italy;

10 Ospedale dell'Angelo e SS. Giovanni e Paolo, Venezia Mestre, Italy;

11 Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy;

12 Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milano, Italy;

13 Department of Oncology and Hematology, Università degli Studi di Milano, Milano, Italy

14 Università dell'Insubria, Varese, Italy;

15 IRCCS Ospedale San Raffaele, Milano, Italy;

16 IRCCS Istituto Clinico Humanitas di Rozzano, Rozzano, Italy;

17 Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy;

18 Università di Perugia, Perugia, Italy;

CC and FL contributed equally to this work.

Running head: Clinical significance of chromatin-spliceosome AML

Contact information for correspondence

Alessandro Rambaldi,

Hematology and Bone Marrow Transplant Unit

ASST Papa Giovanni XXIII Bergamo

Piazza OMS, 1

24127 Bergamo

ITALY

Telephone: +39 035 2673684

Fax: +39 035 2674968

Email: arambaldi@asst-pg23.it

Words count: 234 (abstract) / 3,497 (main text)

Tables/Figures count: 2 tables, 6 figures

Supplemental files count: 1 supplemental file

Trial registration: ClinicalTrials.gov Identifier: NCT00495287

Acknowledgements

This work was partially supported by grants from Agenzia Italiana del Farmaco (Rome, Italy, Project FARM6YMY2N/2006), Fondazione Guido Berlucchi-Onlus (Brescia, Italy, 2006), and Associazione Italiana per la Ricerca sul Cancro (grant IG 2016 n. 18568) (BF).

Competing Interests

The authors declare no competing interests.

Author Contributions

CC, FL and AR designed the research, analyzed and interpreted data, supervised the study and wrote the manuscript. FD, EO, TI, AG, GG, MF, DF, EA, ET, LDP, GR, EB, IC, MT, AMS, DM, PC,

LC, FC, MB, ET, AG, BF, RB performed research and collected data. Genetic studies were performed by RC, KB, LE, PZ, AM. SS and OS performed and supervised genetic studies, collaborated in data interpretation, revised the manuscript and approved the final version. CP analyzed and interpreted data, performed statistical analysis and wrote the manuscript. All authors revised the manuscript and approved the final version before submission.

Abstract

Secondary acute myeloid leukemia (sAML) after myelodysplastic or myeloproliferative disorders is a high-risk category currently identified by clinical history or specific morphological and cytogenetic abnormalities. However, in the absence of these features, uncertainties remain to identify the secondary nature of some cases otherwise defined as *de novo* AML. To test whether a chromatin-spliceosome (CS) mutational signature might better inform the definition of the *de novo* AML group, we analyzed a prospective cohort of 413 newly diagnosed AML patients enrolled into a randomized clinical trial (NILG AML 02/06) and provided with accurate cytogenetic and molecular characterization. Among clinically defined *de novo* AML, 17.6% carried CS mutations (CS-AML) and showed clinical characteristics closer to sAML (older age, lower white blood cell counts and higher rate of multilineage dysplasia). Outcomes in this group were adverse, more similar to those of sAML as compared to *de novo* AML (overall survival, 30% in CS-AML and 17% in sAML vs 61% in *de novo* AML, $P<0.0001$*;* disease free survival, 26% in CS-AML and 22% in sAML vs 54% of *de novo* AML, $P<0.001$) and independently confirmed by multivariable analysis. Allogeneic transplant in first complete remission improved survival in both sAML and CS-AML patients. In conclusion, these findings highlight the clinical significance of identifying CS-AML for improved prognostic prediction and potential therapeutic implications. (NILG AML 02/06: ClinicalTrials.gov Identifier: NCT00495287).

Introduction

According to the current WHO classification (1), sAML is defined either by a previous clinical history of hematological disease, the morphological detection of multilineage dysplasia or specific cytogenetic characteristics; the two latter criteria are additive to clinical history or may be themselves sufficient to diagnose sAML, even in the absence of a known antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) (1,2). However, in clinical practice some uncertainty remains regarding the correct classification of potentially high-risk sAML cases, especially when antecedent history is not thoroughly documented or does not fully satisfy the diagnostic criteria of MDS. Moreover, morphological examination to assess blast counts and multilineage dysplasia shows inter-observer variability that may impair diagnostic reproducibility (3). Finally, cytogenetic analysis, which usually takes a long turnaround time of 5-10 days, may not be always informative because of technical failure or normal result. These features eventually translate into under-recognition of sAML patients and lead to inadequate clinical management, since this high-risk population deems intensive treatment strategies comprising the administration of innovative agents or allocation to clinical trials, potentially able to improve the rates of complete remission (CR) (4–7), followed by a rapid consolidation with allogeneic hematopoietic stem cell transplant (alloHSCT) (7,8). Therefore, more accurate diagnostic approaches are warranted. In this regard, studies focusing on the molecular landscape of sAML and preceding conditions have suggested the possibility of defining distinct subtypes of AML based on their mutational profiles. Mutations in genes involved in chromatin regulation (*ASXL1, EZH2, BCOR, STAG2*) and RNA splicing (*SRSF2, SF3B1, U2AF1, ZRSR2*) have shown high specificity for sAML after MDS (9); these mutations, called secondary-type mutations, occur early in leukemogenesis (likely representing the expansion of clones acquired during previous MDS) (10,11) and often persist in clinical remission, presenting as constitutively chemo-resistant. Although less characterized, sAML cases progressing after MPN display similar features (12,13). However, a closely related mutational signature can be identified also in some *de novo* AML cases (14,15). In the seminal study conducted by Papaemmanuil et al. (14) on a large cohort of AML patients, overlapping mutations in genes regulating RNA splicing (*SRSF2, SF3B1, U2AF1,* and *ZRSR2*), chromatin (*ASXL1, STAG2, BCOR, KMT2A*-PTD, *EZH2*, and *PHF6*), or transcription (*RUNX1*) constituted an independent genomic class, called the chromatin–spliceosome group. Mutations in *RUNX1* and *KMT2A*-PTD frequently co-occurred with other mutations of the signature and, albeit not universally observed in

sAML, have been reported as more significantly associated with high-risk than low-risk MDS (11), consistently occurring at intermediate time points and not as founding mutations (11, 14-16). Strikingly, 91% of patients in this group had a *de novo* AML by clinical definition; although heterogeneous, mutations in this molecular signature were consistently associated with older age, lower white blood cell and blast counts, lower rates of response to induction chemotherapy and higher relapse rates. While these results warrant prospective validation, it can be hypothesized that the presence of these mutations represent the trace of a previous, unrecognized MDS or MPN phase. However, a formal comparison between de novo AML patients carrying CS mutations and sAML patients defined by standard criteria, along with associated outcomes, is currently lacking.

To investigate the clinical significance of the CS mutational signature, we re-assessed patients' diagnosis according to the presence of CS mutations in a large cohort of newly diagnosed AML patients enrolled into a prospective trial (NILG AML 02/06) [ClinicalTrials.gov Identifier: NCT00495287] (17). In this study, we report the characteristics and outcomes of initially defined *de novo* AML patients carrying CS mutations as compared with other clinically defined *de novo* AML patients without CS mutations and patients with sAML defined by standard WHO criteria.

Methods

Patients, treatment, cytogenetic and molecular analyses

The NILG-AML 02/06 multicentric Italian trial (17) enrolled 574 patients with newly diagnosed AML [≥20% bone marrow (BM) blasts] or high-risk MDS (10-19% BM blasts) between 2007 and 2012. All participants were randomized to receive induction with standard-dose idarubicin, cytarabine and etoposide (ICE) or high-dose cytarabine and idarubicin (sHD). Patients not responding to first induction underwent an intensified re-induction with sHD. A consolidative alloHSCT was performed in high-risk patients based on study-specific risk stratification, as previously reported (17). Written informed consent for inclusion in the clinical trial and genetic analyses was provided by all patients. Study protocols were in accordance with the Declaration of Helsinki and approved by the institutional review boards of each participating center.

Informative karyotype was locally obtained at diagnosis for 413 patients. Molecular analyses were centrally performed on samples collected at diagnosis (Supplemental Methods). *NPM1*, *FLT3*-ITD and point mutations, *RUNX1-RUNX1T1*, *CBFb-MYH11*, biallelic *CEBPa* and *KMT2A*-PTD mutations were

tested on all patients using PCR, Sanger sequencing and/or fragment analysis. Targeted NGS was performed on 196 normal karyotype patients using an amplicon-based method (Trusight Myeloid, Illumina, San Diego, California, USA; n=161) amplifying 54 gene regions and a capture-based method (Sophia Myeloid Solution, Sophia Genetics SA, Saint Sulpice, Switzerland; n=35) selecting 30 gene regions (Supplemental Table 1 and 2) (18).

To confirm our results in an independent cohort, we also evaluated a single-center series of AML patients (N=50) treated at ASST Ospedale Papa Giovanni XXIII between 2012 and 2020.

Definition of AML categories

The following AML categories were defined among patients enrolled into the trial: 1) CS-AML: with the specific goal of validating the CS mutational signature, clinically defined *de novo* AML patients were included into this category based on the presence of at least one variant described according to Papaemmanuil et al. (14) including *ASXL1, STAG2, BCOR, EZH2, PHF6, SRSF2, SF3B1, U2AF1, ZRSR2, RUNX1* and *KMT2A*-PTD (or cytogenetic alterations in *KMT2A* gene in the 11q23 cytogenetic region), excluding patients with concurrent WHO-recurrent abnormalities (1); 2) sAML: patients with a documented clinical history of MDS, MDS/MPN or MPN and/or cytogenetic WHO criteria of AML with MDS-related changes (1); 3) *de novo* AML: none of the above. To avoid ambiguous interpretation, morphological WHO criteria of AML with MDS-related changes were not considered in the definition of sAML. Patients with MDS, therapy-related AML or not provided with a cytogenetic and/or molecular characterization were excluded from the analysis.

Statistical analysis

The clinical endpoints of the study were defined according to standard criteria (19). Comparisons between baseline characteristics and AML categories were analyzed using the Mann-Whitney U test for countinuous and Chi-squared or Fisher's exact test for categorical variables. Overall survival (OS) and disease free survival (DFS) were estimated by the Kaplan-Meier method and any differences between AML categories or consolidation treatment were evaluated with log-rank test. Cox models were used to estimate hazard ratios with 95% confidence intervals (CI) in univariate and multivariable analysis on survival outcomes. AlloHSCT was considered as a time-dependent event; outcome data were estimated by the Mantel-Byar method and graphically illustrated by Simon-Makuch plots. All reported

P values are two-sided and set at 5% significance level. All analyses were performed with R software, version 3.5.0.

Results

Characteristics of patients

Among 574 adult patients enrolled in the NILG-AML 02/06 trial (16), 413 (72%) with full genetic characterization resulted evaluable and were classified as 55 CS-AML patients, 100 sAML patients (28 defined by clinical history, of which 24 after MDS or MDS/MPN and 4 after MPN, and 72 defined by cytogenetic criteria) and 258 *de novo* AML patients (Figure 1). The 55 cases re-classified as CS-AML represented 17.6% of otherwise defined *de novo* AML patients and 13% of the whole analyzed cohort.

The main clinical characteristics of patients are reported in Table 1. Compared to *de novo* AML, patients with sAML and CS-AML were similarly older (median age 48, 59 and 58 years respectively, $P<0.0001$) and presented at diagnosis with lower white blood cell counts (WBC) ($P<0.0001$), with no significant differences between the two latter categories. A lower BM blast infiltration was reported in sAML as compared with both *de novo* AML ($P<0.0001$) and CS-AML ($P=0.02$). By morphological analysis, multilineage dysplasia was described at diagnosis in a minor proportion of CS-AML patients (11%), close to that of sAML patients (9%, $P=0.77$) and similarly higher than that of *de novo* AML patients (2%, $P=0.0051$)**.**

The cytogenetic and molecular characteristics of the cohort are summarized in Figure 2 and Supplemental Table 2.

In the CS-AML category (N=55) (Figure 2A-B), the majority of patients (87%) had a normal karyotype; 160 mutations were found in total, with a median of 3 mutations per patient (range 1-6). The most frequently reported mutations of the CS signature were in *KMT2A* (*KMT2A*-PTD), *RUNX1* and *ASXL1* genes (respectively 45.5%, 44.4% and 22.2% of evaluable patients), while other mutations accounted for 5-17.5% of cases. While 54.5% of patients in this category presented with a single CS mutation, overlap and significant associations between CS mutations were observed in 45.5% of cases. Other mutations scored in CS-AML patients included *IDH2, DNMT3A, FLT3*-ITD, *TET2* and *NRAS* (respectively 20%, 15.6%, 14.5% and 11% of evaluable patients), and others (Figure 3 and Figure 4). We also attributed to the CS-AML category 2 patients with not previously described variants (UPN 633, *STAG2* p.Met135Ile and UPN 753, *SRSF2* p.Val18Leu) due to their predicted pathogenicity. One more patient harboring the *RUNX1* p.Ala60V variant (UPN 3) was also included. This variant has been found in familial platelet disorder associated to myeloid malignancy and as such reported in ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000463986).

Among the 100 sAML patients (Figure 2C-D), a huge proportion carried a complex karyotype (58%) and abnormalities of chromosome 7 (12%) or 5 (5%). Nevertheless, 13% of patients in this category had a normal karyotype; 62 mutations were reported in total (median 0, range 0-8), mostly involving CS genes.

The *de novo* AML category (N=258) (Figure 2E-F) included 25% of patients with a core binding factor AML, a high prevalence (65%) of patients with normal karyotype and 10% of patients with other non WHO-recurrent cytogenetic abnormalities. A total of 607 mutations were scored (median 2 per patient, range 0-15), the most frequently represented being *NPM1* (60.7% of patients), *DNMT3A* (49.3%) and *FLT3*-ITD (27.5%).

Outcomes after intensive induction

Patients with *de novo* AML, sAML and CS-AML were equally distributed as to the randomly assigned induction regimen (conventional ICE or high-dose sHD) and showed a comparable performance status (Table 1).

After the first induction cycle, a lower proportion of sAML patients achieved CR (51/100, 51%) as compared to both *de novo* AML (228/258, 88.4%; $P<0.0001$) and CS-AML (43/55, 78.2%; $P=0.002$). However, also CS-AML showed a trend toward an inferior CR rate as compared to *de novo* AML

(*P*=0.07), although this did not reach statistical significance, eventually due to the relative small number of patients in this group. Interestingly, no significantly worse CR rate was observed between these latter groups (*P*=0.14) when accounting for both first induction (performed in all patients) and intensified re-induction (performed in patients who did not respond after first cycle). By contrast, sAML patients did not improve their CR rate (59%) even after undergoing re-induction, as compared with both *de novo* AML (92.6%, *P*<0.0001) and CS-AML (85.5%, *P*=0.001). In addition, early death more frequently occurred in sAML patients (14/100, 14%) than in *de novo* AML (11/258, 4.3%; *P*=0.003) and CS-AML (3/55, 5.5%; *P*=0.17). Globally, 41% of sAML patients, 14.5% of CS-AML patients and 7.3% of *de novo* AML patients did not achieve CR because of early death or chemo-resistance; these patients carried a dismal 1-year OS (17%) (Supplemental Figure 1).

We investigated factors affecting the probability of achieving CR (accounting for both induction cycles) by performing univariate analysis within each AML category. In *de novo* AML, a significantly negative impact was observed for advanced age, impaired performance status, high WBC and the presence of *FLT3*-ITD mutations. Apart from the presence of *SRSF2* mutations among CS-AML patients [HR 0.16 (95% CI 0.02-1.02), *P*=0.05], no other relevant clinical or biological factors (including the intensity of induction regimen) were identified for sAML and CS-AML patients (Supplemental Table 3).

Survival outcomes

The median follow-up for survival analysis was 4.9 years (range 0.2-8.4 years). *De novo* AML patients showed a markedly better 5-years OS (61%) and DFS (54%) than CS-AML (OS 30%, DFS 26%; *P*<0.0001 and *P*=0.0009 respectively) and sAML (OS 17%, DFS 22%; *P*<0.0001 for both comparisons) (Figure 5A and 5B). Patients with sAML carried a significantly worse OS as compared to CS-AML (*P*=0.02) (Figure 5A); however, possibly due to the high mortality rate of non-responding patients, no difference was observed between the two categories when considering only patients achieving CR, who showed an overlapping 5-years DFS (26% and 22% respectively, P=0.32) (Figure 5B). A similar trend of OS according to the respective categories was confirmed on a smaller (N=50), independent single-center cohort (Supplemental Figure 2; for demographic and clinical characteristics of this cohort, see Supplemental Table 6).

According to trial risk stratification criteria, a consolidative alloHSCT in first CR was administered in 18/47 (38.3%) CS-AML, 31/59 (52.5%) sAML and 80/239 (33.5%) *de novo* AML patients, at a median

age of 49.5, 52 and 44.5 years, respectively. By time-dependent analysis, the administration of alloHSCT in first CR carried a 5-years survival advantage in each AML category (CS-AML: 48% vs 24%, *P*=0.07; sAML: 38% vs 8%, *P*=0.0001; *de novo* AML: 75% vs 59%, *P*=0.01) (Figure 6A-C).

By multivariable analysis performed on the whole patients' cohort accounting for age, performance status, WBC count at diagnosis and induction arm (standard vs high-dose regimen), the markedly unfavorable prognosis of the sAML category was evident for each considered outcome [CR: HR 0.09 (95% CI 0.05-0.19), *P*<0.0001; OS: HR 3.71 (95% CI 2.69-5.12), *P*<0.0001; and DFS: HR 2.54 (95% CI 1.76-3.67), *P*<0.0001)]. Although to a lesser degree, also the CS-AML category was independently associated to a negative prognosis, in terms of OS [HR 2.2 (95% CI 1.48-3.25), *P*=0.0001] and DFS [HR 1.89 (95% CI 1.27-2.81), *P*=0.0018], but not CR (Table 2). Other factors affecting clinical outcomes included age ≥60 years, performance status (on CR and OS) and WBC ≥50x10^9/L (on OS and DFS).

Since CS mutations frequently co-occurred within individual patients, we sought to investigate whether specific variants of the signature might be independently responsible for the adverse prognosis of CS-AML patients. In a multivariable analysis performed on the CS-AML cohort including CS-mutations and adjusting for the same variables as in previous analysis (Supplemental Table 4), only *RUNX1* and *U2AF1* independently affected OS [HR 3.55 (95% CI 1.28-9.87), *P*=0.01 and HR 6.87 (95% CI 1.71-27.55), *P*=0.006] and DFS [HR 3.13 (95% CI 1.1-8.95), *P*=0.03 and HR 16.46 (95% CI 3.14-86.31), *P*=0.0009]. Notwithstanding, even after subtracting *RUNX1* and/or *U2AF1*-mutated patients from the first multivariable analysis (Supplemental Table 5), the CS-AML category maintained indipendently worse OS [HR 1.83 (95% CI 1.07-3.14), P=0.0281] and DFS [HR 1.94 (95% CI 1.15-3.26), P=0.0126] as compared to *de novo* AML.

Discussion

In this study, we challenged a CS mutational signature (14) against conventionally defined sAML and de novo AML patients to seek whether a comparison between related outcomes might provide a basis for implementing current clinical and cytogenetic diagnostic criteria of sAML with molecular information. Importantly, the identification of patients carrying CS mutations has been allowed by conventional methods and by commercially available NGS solutions, which can be easily and cost-effectively implemented in the routine diagnostic work-up of AML (20). Since diagnostic uncertainty is

higher in cases lacking informative cytogenetics, we focused the search of CS mutations on patients with normal karyotype; anyway, in previous studies these mutations were infrequently associated with abnormalities of chromosomes 5 and 7 or complex karyotypes (9, 21). To the best of our knowledge, this is the first report formally comparing outcomes of patients with *de novo* AML carrying this mutational profile and sAML (defined by clinical and/or cytogenetic criteria) on a large multicentric prospective cohort. Patients included into the study showed a broad age range representative of real life population, were homogeneously treated with intensive chemotherapy within a prospective clinical trial and showed a long duration of follow-up, which allowed to effectively study the prognostic relevance of CS mutations. As an additional feature, we evaluated the impact of alloHSCT in each AML category.

In keeping with previous observations, in our study the identification of a CS mutational signature revealed markedly high-risk features in about 18% of otherwise defined *de novo* AML patients (9,14,15), which represents a significant proportion of the whole analyzed cohort, quite consistent with that reported by other studies (14, 22). Beyond mutations in *KMT2A*-PTD, *RUNX1* and *ASXL1*, we showed that also mutations in *U2AF1* carry independent prognostic impact; of note, the adverse significance of CS mutations was maintained independently from *RUNX1* and *U2AF1*, suggesting that the full signature might be further evaluated for assignment to the high-risk group of the ELN stratification model (7). Based on these data, it remains unclear whether *RUNX1*-mutated AML, albeit constituting the most represented subgroup within this category, accounts for a separate clinical and prognostic entity.

In addition, we have highlighted that CS-AML more closely resemble sAML than *de novo* AML, in terms of clinical characteristics and outcomes. When considering OS, however, CS-AML stands as an intermediate category showing a slightly but significantly better survival than sAML; as from our data this appears as the consequence of the high rates of early chemo-resistance and related mortality in sAML patients, a possible explanation for this difference resides in the negative impact of complex cytogenetics in the sAML group. Alternatively, this category might contain a mixture of both sAML and true *de novo* cases. As such, the role of the CS signature to accurately diagnose sAML remains not fully elucidated. However, from a practical point of view, the definition of CS-AML as a prognostically homogeneous group might be more clinically significant than a merely ontogenetic classification, as recently showed also for secondary-type mutations (23). In fact, since we observed a survival ad-

vantage in both sAML and CS-AML patients to whom alloHSCT was offered in first CR, patients with a CS molecular profile might be considered for intensive treatment strategies comprising rapid allocation to alloHSCT. The main challenge in this setting, however, would be the improvement of remission rates and depth to extend the access to a potentially curative alloHSCT, by exploiting innovative therapeutics possibly overcoming the inherent long-term chemo-resistance of CS-AML. In this regard, keeping into account the closer similitude between sAML and CS-AML might facilitate the optimization of available treatment strategies as well as the design of dedicated clinical trials. Among potentially useful agents, CPX-351 has been recently approved by FDA and EMA specifically for the treatment of AML with MDS-related changes or therapy-related AML and might provide a similar benefit in fit CS-AML patients (4). Furthermore, in a large phase 1b trial the anti-Bcl-2 agent venetoclax in association with hypomethylating agents has provided promising CR and survival rates even in sAML patients or AML with poor cytogenetics (5), while spliceosome modulators (24, 25) and DOT1L inhibitors (26) may represent a rational candidate for functional targeting of CS-AML and are currently being evaluated in clinical trials involving myeloid neoplasms. Finally, in our dataset *IDH2* mutations were reported in 20% of CS-AML patients, confirming previous observations (14) and representing another potentially important therapeutic target in this population (27).

The bottom line is that an accurate cytogenetic and molecular characterization is required at the diagnosis of AML, making reasonable to wait for these data in order to perform the best treatment decision or enrollment into clinical trials; this approach has recently demonstrated to be safe in clinically stable patients (28). In such context, although conventional cytogenetics is still needed for a correct risk stratification (7), NGS technologies may overcome its limitations and long turnaround time (20), also providing additional information with improved cost-effectiveness.

In conclusion, we have assessed the impact of a CS mutational signature on a large prospective cohort of AML patients employing a standardized, easily implementable NGS method and highlighting the need to detect this signature at diagnosis for an accurate risk prediction, with potentially relevant implications for the clinical management of AML patients.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
2. Weinberg OK, Seetharam M, Ren L, et al. Clinical characterization of acute myeloid leukemia with myelodysplasia-related changes as defined by the 2008 WHO classification system. Blood. 2009;113(9):1906-1908.
3. Naqvi K, Jabbour E, Bueso-Ramos C, et al. Implications of discrepancy in morphologic diagnosis of myelodysplastic syndrome between referral and tertiary care centers. Blood. 2011;118(17):4690-4693.
4. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol. 2018;36(26):2684-2692.
5. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7-17.
6. Döhner H, Dolnik A, Tang L, et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. Leukemia. 2018;32(12):2546-2557.
7. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
8. de Witte T, Hagemeijer A, Suciu S, et al. Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomized European intergroup trial. Haematologica. 2010;95(10):1754-1761.
9. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-1376.
10. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28(2):241-247.
11. Makishima H, Yoshizato T, Yoshida K, et al. Dynamics of clonal evolution in myelodysplastic syndromes. Nat Genet. 2017;49(2):204-212.
12. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia. 2013;27(9):1861-1869.
13. Lasho TL, Mudireddy M, Finke CM, et al. Targeted next-generation sequencing in blast phase myeloproliferative neoplasms. Blood Adv. 2018;2(4):370-380.
14. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.

15. Metzeler KH, Herold T, Rothenberg-Thurley M, et al. Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood. 2016;128(5):686-698.
16. Dicker F, Haferlach C, Sundermann J, et al. Mutation analysis for *RUNX1*, *MLL*-PTD, *FLT3*-ITD, *NPM1* and *NRAS* in 269 patients with MDS or secondary AML. Leukemia. 2010;24(8):1528-1532.
17. Bassan R, Intermesoli T, Masciulli A, et al. Randomized trial comparing standard vs sequential high-dose chemotherapy for inducing early CR in adult AML. Blood Adv. 2019;3(7):1103-1117.
18. Salmoiraghi S, Cavagna R, Zanghì P, et al. High throughput molecular characterization of normal karyotype acute myeloid leukemia in the context of the prospective trial 02/06 of the Northern Italy Leukemia Group (NILG). Cancers. 2020;12(8):2242.
19. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-4649.
20. Levine RL, Valk PJM. Next-generation sequencing in the diagnosis and minimal residual disease assessment of acute myeloid leukemia. Haematologica. 2019;104(5):868-871.
21. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616-3627.
22. Ley TJ, Miller C, Ding L, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368(22):2059-2074.
23. Gardin C, Pautas C, Fournier E, et al. Added prognostic value of secondary AML-like gene mutations in ELN intermediate-risk older AML: ALFA-1200 study results. Blood Adv. 2020;4(9):1942-1949.
24. Brierley CK, Steensma DP. Targeting spliceosome in the treatment of myelodysplastic syndromes and other myeloid neoplasms. Curr Hematol Malig Rep. 2016;11(6):408-415.
25. Steensma DP, Maris MB, Yang J, et al. H3B-8800-G0001-101: A first in human phase I study of a spliceosome modulator in patients with advanced myeloid malignancies. J Clin Oncol. 2017;35:15_suppl:TPS7075.
26. Daigle SR, Olhava EJ, Therkelsen CA, et al. Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor. Cancer Cell. 2011;20(1):53-65.
27. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722-731.
28. Röllig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020;136(7):823-830.

Table 1. Demographic and clinical characteristics of patients by AML category.

Clinical characteristics	CS-AML N=55	*P**	sAML N=100	*P***	*de novo* AML N=258	*P****
Age [years], median (range)	58 (20-72)	0.5542	59 (22-72)	<0.0001	48 (16-73)	0.0001
<60, n(%)	33 (60)	0.4015	53 (53)	<0.0001	207 (80.2)	0.0013
≥60, n(%)	22 (40)		47 (47)		51 (19.8)	
Gender, n (%)		0.0349		0.0076		0.8048
M	25 (45.5)		63 (63)		122 (47.3)	
F	30 (54.5)		37 (37)		136 (52.7)	
ECOG PS, n (%)		0.5674		0.4207		0.9903
0-1	49 (89.1)		92 (92)		230 (89.1)	
2-3	6 (10.9)		8 (8)		28 (10.9)	
Hepatomegaly, n (%)	5 (9.1)	0.5216	6 (6)	0.4916	21 (8.1)	0.7897
Splenomegaly, n (%)	2 (3.6)	0.2150	10 (10)	0.3159	36 (14)	0.0334
Extramedullary involvement, n (%)	6 (10.9)	0.5458	7 (7)	0.0267	41 (15.9)	0.3477
Hemoglobin [g/dL], median (range)	9.3 (5.1-13.8)	0.6334	8.8 (4.3-13.7)	0.1905	9.3 (3-15.8)	0.7040
WBC count [x10^9/L], median (range)	8.1 (1.1-252)	0.1794	4.8 (0.8-237)	<0.0001	22.3 (0.5-282)	0.0004
Platelets, median (range)	77 (12-815)	0.1441	57 (2-338)	0.3649	52 (5-852)	0.0151
BM blast cells (%), median (range)	80 (8-100)	0.0227	64 (2-100)	<0.0001	80 (0-100)	0.2067
AML with multilineage dysplasia, n (%)	6 (10.9)	0.7786	9 (9)	0.0041	5 (1.9)	0.0051
Induction treatment, n (%)		0.7613		0.6852		0.5065
ICE	25 (45.5)		48 (48)		130 (50.4)	
sHD	30 (54.5)		52 (52)		128 (49.6)	

Abbreviations: CS-AML, chromatin-spliceosome acute myeloid leukemia; sAML, secondary acute myeloid leukemia; *de novo* AML, *de novo* acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBC, white blood cell count; BM, bone marrow. *P*-values refer to: *CS-AML vs sAML; **sAML vs *de novo* AML; *** *de novo* AML vs CS-AML. Hepatomegaly was defined as lower liver edge >2 cm from costal margin. Splenomegaly was defined as spleen >1 cm from costal margin, confirmed by ultrasound scan with longitudinal axis >12 cm. Extramedullary AML was defined as AML presenting with central nervous system involvement or mass lesions.

Table 2. Multivariable analysis for complete remission, overall survival and disease free survival on the whole patient cohort.

All patients	**Complete remission**		**Overall survival**		**Disease free survival**	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age [years]						
≥60	0.38 (0.21-0.7)	0.0017	1.67 (1.25-2.23)	0.0005	1.32 (0.95-1.83)	0.1030
ECOG PS						
2-3	0.25 (0.11-0.57)	0.0010	2.32 (1.55-3.47)	<0.0001	1.46 (0.87-2.43)	0.1502
WBC count [x109/L]						
≥50	0.5 (0.24-1.03)	0.0582	1.69 (1.23-2.3)	0.0010	1.59 (1.14-2.21)	0.0063
Induction arm						
ICE	0.87 (0.48-1.57)	0.6486	1.27 (0.97-1.66)	0.0856	1.27 (0.95-1.7)	0.1046
AML category						
sAML	0.09 (0.05-0.19)	<0.0001	3.71 (2.69-5.12)	<0.0001	2.54 (1.76-3.67)	<0.0001
CS-AML	0.51 (0.2-1.37)	0.1608	2.2 (1.48-3.25)	0.0001	1.89 (1.27-2.81)	0.0018
Abbreviations: ICE, idarubicin, cytarabine and etoposide; HR, hazard ratio; CI, confidence interval.						

Figure legends

Figure 1. CONSORT diagram illustrating patient selection. ICE, idarubicin, cytarabine, etoposide; sHD, sequential high-dose chemotherapy; TKI, tyrosine-kinase inhibitors; tAML, therapy-related acute myeloid leukemia.

Figure 2. Cytogenetic and molecular characteristics of AML categories. For each AML category, pie charts (top of the figure) depict the distribution of chromosomal abnormalities, while histograms (bottom) show the frequency of individual mutations. (A, B) CS-AML, (C, D) sAML and (E, F) *de novo* AML. The label "other" includes: for the CS-AML category, abnormalities of chromosome 11 [(other than t(v;11q23.3) and del(11q)] and +8; for the sAML category, del(11q), +8, del(12p), t(5q;12p), t(1p;3q), t(3q;5q) and -Y; for the *de novo* AML category, +8, del(9q), +21, monosomy 21, +13, t(8q;11q), inv(3), monosomy X, -Y, del(16q), add(4q), add(6p), t(13p;17p).

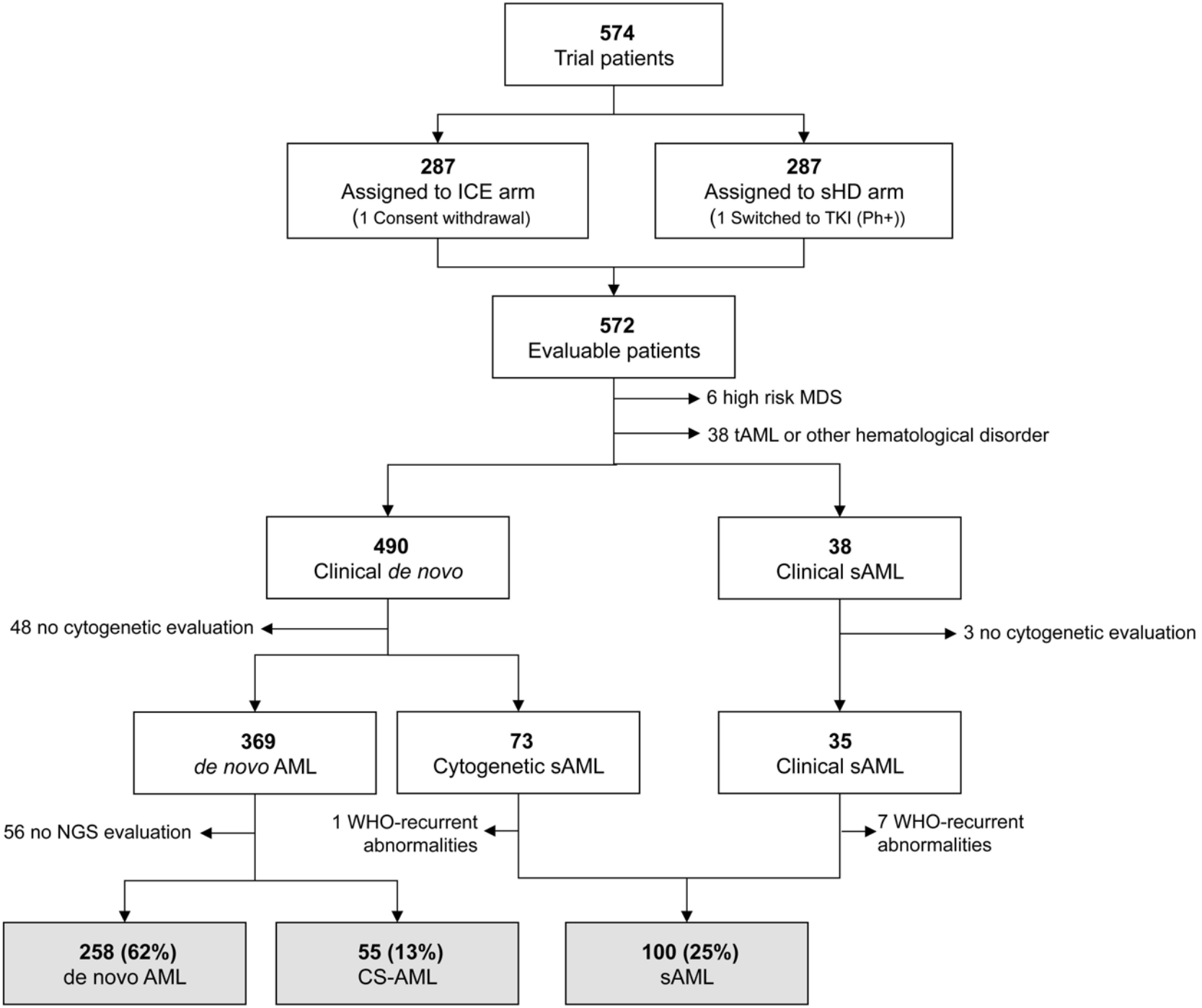
Figure 3. Mutational profile of 55 CS-AML patients. Each column represents an individual CS-AML patient, while each row represents a single gene mutation out of the list at the left. Colored bars indicate the presence of one or more mutations of each gene. Variant types are specified according to the legend at the bottom of the figure.

Figure 4. Patterns of co-occurrence and mutual exclusivity of gene mutations among 55 CS-AML patients. In the lower triangle are shown pairwise associations between gene mutations. For each pair, odds ratios indicate an increased (>1) or decreased (<1) probability of co-occurrence between the two mutations as assessed by the Fisher exact test for statistical significance. The odds ratio of the association is color coded and the significance level is indicated by the number of asterisks in each colored square as reported in the legend at the right of the figure. The upper triangle illustrates the absolute number of occurrences of each molecular pair, shown in green gradient and divided in intervals as reported in the legend. The analysis was performed on the whole study cohort (N=413), excluding mutations occurring in less than 6 patients and not defining AML categories.

Figure 5. Kaplan-Meier survival analysis according to AML category. Survival estimates were calculated at 5 years and not censored at allogeneic transplant. (A) Overall survival; CS-AML vs *de*

novo AML, *P*<0.0001; sAML vs *de novo* AML, *P*<0.0001; CS-AML vs sAML, *P*=0.02. (B) Disease free survival; CS-AML vs *de novo* AML, *P*=0.0009; sAML vs *de novo* AML, *P*<0.0001; CS-AML vs sAML, *P*=0.32.

Figure 6. Simon-Makuch plots of overall survival according to allogeneic hematopoietic stem cell transplant. Transplant was considered as a time-dependent event. Survival estimates were calculated at 5 years from the date of complete remission after induction chemotherapy. (A) CS-AML, (B) sAML and (C) *de novo* AML.

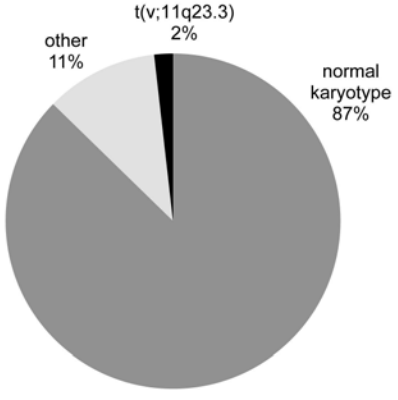

574
Trial patients
287
Assigned to ICE arm
(1 Consent withdrawal)
287
Assigned to sHD arm
(1 Switched to TKI (Ph+))
572
Evaluable patients
6 high risk MDS
38 tAML or other hematological disorder
490
Clinical de novo
38
Clinical sAML
48 no cytogenetic evaluation
3 no cytogenetic evaluation
369
de novo AML
73
Cytogenetic sAML
35
Clinical sAML
56 no NGS evaluation
1 WHO-recurrent abnormalities
7 WHO-recurrent abnormalities
258 (62%)
de novo AML
55 (13%)
CS-AML
100 (25%)
sAML

CS-AML

sAML

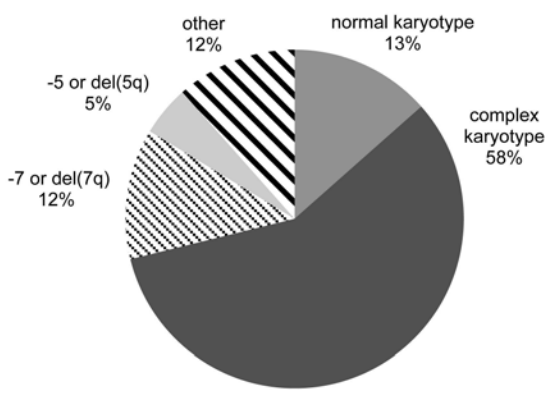
de novo AML

A



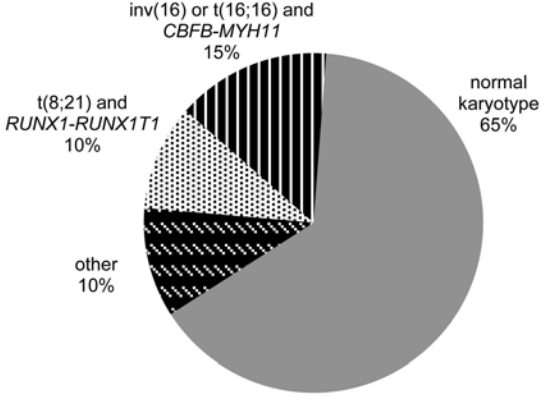
N=55

C



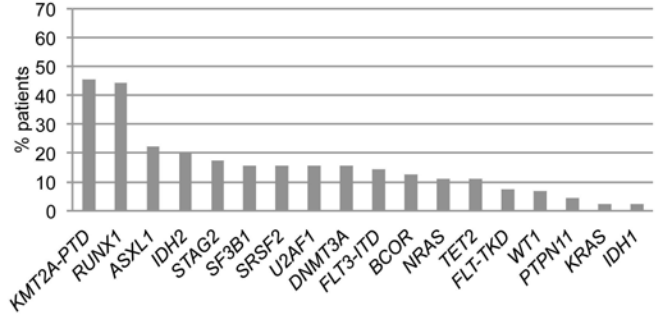
N=100

E

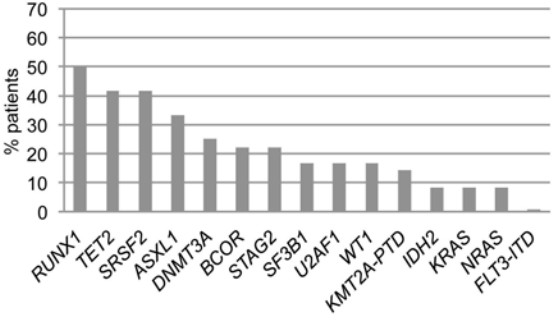


N=258

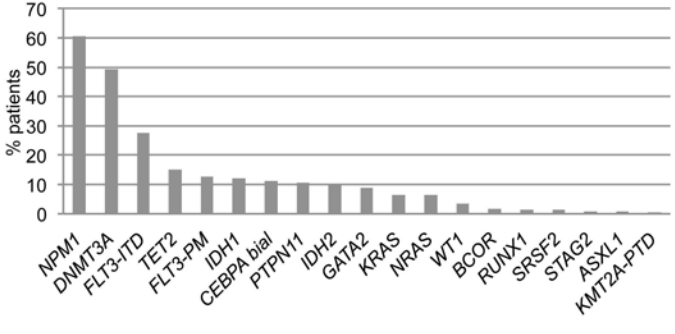
B

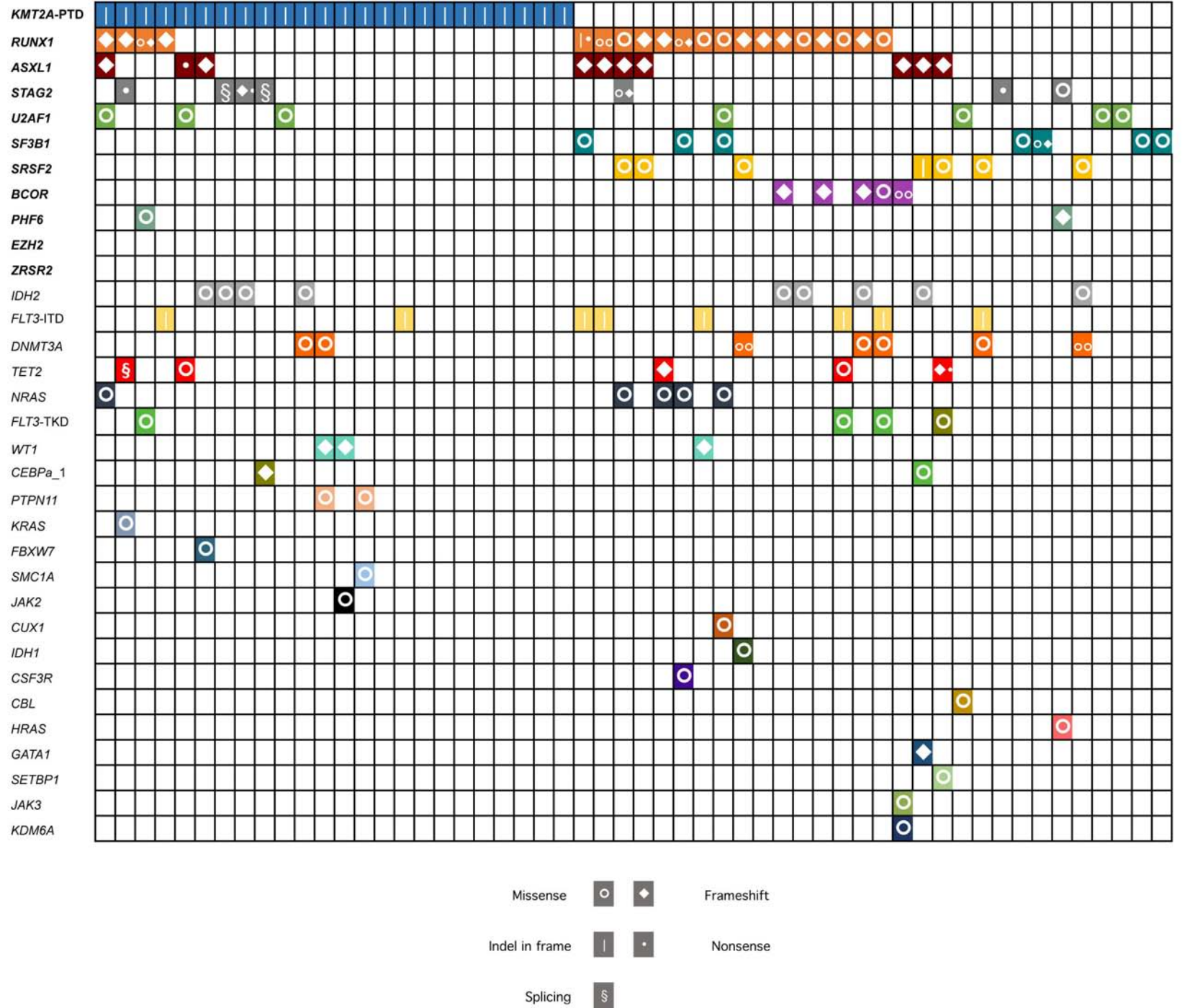


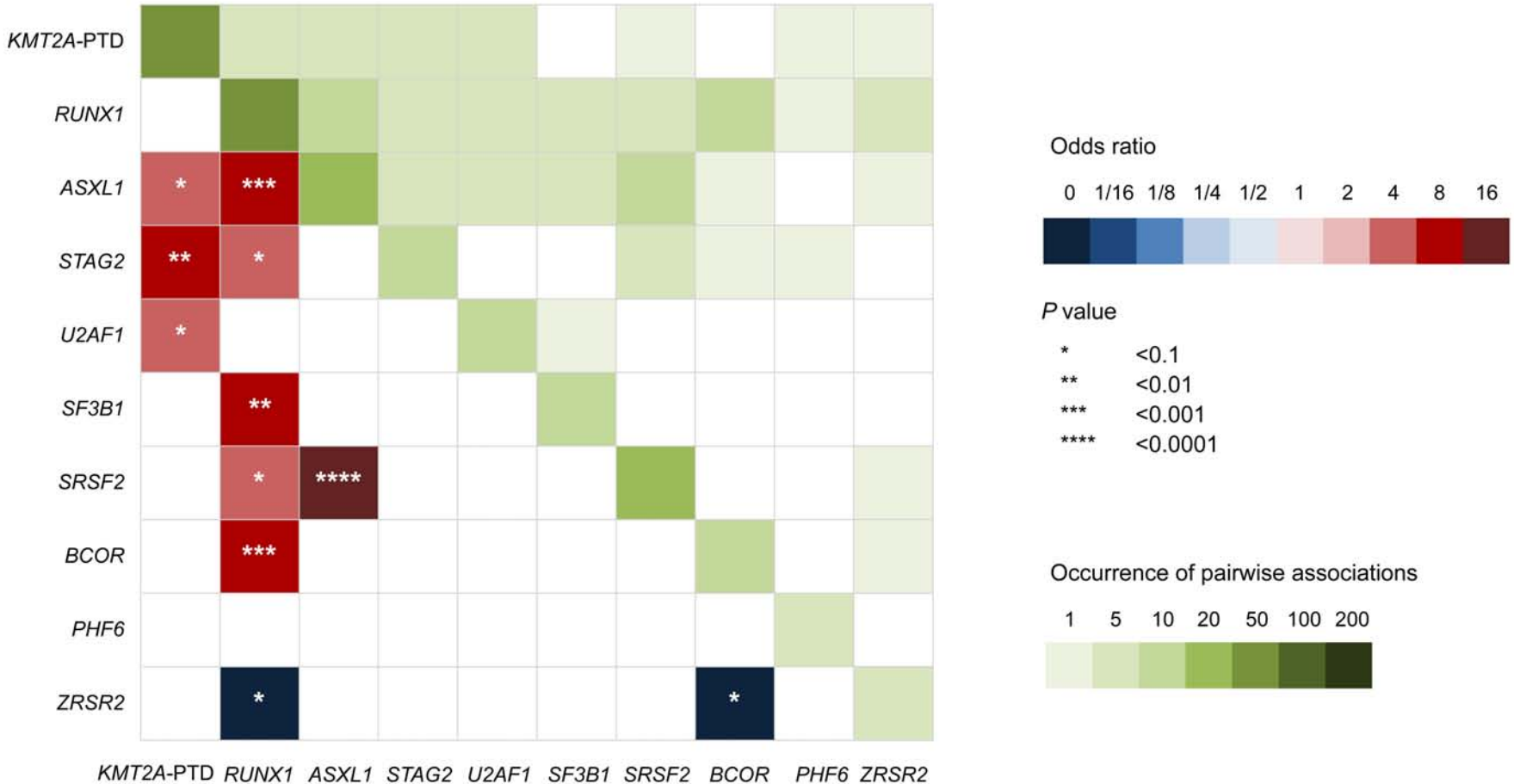
D

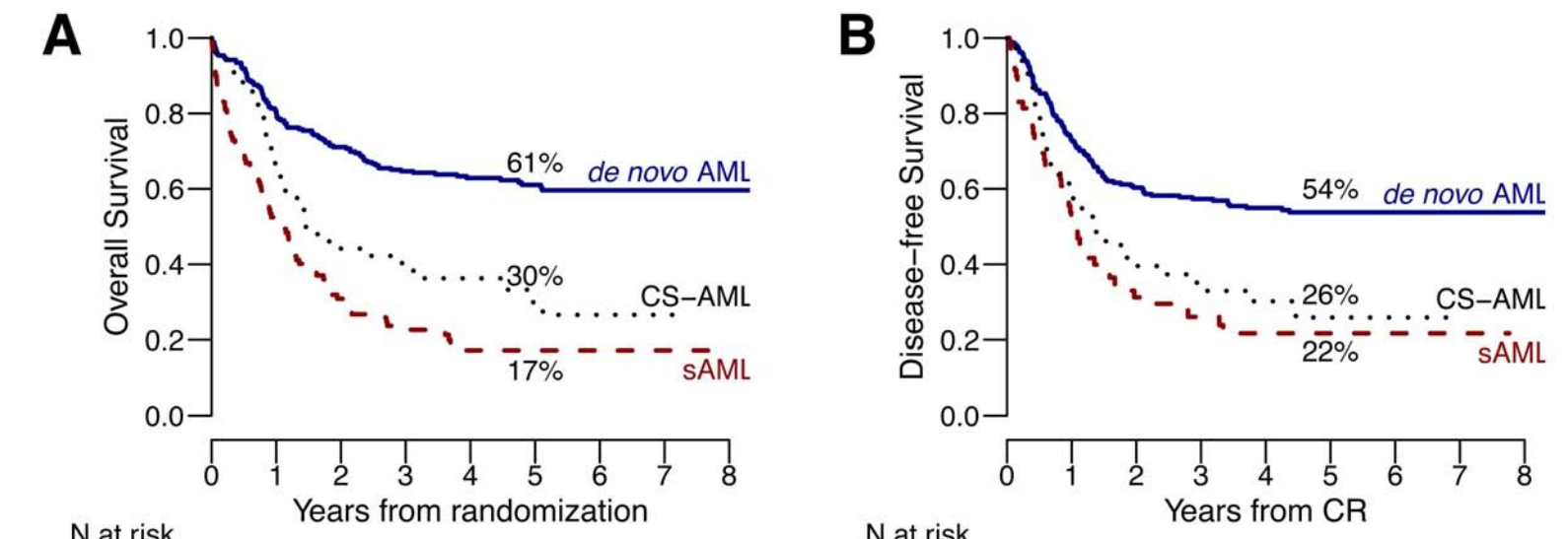


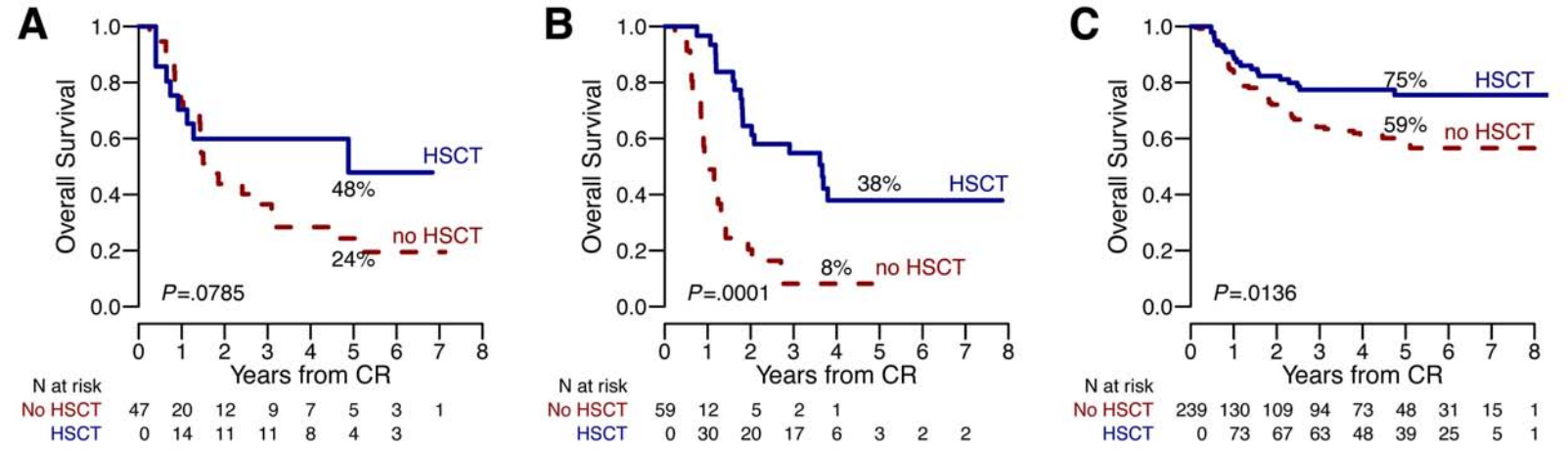
F




KMT2A-PTD
RUNX1
ASXL1
STAG2
U2AF1
SF3B1
SRSF2
BCOR
PHF6
EZH2
ZRSR2
IDH2
FLT3-ITD
DNMT3A
TET2
NRAS
FLT3-TKD
WT1
CEBPa_1
PTPN11
KRAS
FBXW7
SMC1A
JAK2
CUX1
IDH1
CSF3R
CBL
HRAS
GATA1
SETBP1
JAK3
KDM6A
Missense
Frameshift
Indel in frame
Nonsense
Splicing


KMT2A-PTD
RUNX1
ASXL1
STAG2
U2AF1
SF3B1
SRSF2
BCOR
PHF6
ZRSR2
Odds ratio
0 1/16 1/8 1/4 1/2 1 2 4 8 16
P value
* <0.1
** <0.01
*** <0.001
**** <0.0001
Occurrence of pairwise associations
1 5 10 20 50 100 200


A
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
61%
de novo AML
30%
CS–AML
17%
sAML
0 1 2 3 4 5 6 7 8
Years from randomization
N at risk
de novo AML 258 206 179 160 124 89 57 20 2
sAML 100 49 30 22 9 4 2 2
CS–AML 55 35 23 20 15 9 6 1
B
Disease–free Survival
1.0
0.8
0.6
0.4
0.2
0.0
54%
de novo AML
26%
CS–AML
22%
sAML
0 1 2 3 4 5 6 7 8
Years from CR
N at risk
de novo AML 239 173 142 132 100 74 47 18 2
sAML 59 30 18 15 6 3 2 2
CS–AML 47 27 18 15 9 6 5 1


A
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
HSCT
48%
no HSCT
24%
P=.0785
0 1 2 3 4 5 6 7 8
Years from CR
N at risk
No HSCT 47 20 12 9 7 5 3 1
HSCT 0 14 11 11 8 4 3
B
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
38%
HSCT
8%
no HSCT
P=.0001
0 1 2 3 4 5 6 7 8
Years from CR
N at risk
No HSCT 59 12 5 2 1
HSCT 0 30 20 17 6 3 2 2
C
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
75%
HSCT
59%
no HSCT
P=.0136
0 1 2 3 4 5 6 7 8
Years from CR
N at risk
No HSCT 239 130 109 94 73 48 31 15 1
HSCT 0 73 67 63 48 39 25 5 1

Supplemental Appendix

to C. Caprioli et al.:

Clinical significance of chromatin-spliceosome acute myeloid leukemia: a report from the Northern Italy Leukemia Group (NILG) randomized trial 02/06

Supplemental Methods

Molecular analyses

Molecular analyses were performed on mononuclear cells obtained by Ficoll-gradient centrifugation from peripheral blood and/or bone marrow containing at least 20% blasts.

Libraries for targeted NGS were sequenced and demultiplexed on a MiSeq or MiniSeq instrument (Illumina). Variants not reaching the minimum target coverage of 1000x were confirmed by conventional methods. The detection limit/sensitivity for identified variants was set to 5% variant allele frequency, as per manufacturer indication. Frameshift and nonsense variants were always considered as relevant mutations. Single nucleotide variants were retained in the absence of description as genetic polymorphism into public databases of human polymorphisms (NCBI dbSNP (http://www.ncbi.nlm.nih.gov/snp; Build 137) and Exac (http://exac.broadinstitute.org/), taking into account both allele frequency and ethnicity of patients. Functional interpretation for missense variants was performed using SIFT 1.03 (http://sift.jcvi.org) and PolyPhen2.0 (http://genetics.bwh.harvard.edu/pph2). For alterations of splicing sites and splicing related regions, we used the Human Splicing tool (http://www.umd.be/HSF3) to predict alterations in the splicing process. Indeed, the description of the identified mutations in literature was checked in COSMIC database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Supplemental Data

Supplemental Table 1. Gene panels and regions investigated by targeted NGS using Trusight Myeloid (Illumina, San Diego, California, USA) and Sophia Myeloid Solution (Sophia Genetics SA, Saint Sulpice, Switzerland) (indicated with *).

Gene	Target Region (Exons)	Gene	Target Region (Exons)	Gene	Target Region (Exons)
*ABL1**	4-6 4-9*	*FLT3**	14-15, 20 13-15, 20*	*NRAS**	2, 3*
*ASXL1**	12 9,11,12*	*GATA1*	2	*PDGFRA*	12, 14, 18
ATRX	8-10, 17-31	*GATA2*	2-6	*PHF6*	Full
BCOR	Full	*GNAS*	8, 9	*PTEN*	5, 7
BCORL1	Full	*HRAS**	2, 3*	*PTPN11*	3, 13 3, 7-13*
*BRAF**	15*	*IDH1**	4	*RAD21*	Full
*CALR**	9*	*IDH2**	4	*RUNX1**	Full*
*CBL**	8, 9*	*IKZF1*	Full	*SETBP1**	4 (partial) 4*
CBLB	9, 10	*JAK2**	12, 14 Full*	*SF3B1**	13-16 10-16*
CBLC	9, 10	*JAK3*	13	*SMC1A*	2, 11,16-17
CDKN2A	Full	*KDM6A*	Full	*SMC3*	10, 13, 19, 23, 25, 28
*CEBPA**	Full*	*KIT**	2, 8-11, 13, 17 2, 8-11, 13, 17, 18*	*SRSF2**	1*
*CSF3R**	14-17 Full*	*KRAS**	2, 3*	*STAG2*	Full
CUX1	Full	*MLL*	5-8	*TET2**	3-11 Full*
*DNMT3A**	Full*	*MPL**	10*	*TP53**	2-11 Full*
*ETV6**	Full*	*MYD88*	3-5	*U2AF1**	2, 6*
*EZH2**	Full*	*NOTCH1*	26-28, 34	*WT1**	7, 9 6-10*
FBXW7	9-11	*NPM1**	12 11-12*	*ZRSR2**	Full*

Supplemental Table 2. Annotation of gene mutations in the prospective study cohort.

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
6	CS-AML	ASXL1	20	31022904	GA>GA/G	deletion	frameshift	40.12	NM_015338.5	c.2390delA	p.Ser798ValfsTer20		
46	sAML	ASXL1	20	31022628	G>G/T	snv	stop gained	47.88	NM_015338.5	c.2113G>T	p.Glu705Ter		
62	CS-AML	ASXL1	20	31022441	AGGGGGGGG>AGGGGGGGG/AGGGGGGGGG	insertion	frameshift	33.74	NM_015338	c.1934dupG	p.Gly646Trpfs*12		
126	CS-AML	ASXL1	20	31023014	TC>TC/T	deletion	frameshift	46.21	NM_015338.5	c.2500delC	p.His834IlefsTer4		
149	CS-AML	ASXL1	20	31022441	AGGGGGGGG>AGGGGGGGG/AGGGGGGGGG	insertion	frameshift	35.17	NM_015338	c.1934dupG	p.Gly646Trpfs*12		
226	sAML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	38.09	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
265	CS-AML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	35.01	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
369	sAML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	30.89	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
470	CS-AML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	27.65	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
548	*de novo*	ASXL1	20	31023033	C>C/A	snv	missense	11.08	NM_015338.5	c.2518C>A	p.Pro840Thr	deleterious (0.04)	possibly damaging (0.452)
605	CS-AML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	33.73	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
786	CS-AML	ASXL1	20	31024023	TTA>TTA/T	deletion	frameshift	40.49	NM_015338.5	c.3509_3510delTA	p.Leu1170Ter		
1148	CS-AML	ASXL1	20	31022441	A>A/AG	insertion	frameshift	10.25	NM_015338.5	c.1926_1927insG	p.Gly646TrpfsTer12		
1201	sAML	ASXL1	20	31022441	AGGGGGGGG>AGGGGGGGG/AGGGGGGGGG	insertion	frameshift	27.96	NM_015338	c.1934dupG	p.Gly646Trpfs*12		
1308	CS-AML	ASXL1	20	31023383	T>T/TA	insertion	frameshift	42.74	NM_015338.5	c.2868_2869insA	p.Thr957AsnfsTer13		
110	*de novo*	BCOR	X	39914620	C>C/T	snv	splicing	44.59	NM_001123385.1	c.4741+1G>A	p.?		
258	CS-AML	BCOR	X	39933862	TAGAG>TAGAG/T	deletion	frameshift	20.2	NM_001123385.1	c.733_736delCTCT	p.Leu245ThrfsTer20		
635	*de novo*	BCOR	X	39933853	G>G/A	snv	missense	21.83	NM_001123385.1	c.746C>T	p.Pro249Leu	deleterious (0)	probably damaging (0.999)
846	CS-AML	BCOR	X	39914693	TG>TG/T	deletion	frameshift	12.09	NM_001123385.1	c.4668delC	p.Thr1557ProfsTer11		
997	CS-AML	BCOR	X	39911623	GA>GA/G	deletion	frameshift	28.87	NM_001123385.1	c.5006delT	p.Val1669AlafsTer5		
1110	sAML	BCOR	X	39922127	T>T/A	snv	stop gained	49.21	NM_001123385.1	c.4045A>T	p.Lys1349Ter		
1148	CS-AML	BCOR	X	39921466	CCGG>CCGG/C	deletion	inframe deletion	20.16	NM_001123385.1	c.4351_4353delCCG	p.Pro1451del		
1148	CS-AML	BCOR	X	39922057	T>T/C	snv	missense	12.05	NM_001123385.1	c.4115A>G	p.Glu1372Gly	tolerated (0.13)	possibly damaging (0.359)
1270	CS-AML	BCOR	X	39933749	C>C/T	snv	missense	54.79	NM_001123385.1	c.850G>A	p.Asp284Asn	deleterious (0.01)	possibly damaging (0.725)
1343	sAML	BCOR	X	39923086	GT>GT/G	deletion	frameshift	25.25	NM_001123385.1	c.3621delA	p.Lys1207AsnfsTer31		
548	*de novo*	BCORL1	X	129185889	A>A/G	snv	missense	27.91	NM_021946.4	c.4751A>G	p.Asp1584Gly	deleterious (0.01)	possibly damaging (0.712)
548	*de novo*	BCORL1	X	129148079	C>C/G	snv	missense	13.4	NM_021946.4	c.1331C>G	p.Thr444Ser	tolerated (0.38)	benign (0.018)
1110	sAML	BCORL1	X	129148456	G>G/GC	insertion	frameshift	28.71	NM_021946.4	c.1708_1709insC	p.Ser572GlnfsTer31		
1110	sAML	BCORL1	X	129148479	A>A/AG	insertion	frameshift	18.46	NM_021946.4	c.1731_1732insG	p.Pro578AlafsTer25		
1110	sAML	BCORL1	X	129148480	C>C/G	snv	missense	17.68	NM_021946.4	c.1732C>G	p.Pro578Ala	tolerated (0.61)	benign (0.028)
1343	sAML	BCORL1	X	129189840	G>G/A	snv	stop gained	31.9	NM_021946.4	c.4865G>A	p.Trp1622Ter		
166	CS-AML	CBL	11	119149251	G>G/A	snv	missense	32.29	NM_005188.3	c.1259G>A	p.Arg420Gln		probably damaging (0.998)
319	*de novo*	CBL	11	119149241	C>C/T	snv	missense	91.96	NM_005188.3	c.1249C>T	p.Pro417Ser		probably damaging (1)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
854	*de novo*	CBL	11	119148931	G>G/A	snv	missense	42.68	NM_005188.3	c.1151G>A	p.Cys384Tyr		probably damaging (0.999)
1285	*de novo*	CBL	11	119149251	G>G/A	snv	missense	31.25	NM_005188.3	c.1259G>A	p.Arg420Gln		probably damaging (0.998)
1324	sAML	CBL	11	119148931	G>G/A	snv	missense	93.46	NM_005188.3	c.1151G>A	p.Cys384Tyr		probably damaging (0.999)
319	*de novo*	CDKN2A	9	21974792	G>G/T	snv	stop gained	51.41	NM_001195132.1	c.35C>A	p.Ser12Ter		
66	*de novo*	CEBPA	19	33793265	AGGTGGCT>AGGTGGCT/A	deletion	frameshift	48.57	NM_004364.3	c.49_55delAGCCACC	p.Ser17CysfsTer141		
66	*de novo*	CEBPA	19	33792378	G>G/GCACCTTCTGCTGCGTCTC	insertion	inframe insertion	36.72	NM_004364.3	c.925_942dupGAGACGCAGCAGAAGGTG	p.Glu309_Val314dup		
80	*de novo*	CEBPA	19	33792392	G>G/GTCTTAGACT	insertion	inframe insertion	41.08	NM_004364.3	c.928_929insAGTCTAAGA	p.Thr310_Gln310insLysSerLys		
86	*de novo*	CEBPA	19	33793238	C>C/CAG	insertion	frameshift	46.57	NM_004364.3	c.82_83insCT	p.Ser28ThrfsTer133		
86	*de novo*	CEBPA	19	33792384	TCTG>TCTG/T	deletion	inframe deletion	45.94	NM_004364.3	c.934_936delCAG	p.Gln312del		
94	*de novo*	CEBPA	19	33792387	G>G/GCTGCGTCTCCACGTTGCGCTGCTTGGC	insertion	inframe	44	NM_004364	c.907_933dup	p.Ala303_Gln311dup		
94	*de novo*	CEBPA	19	33793082	TC>TC/TCC	insertion	frameshift	40.64	NM_004364	c.238dupG	p.Asp80Glyfs*28		
96	*de novo*	CEBPA	19	33793205	GGGCCCGCGCCCCGGGGAAA>GGGCCCGCGCCCCGGGGAAA/G	deletion	frameshift	59.64	NM_004364.3	c.97_115delTTTCCCCGGGGCGCGGGCC	p.Phe33ProfsTer121		
96	*de novo*	CEBPA	19	33792734	G>G/A	snv	missense	10.74	NM_004364.3	c.587C>T	p.Pro196Leu	tolerated (0.62)	benign (0.028)
196	*de novo*	CEBPA	19	33793154	C>C/CA	insertion	frameshift	44.81	NM_004364.3	c.166dupT	p.Cys56LeufsTer52		
196	*de novo*	CEBPA	19	33792437	G>G/T	snv	missense	43.72	NM_004364.3	c.884C>A	p.Ala295Glu	deleterious (0)	probably damaging (0.997)
241	*de novo*	CEBPA	19	33792731	G>G/GGCGGGT	insertion	inframe insertion	40.96	NM_004364.3	c.584_589dupACCCGC	p.His195_Pro196dup		
269	*de novo*	CEBPA	19	33792384	T>T/TCTG	insertion	inframe insertion	90.42	NM_004364.3	c.934_936dupCAG	p.Gln312dup		
274	*de novo*	CEBPA	19	33792391	C>C/CGAG	insertion	missense	46.23	NM_004364.3	c.929_930insCTC	p.Thr310_Gln311insSer		
274	*de novo*	CEBPA	19	33793252	C>C/CG	insertion	frameshift	29.47	NM_004364.3	c.68dupC	p.His24AlafsTer84		
296	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe insertion	36.92	NM_004364.3	c.937_939dupAAG	p.Lys313dup		
297	*de novo*	CEBPA	19	33792391	C>C/CA	insertion	frameshift	44.34	NM_004364.3	c.929_930insT	p.Gln311AlafsTer10		
297	*de novo*	CEBPA	19	33792392	G>G/GAC	insertion	frameshift	44.7	NM_004364.3	c.928_929insGT	p.Thr310SerfsTer9		
297	*de novo*	CEBPA	19	33793203	CG>CG/C	deletion	frameshift	55.43	NM_004364.3	c.117delC	p.Ala40ArgfsTer120		
362	*de novo*	CEBPA	19	33792393	T>T/TCTC	insertion	inframe insertion	45.99	NM_004364.3	c.925_927dupGAG	p.Glu309dup		
402	*de novo*	CEBPA	19	33792350	A>A/T	snv	missense	53.69	NM_004364.3	c.971T>A	p.Leu324Gln	deleterious (0.01)	probably damaging (1)
402	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe insertion	37.69	NM_004364.3	c.937_939dupAAG	p.Lys313dup		
413	CS-AML	CEBPA	19	33793242	TGGGCGCGTGCG>TGGGCGCGTGCG/T	deletion	frameshift	27.49	NM_004364.3	c.68_78delCGCACGCGCCC	p.Pro23GlnfsTer81		
441	*de novo*	CEBPA	19	33792833	TCC>TCC/TCCCC	insertion	frameshift	46.37	NM_004364	c.486_487dupGG	p.Glu163Glyfs*156		
447	sAML	CEBPA	19	33792891	CCAGCCTGCCGTCCAGGTAGCCGGCGGCCGCG>CCAGCCTGCCGTCCAGGTAGCCGGCGGCCGCG/C	deletion	frameshift	29	NM_004364	c.399_429del	p.Cys133Trpfs*17		
508	*de novo*	CEBPA	19	33792393	TCTCCACGTTGCGCTG>TCTCCACGTTGCGCTG/T	deletion	inframe deletion	42.8	NM_004364.3	c.913_927delCAGCGCAACGTGGAG	p.Gln305_Glu309delinsdel		
521	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe	43.29	NM_004364	c.937_939dupAAG	p.Lys313dup		
521	*de novo*	CEBPA	19	33793033	GCCC>GCCC/GCC	deletion	frameshift	41.37	NM_004364	c.287delG	p.Gly96Alafs*64		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
835	*de novo*	CEBPA	19	33792384	T>T/TCTG	insertion	inframe insertion	53.02	NM_004364.3	c.934_936dupCAG	p.Gln312dup		
835	*de novo*	CEBPA	19	33793115	T>T/TCGTAAGA	insertion	frameshift	51.59	NM_004364.3	c.205_206insTCTTACG	p.Asp69ValfsTer41		
865	*de novo*	CEBPA	19	33792781	AGGG>AGGG/AGGGG	insertion	frameshift	31.11	NM_004364	c.539dupC	p.Tyr181Leufs*140		
866	*de novo*	CEBPA	19	33793252	CGGGGGG>CGGGGGG/CGGGGG	deletion	frameshift	41.05	NM_004364	c.68delC	p.Pro23Argfs*137		
866	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe	37.85	NM_004364	c.937_939dupAAG	p.Lys313dup		
877	*de novo*	CEBPA	19	33793141	C>C/CG	insertion	frameshift	53.09	NM_004364.3	c.179dupC	p.Ser61ValfsTer47		
924	*de novo*	CEBPA	19	33793073	TG>TG/T	deletion	frameshift	53.04	NM_004364.3	c.247delC	p.Gln83SerfsTer77		
924	*de novo*	CEBPA	19	33792386	T>T/TGCC	insertion	inframe insertion	45.34	NM_004364.3	c.934_935insGGC	p.Gln312_Lys312insArg		
1137	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe insertion	43.41	NM_004364.3	c.937_939dupAAG	p.Lys313dup		
1234	*de novo*	CEBPA	19	33793174	CG>CG/C	deletion	frameshift	26.03	NM_004364.3	c.146delC	p.Pro49ArgfsTer111		
1234	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe insertion	25.07	NM_004364.3	c.937_939dupAAG	p.Lys313dup		
1294	*de novo*	CEBPA	19	33793174	CGGGG>CGGGG/CGGG	deletion	frameshift	45.32	NM_004364	c.146delC	p.Pro49Argfs*111		
1294	*de novo*	CEBPA	19	33792381	C>C/CCTT	insertion	inframe	43.57	NM_004364	c.937_939dupAAG	p.Lys313dup		
1352	*de novo*	CEBPA	19	33792391	C>C/CCTT	insertion	missense	39.55	NM_004364.3	c.929_930insAAG	p.Thr310_Gln311insArg		
1352	*de novo*	CEBPA	19	33793258	G>G/GCT	insertion	frameshift	38.66	NM_004364.3	c.61_62dupAG	p.Ser21ArgfsTer140		
1375	*de novo*	CEBPA	19	33793242	TGGGCGCGTGCG>TGGGCGCGTGCG/T	deletion	frameshift	61.75	NM_004364.3	c.68_78delCGCACGCGCCC	p.Pro23GlnfsTer81		
1375	*de novo*	CEBPA	19	33792380	A>A/AT	insertion	frameshift	42.76	NM_004364.3	c.940_941insA	p.Val314AspfsTer7		
1375	*de novo*	CEBPA	19	33792381	C>C/CTT	insertion	frameshift	42.55	NM_004364.3	c.939_940insAA	p.Val314LysfsTer5		
66	*de novo*	CSF3R	1	36933434	G>G/A	snv	missense	39.27	NM_156039.3	c.1853C>T	p.Thr618Ile	deleterious (0)	probably damaging (0.999)
505	CS-AML	CSF3R	1	36932125	G>G/A	snv	missense	13.24	NM_156039.3	c.2425C>T	p.Pro809Ser	deleterious (0)	probably damaging (0.999)
1236	*de novo*	CSF3R	1	36932296	G>G/A	snv	stop gained	11.32	NM_156039.3	c.2254C>T	p.Gln752Ter		
102	CS-AML	CUX1	7	101837153	G>G/A	snv	missense	48.46	NM_001202543.1	c.1141G>A	p.Glu381Lys	tolerated (0.55)	possibly damaging (0.629)
548	*de novo*	CUX1	7	101821800	G>G/A	snv	missense	18.85	NM_001202543.1	c.913G>A	p.Ala305Thr	deleterious (0.02)	probably damaging (0.998)
548	*de novo*	CUX1	7	101840469	C>C/T	snv	missense	11.17	NM_001202543.1	c.1811C>T	p.Pro604Leu	deleterious (0)	probably damaging (0.971)
548	*de novo*	CUX1	7	101844649	C>C/T	snv	missense	10.78	NM_001202543.1	c.2105C>T	p.Ala702Val	tolerated (0.22)	benign (0.003)
10	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	30.53	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
14	*de novo*	DNMT3A	2	25458598	A>A/AGATGTCC	insertion	frameshift	45.1	NM_022552.4	c.2568_2574dupGGACATC	p.Leu859GlyfsTer7		
20	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	50.51	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
32	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	40.59	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
43	*de novo*	DNMT3A	2	25457242	C>C/G	snv	missense	40.45	NM_022552.4	c.2645G>C	p.Arg882Pro	deleterious (0)	probably damaging (0.988)
64	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	45.06	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
92	*de novo*	DNMT3A	2	25463184	G>G/A	snv	missense	27.39	NM_022552	c.2309C>T	p.Ser770Leu	tolerated (0.996)	probably damaging (1)
101	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	40.95	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
110	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	44.31	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
124	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	38.19	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
131	CS-AML	DNMT3A	2	25470585	A>A/T	snv	missense	49.18	NM_022552.4	c.889T>A	p.Trp297Arg	deleterious (0)	probably damaging (0.964)
131	CS-AML	DNMT3A	2	25466805	G>G/T	snv	missense	46.5	NM_022552.4	c.1898C>A	p.Pro633His	deleterious (0)	probably damaging (0.985)
132	sAML	DNMT3A	2	25467476	G>G/A	snv	nonsense	41.6	NM_022552	c.1600C>T	p.Gln534*		
137	*de novo*	DNMT3A	2	25463181	C>C/T	snv	missense	45.4	NM_022552.4	c.2312G>A	p.Arg771Gln	deleterious (0.04)	probably damaging (0.969)
163	*de novo*	DNMT3A	2	25457243	G>G/T	snv	missense	41.67	NM_022552.4	c.2644C>A	p.Arg882Ser	deleterious (0)	probably damaging (0.975)
170	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	43.76	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
182	*de novo*	DNMT3A	2	25470484	C>C/T	snv	stop gained	43.44	NM_022552.4	c.990G>A	p.Trp330Ter		
185	*de novo*	DNMT3A	2	25467172	CCCA>CCCA/C	deletion	inframe deletion	36.66	NM_022552.4	c.1700_1702delTGG	p.Val567del		
213	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	40.35	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
241	*de novo*	DNMT3A	2	25458694	A>A/T	snv	missense	41.88	NM_022552.4	c.2479T>A	p.Phe827Ile	deleterious (0.02)	probably damaging (0.902)
242	CS-AML	DNMT3A	2	25457242	C>C/T	snv	missense	45.35	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
247	*de novo*	DNMT3A	2	25463541	G>G/C	snv	missense	48.45	NM_022552.4	c.2141C>G	p.Ser714Cys	deleterious (0.02)	probably damaging (0.975)
272	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	48.7	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
275	*de novo*	DNMT3A	2	25463266	GCC>GCC/GC	deletion	frameshift	42.53	NM_022552	c.2226delG	p.Lys744Argfs*35		
277	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	43.28	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
319	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	43.46	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
320	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	36.53	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
325	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	49.23	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
342	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	20.9	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
342	*de novo*	DNMT3A	2	25470968	C>C/T	snv	missense	19.7	NM_022552	c.793G>A	p.Val265Met	tolerated (0.99)	possibly damaging (0.593)
352	*de novo*	DNMT3A	2	25467449	C>C/A	snv	missense	10.7	NM_022552	c.1627G>T	p.Gly543Cys	tolerated (1)	probably damaging (0.999)
377	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	17.3	NM_022552	c.2644C>T	p.Arg882Cys	tolerated (1)	probably damaging (0.936)
379	*de novo*	DNMT3A	2	25467495	CT>CT/C	deletion	frameshift	36.63	NM_022552.4	c.1580delA	p.Gln527ArgfsTer124		
406	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	43.37	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
407	*de novo*	DNMT3A	2	25457159	CA>CA/C	deletion	frameshift	47	NM_022552.4	c.2727delT	p.Phe909LeufsTer13		
421	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	45.7	NM_022552	c.2644C>T	p.Arg882Cys	tolerated (1)	probably damaging (0.936)
447	sAML	DNMT3A	2	25463568	A>A/T	snv	missense	42.02	NM_022552	c.2114T>A	p.Ile705Asn	tolerated (1)	probably damaging (0.978)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
447	sAML	DNMT3A	2	25464428	T>T/C	snv	splicing	41.65	NM_022552	c.2082+3A>G	p.?		
477	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	45.85	NM_022552	c.2644C>T	p.Arg882Cys	tolerated (1)	probably damaging (0.936)
507	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	12.26	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
527	*de novo*	DNMT3A	2	25469028	C>C/A	snv	splicing	48.18	NM_022552.4	c.1429+1G>T	p.?		
548	*de novo*	DNMT3A	2	25468915	A>A/G	snv	missense	43.18	NM_022552.4	c.1448T>C	p.Val483Ala	deleterious (0.02)	possibly damaging (0.703)
548	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	36.13	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
583	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	44.96	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
616	*de novo*	DNMT3A	2	25467023	C>C/T	snv	splicing	32.01	NM_022552	c.1851+1G>A	p.?		
666	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	38.39	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
683	*de novo*	DNMT3A	2	25461998	C>C/T	snv	splicing	48.04	NM_022552.4	c.2408+1G>A	p.?		
683	*de novo*	DNMT3A	2	25505534	G>G/A	snv	missense	17.57	NM_022552.4	c.224C>T	p.Ser75Phe	deleterious (0.05)	benign (0.012)
733	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	45.01	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
753	CS-AML	DNMT3A	2	25462020	C>C/T	snv	missense	55.14	NM_022552.4	c.2387G>A	p.Gly796Asp	deleterious (0)	probably damaging (0.998)
753	CS-AML	DNMT3A	2	25470498	G>G/A	snv	missense	43.7	NM_022552.4	c.976C>T	p.Arg326Cys	deleterious (0.03)	probably damaging (1)
761	*de novo*	DNMT3A	2	25470461	AC>AC/A	deletion	frameshift	37.05	NM_022552.4	c.1012delG	p.Val338TrpfsTer7		
766	*de novo*	DNMT3A	2	25466797	C>C/T	snv	missense	48.45	NM_022552.4	c.1906G>A	p.Val636Met	deleterious (0)	probably damaging (0.999)
790	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	33.87	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
803	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	50.8	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
824	*de novo*	DNMT3A	2	25457242	C>C/G	snv	missense	34.41	NM_022552	c.2645G>C	p.Arg882Pro	tolerated (0.969)	possibly damaging (0.738)
830	*de novo*	DNMT3A	2	25467433	A>A/G	snv	missense	44.87	NM_022552.4	c.1643T>C	p.Met548Thr	deleterious (0)	probably damaging (0.96)
847	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	46.23	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
852	*de novo*	DNMT3A	2	25458626	AG>AG/A	deletion	frameshift	46.48	NM_022552.4	c.2546delC	p.Pro849LeufsTer4		
865	*de novo*	DNMT3A	2	25464465	T>T/ TACATGATCTTCC CCTGGTGCCGCA CCATGCCCACCG TGATGGAGTCC	insertion	frameshift	37.0	NM_022552	c.2001_2047dup	p.Tyr683Trpfs*38		
867	*de novo*	DNMT3A	2	25468174	T>T/C	snv	missense	51.22	NM_022552.4	c.1502A>G	p.Asn501Ser	tolerated (0.1)	benign (0.037)
931	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	42.63	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
981	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	47.74	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
997	CS-AML	DNMT3A	2	25463308	G>G/A	snv	missense	26.13	NM_022552.4	c.2185C>T	p.Arg729Trp	deleterious (0)	probably damaging (1)
1042	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	45.7	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	possibly damaging (0.043)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
1095	*de novo*	DNMT3A	2	25467478	T>T/C	snv	missense	43.5	NM_022552	c.1598A>G	p.Tyr533Cys	tolerated (0.983)	probably damaging (0.993)
1100	*de novo*	DNMT3A	2	25467209	T>T/G	snv	splicing	44.98	NM_022552.4	c.1668-2A>C	p.?		
1110	sAML	DNMT3A	2	25467428	C>C/T	snv	missense	58.7	NM_022552.4	c.1648G>A	p.Gly550Arg	deleterious (0.01)	probably damaging (0.893)
1110	sAML	DNMT3A	2	25463181	C>C/G	snv	missense	22.51	NM_022552.4	c.2312G>C	p.Arg771Pro	deleterious (0)	probably damaging (0.996)
1140	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	45.92	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
1147	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	44.77	NM_022552	c.2644C>T	p.Arg882Cys	tolerated (1)	probably damaging (0.936)
1166	CS-AML	DNMT3A	2	25457242	C>C/T	snv	missense	24.63	NM_022552.4	c.2645G>A	p.Arg88His	deleterious (0.04)	probably damaging (0.956)
1168	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	46.89	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
1191	*de novo*	DNMT3A	2	25466797	C>C/A	snv	missense	42.16	NM_022552.4	c.1906G>T	p.Val636Leu	deleterious (0)	probably damaging (0.974)
1199	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	44.12	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
1222	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	30	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
1270	CS-AML	DNMT3A	2	25463181	C>C/T	snv	missense	35.8	NM_022552.4	c.2312G>A	p.Arg771Gln	deleterious (0.04)	probably damaging (0.969)
1285	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	24.18	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
1290	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	37.14	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
1314	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	41.19	NM_022552.4	c.2645G>A	p.Arg882His	deleterious (0.04)	probably damaging (0.956)
1335	CS-AML	DNMT3A	2	25457231	G>G/C	snv	missense	40.92	NM_022552.4	c.2656C>G	p.Gln886Glu	deleterious (0)	possibly damaging (0.871)
1338	*de novo*	DNMT3A	2	25457243	G>G/A	snv	missense	45.05	NM_022552.4	c.2644C>T	p.Arg882Cys	deleterious (0)	probably damaging (0.986)
1351	*de novo*	DNMT3A	2	25468135	C>C/T	snv	missense	48.96	NM_022552.4	c.1541G>A	p.Cys514Tyr	deleterious (0)	probably damaging (0.992)
1364	*de novo*	DNMT3A	2	25470971	G>G/GCTCA	insertion	frameshift	44.59	NM_022552.4	c.786_789dupTGAG	p.Pro264Ter		
1370	*de novo*	DNMT3A	2	25457242	C>C/T	snv	missense	40.94	NM_022552	c.2645G>A	p.Arg882His	tolerated (0.998)	benign (0.043)
1376	*de novo*	DNMT3A	2	25463541	G>G/C	snv	missense	44.06	NM_022552.4	c.2141C>G	p.Ser714Cys	deleterious (0.02)	probably damaging (0.975)
168	*de novo*	ETV6	12	11992218	G>G/GCCC	insertion	inframe insertion	13.71	NM_001987.4	c.308_309insCCC	p.Arg103_Tyr104insPro		
1308	CS-AML	FBXW7	4	153249384	C>C/T	snv	missense	38.73	NM_033632.3	c.1394G>A	p.Arg465His	deleterious (0)	probably damaging (1)
14	*de novo*	FLT3	13	28608263	T>T/TCATATTCTCTGAAATCAACGTAGC	insertion	inframe insertion	30.51	NM_004119.2	c.1792_1793insGCTACGTTGATTTCAGAGAATATG	p.Glu598_Tyr598insGlyTyrValAspPheArgGluTyr		
20	*de novo*	FLT3	13	28592641	T>T/G	snv	missense	36.61	NM_004119.2	c.2504A>C	p.Asp835Ala	deleterious (0)	probably damaging (0.999)
32	*de novo*	FLT3	13	28592623	T>T/G	snv	missense	13.69	NM_004119	c.2522A>C	p.Asn841Thr	tolerated (0.998)	possibly damaging (0.176)
43	*de novo*	FLT3	13	28592623	T>T/A	snv	missense	40.73	NM_004119.2	c.2522A>T	p.Asn841Ile	deleterious (0)	probably damaging (0.99)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
62	CS-AML	FLT3	13	28608257	T>T/TCATATTCATATTCTCTGAAATCAACGTAGAAGTACTCATTATCTGAGC	insertion	inframe	43	NM_004119	c.1798_1799ins48	p.Tyr599_Asp600ins16		
149	CS-AML	FLT3	13	28592640	A>A/C	snv	missense	43.32	NM_004119	c.2505T>G	p.Asp835Glu	tolerated (0.998)	probably damaging (0.951)
241	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	39.8	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
247	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	37.4	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
277	*de novo*	FLT3	13	28608262	T>T/TTCATATTCTCTGAAA	insertion	inframe insertion	35.81	NM_004119.2	c.1779_1793dupTTTCAGAGAATATGA	p.Asp593_Tyr597dup		
325	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	29.3	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
325	*de novo*	FLT3	13	28608268	T>T/TTCTCTGAAATCAACGTAG	insertion	inframe insertion	7.24	NM_004119.2	c.1770_1787dupCTACGTTGATTTCAGAGA	p.Glu596_Tyr596insAspTyrValAspPheArg		
342	*de novo*	FLT3	13	28608272	C>C/CTGAAATCAACGTAGAAGTACTCATTATCTGAGGAGCCGGTCT	insertion	inframe	15.2	NM_004119	c.1783_1784ins42	p.Phe594_Arg595ins14		
342	*de novo*	FLT3	13	28608262	T>T/TTCATATTCTCTGAAATCAACGTAGAAGTCC	insertion	inframe	5.8	NM_004119	c.1793_1794ins30	p.Glu598_Tyr599ins10		
378	CS-AML	FLT3	13	28608320	A>A/C	snv	missense	23.94	NM_004119.2	c.1736T>G	p.Val579Gly	deleterious (0)	possibly damaging (0.712)
405	*de novo*	FLT3	13	28608262	T>T/TTCATATTCTCTGAAATCAACG	insertion	inframe insertion	28.25	NM_004119.2	c.1773_1793dupCGTTGATTTCAGAGAATATGA	p.Glu598_Tyr598insAspValAspPheArgGluTyr		
421	*de novo*	FLT3	13	28608275	A>A/AAATCAACGTAGAAGTACTCATTATCCG	insertion	inframe	34.9	NM_004119	c.1780_1781ins27	p.Ser585_Asp593dup		
527	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	45.98	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
548	*de novo*	FLT3	13	28592642	C>C/G	snv	missense	24.89	NM_004119.2	c.2503G>C	p.Asp835His	deleterious (0)	probably damaging (0.999)
552	*de novo*	FLT3	13	28608221	A>A/AACTCTAAATTTTCTCTTGGAAACTCCCATTTGAGATCATATTCATATTCTCTGAAATCAACGTAGAAGT	insertion	inframe	41	NM_004119	c.1766_1834dup	p.Tyr589_Glu611dup		
582	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	42.22	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
588	*de novo*	FLT3	13	28608272	C>C/CTGAAATCAACGTAGAAGTACTCATTATCTT	insertion	inframe	9	NM_004119	c.1783_1784ins30	p.Phe594_Arg595ins10		
616	*de novo*	FLT3	13	28608262	T>T/TTCATATTCTCTGAAATCAACGTAGAAGTACTCATTATCTGAGGAGCCGGTC	insertion	inframe	14	NM_004119	c.1743_1793dup	p.Thr582_Glu598dup		
683	*de novo*	FLT3	13	28608278	T>T/G	snv	missense	15.64	NM_004119.2	c.1778A>C	p.Asp593Ala	deleterious (0.01)	possibly damaging (0.698)
733	*de novo*	FLT3	13	28608254	A>A/AGATCATATTCATATTCTAGGG	insertion	inframe insertion	80.28	NM_004119.2	c.1801_1802insCCCTAGAATATGAATATGATC	p.Leu601_Lys601insProLeuGluTyrGluTyrAsp		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
865	*de novo*	FLT3	13	28608249	A>A/ ATTTGAGATCATA TTCATATTCTCTG AAATCAACGTAG AAGTACTCATTAT CTGAGGAGCC	insertion	inframe	47.0	NM_004119	c.1747_1806dup	p.Gly583_Lys602dup		
877	*de novo*	FLT3	13	28592628	A>A/T	snv	missense	40.53	NM_004119.2	c.2517T>A	p.Asp839Glu	deleterious (0)	probably damaging (0.996)
931	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	19.65	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
940	CS-AML	FLT3	13	28592642	C>C/A	snv	missense	23.4	NM_004119	c.2503G>T	p.Asp835Tyr	tolerated (0.999)	probably damaging (0.999)
940	CS-AML	FLT3	13	28608256	A>A/ ATCATATTCATATT CTCTGAAATCAAT GAGT	insertion	inframe	10.3	NM_004119	c.1799_1800ins30	p.Tyr599_Asp600ins 10		
1025	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	37.75	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
1042	*de novo*	FLT3	13	28608218	C>C/ CCAAACTCTAAAT TTTCTCTTGGAA ACTCCCATTTGA GATCATATT	insertion	coding	64.7	NM_004119	c.1793_1837dup	p.Glu598_Phe612du p		
1095	*de novo*	FLT3	13	28608262	T>T/ TTCATATTCTCTG AAATCAACGTAG	insertion	inframe	27	NM_004119	c.1770_1793dup	p.Tyr597_Glu598ins 8		
1100	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	29.27	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
1168	*de novo*	FLT3	13	28592620	T>T/C	snv	missense	39.62	NM_004119.2	c.2525A>G	p.Tyr842Cys	deleterious (0)	probably damaging (1)
1222	*de novo*	FLT3	13	28608219	C>C/ CAAACTCTAAATT TTCTCTTGGAAA CTCCCATTTGAG	insertion	inframe	15	NM_004119	c.1801_1836dup	p.Leu601_Phe612du p		
1236	*de novo*	FLT3	13	28592642	C>C/A	snv	missense	38.28	NM_004119.2	c.2503G>T	p.Asp835Tyr	deleterious (0)	probably damaging (1)
1290	*de novo*	FLT3	13	28608218	C>C/ CCAAACTCTAAAT TTTCTCTTGGAA ACTCCCATTTGA GATCATATTCATA TTCTCTGAAATC GG	insertion	splicing	17.0	NM_004119	c.1837_1837+1ins63	p.?		
1379	*de novo*	FLT3	13	28608246	C>C/ CCCATTTGAGAT CATA	insertion	inframe insertion	41.11	NM_004119.2	c.1795_1809dupTAT GATCTCAAATGG	p.Tyr599_Trp603dup		
82	sAML	GATA1	X	48649520	G>G/T	snv	stop gained	15	NM_002049.3	c.4G>T	p.Glu2Ter		
126	CS-AML	GATA1	X	48649533	T>T/TG	insertion	frameshift	61.96	NM_002049.3	c.17_18insG	p.Ser8ValfsTer32		
28	*de novo*	GATA2	3	128202731	C>C/T	snv	missense	27.16	NM_032638.4	c.989G>A	p.Arg330Gln	deleterious (0)	probably damaging (0.902)
96	*de novo*	GATA2	3	128200720	C>C/T	snv	missense	42.24	NM_032638.4	c.1085G>A	p.Arg362Gln	deleterious (0)	probably damaging (0.973)
158	*de novo*	GATA2	3	128200744	G>G/C	snv	missense	13.89	NM_032638.4	c.1061C>G	p.Thr354Arg	deleterious (0)	probably damaging (0.996)
269	*de novo*	GATA2	3	128202794	T>T/A	snv	missense	48.93	NM_032638.4	c.926A>T	p.Asp309Val	deleterious (0)	probably damaging (0.998)
274	*de novo*	GATA2	3	128202767	G>G/A	snv	missense	45.49	NM_032638.4	c.953C>T	p.Ala318Val	deleterious (0)	probably damaging (0.991)
297	*de novo*	GATA2	3	128202810	G>G/C	snv	missense	51.02	NM_032638.4	c.910C>G	p.Pro304Ala	deleterious (0)	probably damaging (0.991)
402	*de novo*	GATA2	3	128202731	C>C/A	snv	missense	24.82	NM_032638.4	c.989G>T	p.Arg330Leu	deleterious (0)	probably damaging (0.942)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
635	*de novo*	GATA2	3	128202759	G>G/A	snv	missense	42.8	NM_032638.4	c.961C>T	p.Leu321Phe	deleterious (0)	probably damaging (0.99)
703	*de novo*	GATA2	3	128204906	T>T/A	snv	stop gained	11.8	NM_032638.4	c.535A>T	p.Lys179Ter		
1352	*de novo*	GATA2	3	128202759	G>G/A	snv	missense	13.93	NM_032638.4	c.961C>T	p.Leu321Phe	deleterious (0)	probably damaging (0.99)
548	*de novo*	GNAS	20	57484414	C>C/T	snv	missense	12.61	NM_080425.2	c.2524C>T	p.Arg842Cys	deleterious (0)	probably damaging (1)
633	CS-AML	HRAS	11	533878	C>C/T	snv	missense	14.34	NM_005343.2	c.178G>A	p.Gly60Ser	deleterious (0)	probably damaging (0.998)
32	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	38.46	NM_005896	c.395G>A	p.Arg132His	tolerated (0.986)	benign (0.06)
43	*de novo*	IDH1	2	209113113	G>G/C	snv	missense	47.73	NM_005896.2	c.394C>G	p.Arg132Gly	deleterious (0)	probably damaging (0.997)
64	*de novo*	IDH1	2	209113113	G>G/A	snv	missense	49.06	NM_005896.2	c.394C>T	p.Arg132Cys	deleterious (0.02)	possibly damaging (0.791)
92	*de novo*	IDH1	2	209113113	G>G/C	snv	missense	21.81	NM_005896	c.394C>G	p.Arg132Gly	tolerated (0.999)	probably damaging (0.907)
131	CS-AML	IDH1	2	209113113	G>G/A	snv	missense	55.52	NM_005896.2	c.394C>T	p.Arg132Cys	deleterious (0.02)	possibly damaging (0.791)
137	*de novo*	IDH1	2	209113113	G>G/A	snv	missense	48.39	NM_005896.2	c.394C>T	p.Arg132Cys	deleterious (0.02)	possibly damaging (0.791)
163	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	42.46	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
185	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	30.29	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
192	*de novo*	IDH1	2	209113113	G>G/T	snv	missense	49.33	NM_005896.2	c.394C>A	p.Arg132Ser	deleterious (0)	probably damaging (0.996)
312	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	42.98	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
319	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	48.14	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
407	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	46.14	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
432	*de novo*	IDH1	2	209113113	G>G/T	snv	missense	35.74	NM_005896	c.394C>A	p.Arg132Ser	tolerated (1)	probably damaging (0.878)
511	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	47.21	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
588	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	35.27	NM_005896	c.395G>A	p.Arg132His	tolerated (0.986)	benign (0.06)
684	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	21.11	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
703	*de novo*	IDH1	2	209113113	G>G/T	snv	missense	43.46	NM_005896.2	c.394C>A	p.Arg132Ser	deleterious (0)	probably damaging (0.996)
867	*de novo*	IDH1	2	209113112	C>C/T	snv	missense	11.83	NM_005896.2	c.395G>A	p.Arg132His	deleterious (0)	possibly damaging (0.629)
3	CS-AML	IDH2	15	90631838	C>C/T	snv	missense	41.6	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
101	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	50	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
126	CS-AML	IDH2	15	90631934	C>C/T	snv	missense	44.77	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
258	CS-AML	IDH2	15	90631934	C>C/T	snv	missense	20.98	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
352	*de novo*	IDH2	15	90631838	C>C/T	snv	missense	13.8	NM_002168	c.515G>A	p.Arg172Lys	tolerated (0.999)	probably damaging (0.999)
380	CS-AML	IDH2	15	90631934	C>C/T	snv	missense	22.76	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
406	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	44.78	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
507	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	42.83	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
527	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	47.56	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
616	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	31.93	NM_002168	c.419G>A	p.Arg140Gln	tolerated (1)	probably damaging (0.998)
753	CS-AML	IDH2	15	90631838	C>C/T	snv	missense	45.11	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
847	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	18.59	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
853	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	46.99	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
858	*de novo*	IDH2	15	90631839	T>T/A	snv	missense	39.22	NM_002168.2	c.514A>T	p.Arg172Trp	deleterious (0)	probably damaging (1)
867	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	23.71	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
919	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	47.53	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
997	CS-AML	IDH2	15	90631838	C>C/T	snv	missense	31.43	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
1042	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	49.7	NM_002168	c.419G>A	p.Arg140Gln	tolerated (1)	probably damaging (0.998)
1110	sAML	IDH2	15	90631934	C>C/T	snv	missense	28.99	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
1191	*de novo*	IDH2	15	90631838	C>C/T	snv	missense	43.26	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
1308	CS-AML	IDH2	15	90631838	C>C/T	snv	missense	46.6	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
1335	CS-AML	IDH2	15	90631838	C>C/T	snv	missense	43.8	NM_002168.2	c.515G>A	p.Arg172Lys	deleterious (0)	probably damaging (1)
1337	CS-AML	IDH2	15	90631934	C>C/T	snv	missense	40.35	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
1373	*de novo*	IDH2	15	90631934	C>C/T	snv	missense	25	NM_002168.2	c.419G>A	p.Arg140Gln	deleterious (0)	probably damaging (1)
132	sAML	JAK2	9	5073770	G>G/T	snv	missense	14.2	NM_004972	c.1849G>T	p.Val617Phe	tolerated (0.998)	probably damaging (0.934)
222	sAML	JAK2	9	5073770	G>G/T	snv	missense	46.69	NM_004972.3	c.1849G>T	p.Val617Phe	deleterious (0.01)	probably damaging (0.967)
377	*de novo*	JAK2	9	5090452	G>G/A	snv	missense	51.1	NM_004972	c.2768G>A	p.Arg923His	tolerated (0.962)	possibly damaging (0.689)
623	CS-AML	JAK2	9	5055741	A>A/T	snv	missense	49.1	NM_004972	c.1009A>T	p.Asn337Tyr	tolerated (0.981)	benign (0.081)
1148	CS-AML	JAK3	19	17947985	G>G/T	snv	stop gained	27.38	NM_000215.3	c.1739C>A	p.Ser580Ter		
582	*de novo*	KDM6A	X	44879925	C>C/T	snv	stop gained	42.61	NM_021140.2	c.514C>T	p.Arg172Ter		
852	*de novo*	KDM6A	X	44919270	C>C/T	snv	stop gained	15.77	NM_021140.2	c.1198C>T	p.Gln400Ter		
1148	CS-AML	KDM6A	X	44910996	C>C/T	snv	stop gained	15.62	NM_021140.2	c.697C>T	p.Gln233Ter		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
877	*de novo*	KMT2A	11	118352549	C>C/A	snv	missense	50.32	NM_001197104.1	c.3754C>A	p.Pro1252Thr	deleterious (0.01)	benign (0.008)
32	*de novo*	KRAS	12	25398284	C>C/G	snv	missense	14.81	NM_004985	c.35G>C	p.Gly12Ala	tolerated (0.997)	possibly damaging (0.773)
91	*de novo*	KRAS	12	25380256	T>T/A	snv	missense	24.12	NM_033360.2	c.202A>T	p.Arg68Trp	deleterious (0)	probably damaging (1)
163	*de novo*	KRAS	12	25398284	C>C/G	snv	missense	25.24	NM_033360.2	c.35G>C	p.Gly12Ala	deleterious (0.02)	possibly damaging (0.739)
220	*de novo*	KRAS	12	25398281	C>C/T	snv	missense	17.32	NM_033360.2	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.517)
274	*de novo*	KRAS	12	25398284	C>C/A	snv	missense	30.78	NM_033360.2	c.35G>T	p.Gly12Val	deleterious (0)	probably damaging (0.984)
275	*de novo*	KRAS	12	25398281	C>C/T	snv	missense	31.86	NM_004985	c.38G>A	p.Gly13Asp	tolerated (0.988)	possibly damaging (0.506)
387	CS-AML	KRAS	12	25398284	C>C/T	snv	missense	43.84	NM_033360.2	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.387)
766	*de novo*	KRAS	12	25380238	T>T/G	snv	missense	14.02	NM_033360.2	c.220A>C	p.Thr74Pro	deleterious (0.02)	probably damaging (0.996)
824	*de novo*	KRAS	12	25398284	C>C/G	snv	missense	22.82	NM_004985	c.35G>C	p.Gly12Ala	tolerated (0.997)	possibly damaging (0.773)
1147	*de novo*	KRAS	12	25398278	A>A/ACGC	insertion	inframe	29.37	NM_004985	c.38_40dupGCG	p.Gly13dup		
1343	sAML	KRAS	12	25398284	C>C/T	snv	missense	29.71	NM_033360.2	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.387)
852	*de novo*	NOTCH1	9	139390622	CG>CG/C	deletion	frameshift	15.26	NM_017617.3	c.7568delC	p.Ser2523CysfsTer66		
10	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	28.11	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
14	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	43.29	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
20	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	36.45	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
32	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	14.52	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
43	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	39.36	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
64	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	40.48	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
91	*de novo*	NPM1	5	170837544	T>T/TCTGC	insertion	frameshift	41.16	NM_002520.6	c.860_861insCTGC	p.Trp288CysfsTer12		
92	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	15.3	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
108	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	36.95	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
110	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	39.21	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
124	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.7	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
137	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	39.52	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
158	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.25	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
163	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.67	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
168	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	18.36	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
170	*de novo*	NPM1	5	170837544	T>T/TCTGC	insertion	frameshift	24.04	NM_002520	c.863_864insCCTG	p.Trp288CysfsTer12		
182	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.67	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
185	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	37.13	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
192	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	34.29	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
213	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	39.68	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
220	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	39.86	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
241	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.66	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
246	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	36.27	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
247	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.01	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
261	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	34.74	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
272	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	47.94	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
275	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	19.2	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
277	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.07	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
312	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	44.04	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
319	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.8	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
320	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.21	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
323	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	36.46	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
325	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	45.32	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
342	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	15.7	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
352	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	7.8	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
377	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	16.4	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
379	*de novo*	NPM1	5	170837544	T>T/TCTGC	insertion	frameshift	33.58	NM_002520.6	c.860_861insCTGC	p.Trp288CysfsTer12		
405	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	34.31	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
407	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.89	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
421	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.5	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
423	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.43	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
432	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	30.11	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
441	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	27.05	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
455	*de novo*	NPM1	5	170837557	G>G/GGCTC	insertion	frameshift	15.2	NM_002520	c.873_874insGCTC	Trp290Fs*10		
477	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	33.85	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
507	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	23.03	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
511	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	25.38	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
527	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	42.35	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
531	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	45.27	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
548	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	39.7	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
552	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	40.56	NM_002520	c.863_864insCATG	p.Trp288CysfsTer12		
582	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	40.64	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
583	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	35.47	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
588	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	17.82	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
616	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	14.61	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
659	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	43.21	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
666	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	34.68	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
667	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	41.58	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
683	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.19	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
684	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
693	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	46.14	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
703	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	44.45	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
716	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	43.04	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
733	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	43.7	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
761	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	40.35	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
766	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	35.76	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
790	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	33.87	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
803	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.47	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
824	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	16.4	NM_002520	c.863_864insCATG	p.Trp288CysfsTer12		
830	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	40.53	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
838	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.41	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
847	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	37.2	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
852	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.89	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
853	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	40.64	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
854	*de novo*	NPM1	5	170837544	T>T/TCTGC	insertion	frameshift	38.16	NM_002520.6	c.860_861insCTGC	p.Trp288CysfsTer12		
865	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	23.62	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
867	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	28.58	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
877	*de novo*	NPM1	5	170837547	G>G/GTTAC	insertion	frameshift	42.71	NM_002520.6	c.863_864insTTAC	p.Trp288CysfsTer12		
919	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	45.4	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
931	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.44	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
981	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.22	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1025	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	46.72	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1042	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	40.2	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
1095	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	18.54	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
1100	*de novo*	NPM1	5	170837548	G>G/C	snv	missense	34.62	NM_002520.6	c.864G>C	p.Trp288Cys	deleterious (0)	probably damaging (0.88)
1140	*de novo*	NPM1	5	170837544	T>T/TCTGC	insertion	frameshift	41.76	NM_002520.6	c.860_861insCTGC	p.Trp288CysfsTer12		
1147	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	23.8	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
1168	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	36.08	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1199	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	43.61	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1219	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	43.08	NM_002520.6	c.861_862insTGCA	p.Trp288CysfsTer12		
1222	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	16.18	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
1236	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	37.53	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1285	*de novo*	NPM1	5	170837545	C>C/CTGCT	insertion	frameshift	13.34	NM_002520.6	c.861_862insTGCT	p.Trp288CysfsTer12		
1290	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	23.43	NM_002520	c.860_863dupTCTG	p.Trp288CysfsTer12		
1298	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	35.82	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1314	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	38.39	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1338	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1351	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	41.92	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1364	*de novo*	NPM1	5	170837545	C>C/CTGCT	insertion	frameshift	39.9	NM_002520.6	c.861_862insTGCT	p.Trp288CysfsTer12		
1370	*de novo*	NPM1	5	170837545	C>C/CTGCA	insertion	frameshift	23.33	NM_002520	c.863_864insCATG	p.Trp288CysfsTer12		
1376	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	40	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
1379	*de novo*	NPM1	5	170837543	C>C/CTCTG	insertion	frameshift	42.3	NM_002520.6	c.859_860insTCTG	p.Trp288CysfsTer12		
6	CS-AML	NRAS	1	115258747	C>C/T	snv	missense	12.37	NM_002524.4	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.459)
61	CS-AML	NRAS	1	115256530	G>G/T	snv	missense	55.83	NM_002524.4	c.181C>A	p.Gln61Lys	deleterious (0.01)	possibly damaging (0.751)
102	CS-AML	NRAS	1	115258744	C>C/T	snv	missense	20.01	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)
108	*de novo*	NRAS	1	115258744	C>C/T	snv	missense	25.09	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)
185	*de novo*	NRAS	1	115258744	C>C/T	snv	missense	31.21	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
274	*de novo*	NRAS	1	115258747	C>C/T	snv	missense	12.78	NM_002524.4	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.459)
320	*de novo*	NRAS	1	115258748	C>C/T	snv	missense	40.03	NM_002524.4	c.34G>A	p.Gly12Ser	deleterious (0.03)	possibly damaging (0.475)
404	*de novo*	NRAS	1	115258744	C>C/T	snv	missense	13.35	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)
447	sAML	NRAS	1	115258744	C>C/T	snv	missense	22.48	NM_002524	c.38G>A	p.Gly13Asp	tolerated (0.971)	possibly damaging (0.383)
447	sAML	NRAS	1	115258747	C>C/G	snv	missense	12.68	NM_002524	c.35G>C	p.Gly12Ala	tolerated (0.968)	possibly damaging (0.589)
470	CS-AML	NRAS	1	115258747	C>C/A	snv	missense	23.08	NM_002524.4	c.35G>T	p.Gly12Val	deleterious (0)	possibly damaging (0.58)
505	CS-AML	NRAS	1	115258744	C>C/T	snv	missense	38.67	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)
548	*de novo*	NRAS	1	115256477	G>G/T	snv	missense	33.48	NM_002524.4	c.234C>A	p.Phe78Leu	deleterious (0)	possibly damaging (0.784)
830	*de novo*	NRAS	1	115258747	C>C/T	snv	missense	38.48	NM_002524.4	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.459)
931	*de novo*	NRAS	1	115258744	C>C/T	snv	missense	22.8	NM_002524.4	c.38G>A	p.Gly13Asp	deleterious (0.03)	possibly damaging (0.394)
1140	*de novo*	NRAS	1	115258747	C>C/T	snv	missense	21.47	NM_002524.4	c.35G>A	p.Gly12Asp	deleterious (0)	possibly damaging (0.459)
241	*de novo*	PHF6	X	133527636	C>C/T	snv	stop gained	49.49	NM_032458.2	c.346C>T	p.Arg116Ter		
378	CS-AML	PHF6	X	133551270	T>T/G	snv	missense	40.47	NM_032458.2	c.906T>G	p.His302Gln	deleterious (0.01)	possibly damaging (0.816)
423	*de novo*	PHF6	X	133551239	G>G/A	snv	missense	60.97	NM_032458.2	c.875G>A	p.Cys292Tyr	deleterious (0)	probably damaging (0.995)
633	CS-AML	PHF6	X	133511739	T>T/TA	insertion	frameshift	41.23	NM_032458.2	c.92_93insA	p.Leu32ThrfsTer4		
830	*de novo*	PHF6	X	133551333	G>G/A	snv	splicing	69.21	NM_032458.2	c.968+1G>A	p.?		
13	CS-AML	PTPN11	12	112926852	C>C/T	snv	missense	39.78	NM_002834.3	c.1472C>T	p.Pro491Leu	tolerated (0.19)	probably damaging (0.894)
64	*de novo*	PTPN11	12	112926910	G>G/C	snv	missense	22.89	NM_002834.3	c.1530G>C	p.Gln510His	deleterious (0)	probably damaging (0.99)
91	*de novo*	PTPN11	12	112888261	G>G/C	snv	missense	53.16	NM_002834.3	c.277G>C	p.Gly93Arg	deleterious (0)	probably damaging (0.993)
110	*de novo*	PTPN11	12	112888156	A>A/T	snv	missense	23.06	NM_002834.3	c.172A>T	p.Asn58Tyr	deleterious (0.01)	probably damaging (0.91)
182	*de novo*	PTPN11	12	112926888	G>G/C	snv	missense	41.01	NM_002834.3	c.1508-1509GG>CT	p.Gly503Ala	deleterious (0)	probably damaging (0.993)
213	*de novo*	PTPN11	12	112888210	G>G/A	snv	missense	9.95	NM_002834.3	c.226G>A	p.Glu76Lys	deleterious (0.02)	probably damaging (0.915)
455	*de novo*	PTPN11	12	112888198	G>G/A	snv	missense	23.66	NM_002834	c.214G>A	p.Ala72Thr	tolerated (0.998)	probably damaging (0.956)
477	*de novo*	PTPN11	12	112888165	G>G/A	snv	missense	35.57	NM_002834	c.181G>A	p.Asp61Asn	tolerated (0.999)	probably damaging (0.986)
616	*de novo*	PTPN11	12	112926248	G>G/A	snv	missense	15.23	NM_002834	c.1381G>A	p.Ala461Thr	tolerated (0.999)	probably damaging (0.999)
684	*de novo*	PTPN11	12	112926872	C>C/T	snv	missense	16.23	NM_002834.3	c.1492C>T	p.Arg498Trp	deleterious (0.02)	possibly damaging (0.899)
693	*de novo*	PTPN11	12	112888162	G>G/C	snv	missense	17.48	NM_002834.3	c.178G>C	p.Gly60Arg	deleterious (0)	probably damaging (0.999)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
847	*de novo*	PTPN11	12	112888163	G>G/C	snv	missense	19.37	NM_002834.3	c.179G>C	p.Gly60Ala	deleterious (0.01)	probably damaging (0.997)
852	*de novo*	PTPN11	12	112888165	G>G/T	snv	missense	37.73	NM_002834.3	c.181G>T	p.Asp61Tyr	deleterious (0)	probably damaging (0.998)
1152	*de novo*	PTPN11	12	112888190	A>A/T	snv	missense	13.05	NM_002834.3	c.206A>T	p.Glu69Val	deleterious (0)	possibly damaging (0.705)
1152	*de novo*	PTPN11	12	112888165	G>G/C	snv	missense	11.17	NM_002834.3	c.181G>C	p.Asp61His	deleterious (0)	probably damaging (0.996)
1166	CS-AML	PTPN11	12	112888163	G>G/C	snv	missense	17.06	NM_002834.3	c.179G>C	p.Gly60Ala	deleterious (0.01)	probably damaging (0.997)
1219	*de novo*	PTPN11	12	112926885	C>C/T	snv	missense	44.68	NM_002834.3	c.1505C>T	p.Ser502Leu	deleterious (0)	probably damaging (1)
1376	*de novo*	PTPN11	12	112888211	A>A/G	snv	missense	33.11	NM_002834.3	c.227A>G	p.Glu76Gly	deleterious (0)	possibly damaging (0.767)
320	*de novo*	RAD21	8	117866660	CACTGTCAACAATT>CACTGTCAACAATT/C	deletion	frameshift	39.4	NM_006265.2	c.972_984delAATTGTTGACAGT	p.Ile325SerfsTer32		
548	*de novo*	RAD21	8	117870612	T>T/TA	insertion	frameshift	49.2	NM_006265.2	c.459dupT	p.Ile154TyrfsTer6		
548	*de novo*	RAD21	8	117869584	C>C/T	snv	missense	11.98	NM_006265.2	c.610G>A	p.Glu204Lys	tolerated (0.35)	benign (0.052)
1236	*de novo*	RAD21	8	117869505	C>C/T	snv	splicing	37.9	NM_006265.2	c.688+1G>A	p.?		
3	CS-AML	RUNX1	21	36259312	G>G/A	snv	missense	50.81	NM_001754.4	c.179C>T	p.Ala60Val	tolerated (0.2)	benign (0.003)
6	CS-AML	RUNX1	21	36259373	A>A/AGCGGCGG	insertion	frameshift	23.36	NM_001754.4	c.111_117dupCCGCCGC	p.Phe40ProfsTer100		
61	CS-AML	RUNX1	21	36171756	G>G/GT	insertion	frameshift	42.87	NM_001754.4	c.808dupA	p.Thr270AsnfsTer330		
62	CS-AML	RUNX1	21	36231783	G>G/A	snv	nonsense	45.01	NM_001754	c.601C>T	p.Arg201*		
62	CS-AML	RUNX1	21	36252920	T>T/TAGCATTTCTCAGCTC	insertion	inframe	39	NM_001754	c.427_441dupGAGCTGAGAAATGCT	p.Glu143_Ala147dup		
82	sAML	RUNX1	21	36259166	T>T/C	snv	missense	49.85	NM_001754.4	c.325A>G	p.Asn109Asp	deleterious (0)	probably damaging (0.987)
82	sAML	RUNX1	21	36231792	C>C/T	snv	missense	39.3	NM_001754.4	c.592G>A	p.Asp198Asn	deleterious (0)	possibly damaging (0.216)
102	CS-AML	RUNX1	21	36231782	C>C/T	snv	missense	14.36	NM_001754.4	c.602G>A	p.Arg201Gln	deleterious (0)	benign (0.135)
131	CS-AML	RUNX1	21	36164707	G>G/GC	insertion	frameshift	38.55	NM_001754.4	c.1167dupG	p.Gln390AlafsTer210		
139	CS-AML	RUNX1	21	36206705	A>A/G	snv	splicing	25.44	NM_001754.4	c.805+2T>C	p.?		
139	CS-AML	RUNX1	21	36252869	C>C/CGGGTTAGGTT	insertion	frameshift	15.66	NM_001754.4	c.492_493insAACCTAACCC	p.Gly165AsnfsTer51		
226	sAML	RUNX1	21	36259229	C>C/A	snv	stop gained	43.33	NM_001754.4	c.262G>T	p.Glu88Ter		
250	CS-AML	RUNX1	21	36164903	T>T/TGCCGCTGCAGGGC	insertion	frameshift	30.97	NM_001754.4	c.968-9_971dupGCCCTGCAGCGGC	p.Asp326CysfsTer278		
258	CS-AML	RUNX1	21	36171600	G>G/GA	insertion	frameshift	18.84	NM_001754.4	c.964dupT	p.Ser322PhefsTer278		
265	CS-AML	RUNX1	21	36231782	C>C/T	snv	missense	46.39	NM_001754.4	c.602G>A	p.Arg201Gln	deleterious (0)	benign (0.135)
265	CS-AML	RUNX1	21	36252940	G>G/A	snv	missense	42	NM_001754.4	c.422C>T	p.Ser141Leu	deleterious (0.03)	probably damaging (0.994)
361	CS-AML	RUNX1	21	36259172	G>G/A	snv	missense	39.84	NM_001754.4	c.319C>T	p.Arg107Cys	deleterious (0)	probably damaging (0.998)
369	sAML	RUNX1	21	36252933	CTCAGCCGAGTAGTTTTCATCA>CTCAGCCGAGTAGTTTTCATCA/C	deletion	missense	13.91	NM_001754.4	c.408_428delTGATGAAAACTACTCGGCTGA	p.Asn136_Glu143delinsLys		
378	CS-AML	RUNX1	21	36231805	GATGGCTCTGTGGTAGGT>GATGGCTCTGTGGTAGGT/G	deletion	frameshift	63.13	NM_001754.4	c.562_578delACCTACCACAGAGCCAT	p.Thr188GlnfsTer19		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
378	CS-AML	RUNX1	21	36252875	A>A/C	snv	missense	44.72	NM_001754.4	c.487T>G	p.Phe163Val	deleterious (0)	probably damaging (0.995)
387	CS-AML	RUNX1	21	36259245	C>C/CA	insertion	frameshift	44.55	NM_001754.4	c.245dupT	p.Ala83GlyfsTer55		
470	CS-AML	RUNX1	21	36252910	A>A/C	snv	missense	35.38	NM_001754.4	c.452T>G	p.Met151Arg	deleterious (0)	probably damaging (0.999)
505	CS-AML	RUNX1	21	36259335	CA>CA/C	deletion	frameshift	49.6	NM_001754.4	c.155delT	p.Met52ArgfsTer20		
505	CS-AML	RUNX1	21	36252865	C>C/A	snv	missense	47.41	NM_001754.4	c.497G>T	p.Arg166Leu	deleterious (0.01)	probably damaging (0.992)
508	*de novo*	RUNX1	21	36206833	C>C/A	snv	stop gained	32.14	NM_001754.4	c.679G>T	p.Glu227Ter		
605	CS-AML	RUNX1	21	36231855	TG>TG/T	deletion	frameshift	79.19	NM_001754.4	c.528delC	p.Ile177SerfsTer34		
733	*de novo*	RUNX1	21	36164479	T>T/C	snv	missense	62.11	NM_001754.4	c.1396A>G	p.Met466Val	deleterious (0.02)	probably damaging (0.922)
846	CS-AML	RUNX1	21	36171622	CAG>CAG/C	deletion	frameshift	11.85	NM_001754.4	c.941_942delCT	p.Ser314CysfsTer285		
940	CS-AML	RUNX1	21	36231773	C>C/T	snv	missense	78.5	NM_001754	c.611G>A	p.Arg204Gln	tolerated (0.999)	probably damaging (0.994)
997	CS-AML	RUNX1	21	36259327	G>G/GA	insertion	frameshift	27.37	NM_001754.4	c.163_164insT	p.Ala55ValfsTer83		
997	CS-AML	RUNX1	21	36259328	C>C/G	snv	missense	27.91	NM_001754.4	c.163G>C	p.Ala55Pro	tolerated (0.29)	benign (0.016)
997	CS-AML	RUNX1	21	36259329	C>C/G	snv	missense	27.64	NM_001754.4	c.162G>C	p.Glu54Asp	tolerated (0.45)	probably damaging (0.989)
1110	sAML	RUNX1	21	36252866	G>G/C	snv	missense	26.3	NM_001754.4	c.496C>G	p.Arg166Gly	deleterious (0)	probably damaging (0.996)
1201	sAML	RUNX1	21	36164611	C>C/A	snv	nonsense	65.22	NM_001754	c.1264G>T	p.Glu422*		
1270	CS-AML	RUNX1	21	36252865	C>C/A	snv	missense	68.23	NM_001754.4	c.497G>T	p.Arg166Leu	deleterious (0.01)	probably damaging (0.992)
1343	sAML	RUNX1	21	36171612	G>G/GA	insertion	frameshift	28.77	NM_001754.4	c.952dupT	p.Ser318PhefsTer282		
149	CS-AML	SETBP1	18	42531907	G>G/A	snv	missense	42.06	NM_015559	c.2602G>A	p.Asp868Asn	tolerated (1)	probably damaging (0.998)
1095	*de novo*	SETBP1	18	42531194	C>C/T	snv	missense	44.87	NM_015559	c.1889C>T	p.Ala630Val	tolerated (0.895)	benign (0.017)
62	CS-AML	SF3B1	2	198267705	C>C/T	snv	missense	47.23	NM_012433	c.1774G>A	p.Glu592Lys	tolerated (0.999)	probably damaging (0.999)
82	sAML	SF3B1	2	198266834	T>T/C	snv	missense	31.47	NM_012433.2	c.2098A>G	p.Lys700Glu	deleterious (0.01)	probably damaging (0.993)
102	CS-AML	SF3B1	2	198267480	T>T/C	snv	missense	38.63	NM_012433.2	c.1877A>G	p.Asn626Ser	deleterious (0)	probably damaging (0.975)
369	sAML	SF3B1	2	198266834	T>T/C	snv	missense	43.5	NM_012433.2	c.2098A>G	p.Lys700Glu	deleterious (0.01)	probably damaging (0.993)
505	CS-AML	SF3B1	2	198266834	T>T/C	snv	missense	47.79	NM_012433.2	c.2098A>G	p.Lys700Glu	deleterious (0.01)	probably damaging (0.993)
518	CS-AML	SF3B1	2	198267360	T>T/A	snv	missense	31.79	NM_012433.2	c.1997A>T	p.Lys666Met	deleterious (0)	probably damaging (0.997)
519	CS-AML	SF3B1	2	198267359	C>C/G	snv	missense	49.79	NM_012433.2	c.1998G>C	p.Lys666Asn	deleterious (0)	probably damaging (0.993)
519	CS-AML	SF3B1	2	198266803	G>G/GC	insertion	frameshift	11.67	NM_012433.2	c.2128dupG	p.Ala710GlyfsTer5		
1043	CS-AML	SF3B1	2	198266834	T>T/C	snv	missense	34.48	NM_012433	c.2098A>G	p.Lys700Glu	tolerated (0.996)	probably damaging (0.999)
1275	CS-AML	SF3B1	2	198267359	C>C/A	snv	missense	35.42	NM_012433.2	c.1998G>T	p.Lys666Asn	deleterious (0)	probably damaging (0.993)
13	CS-AML	SMC1A	X	53441941	C>C/T	snv	missense	85.22	NM_006306.2	c.287G>A	p.Arg96His	deleterious (0)	probably damaging (1)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
91	*de novo*	SMC3	10	112343991	G>G/T	snv	missense	33.12	NM_005445.3	c.1142G>T	p.Arg381Leu	deleterious (0.01)	probably damaging (0.999)
847	*de novo*	SMC3	10	112343991	G>G/A	snv	missense	20.75	NM_005445.3	c.1142G>A	p.Arg381Gln	deleterious (0.02)	probably damaging (0.973)
931	*de novo*	SMC3	10	112356174	G>G/C	snv	missense	24.34	NM_005445.3	c.1982G>C	p.Arg661Pro	deleterious (0.01)	probably damaging (0.996)
46	sAML	SRSF2	17	74732935	CGGCGGCTGTGGTGTGAGTCCGGGG>CGGCGGCTGTGGTGTGAGTCCGGGG/C	deletion	inframe deletion	56.78	NM_001195427.1	c.284_307delCCCCGGACTCACACCACAGCCGCC	p.Pro95_Arg103del		
126	CS-AML	SRSF2	17	74732935	CGGCGGCTGTGGTGTGAGTCCGGGG>CGGCGGCTGTGGTGTGAGTCCGGGG/C	deletion	inframe deletion	72.04	NM_001195427.1	c.284_307delCCCCGGACTCACACCACAGCCGCC	p.Pro95_Arg103del		
131	CS-AML	SRSF2	17	74732959	G>G/C	snv	missense	48.48	NM_001195427.1	c.284C>G	p.Pro95Arg	deleterious (0.02)	possibly damaging (0.668)
149	CS-AML	SRSF2	17	74732959	G>G/T	snv	missense	39.53	NM_003016	c.284C>A	p.Pro95His	tolerated (0.999)	probably damaging (0.984)
226	sAML	SRSF2	17	74732959	G>G/C	snv	missense	25.75	NM_001195427.1	c.284C>G	p.Pro95Arg	deleterious (0.02)	possibly damaging (0.668)
242	CS-AML	SRSF2	17	74732959	G>G/T	snv	missense	51.12	NM_001195427.1	c.284C>A	p.Pro95His	deleterious (0.01)	probably damaging (0.979)
246	*de novo*	SRSF2	17	74732959	G>G/C	snv	missense	43.95	NM_001195427.1	c.284C>G	p.Pro95Arg	deleterious (0.02)	possibly damaging (0.668)
470	CS-AML	SRSF2	17	74733073	A>A/T	snv	missense	32.07	NM_001195427.1	c.170T>A	p.Phe57Tyr	deleterious (0.05)	probably damaging (0.914)
605	CS-AML	SRSF2	17	74732959	G>G/C	snv	missense	51.99	NM_001195427.1	c.284C>G	p.Pro95Arg	deleterious (0.02)	possibly damaging (0.668)
753	CS-AML	SRSF2	17	74733191	C>C/A	snv	missense	67.43	NM_001195427.1	c.52G>T	p.Val18Leu	deleterious (0.01)	probably damaging (0.857)
1201	sAML	SRSF2	17	74732959	G>G/T	snv	missense	40.19	NM_003016	c.284C>A	p.Pro95His	tolerated (0.999)	probably damaging (0.984)
1298	*de novo*	SRSF2	17	74732959	G>G/C	snv	missense	44.04	NM_001195427.1	c.284C>G	p.Pro95Arg	deleterious (0.02)	possibly damaging (0.668)
1324	sAML	SRSF2	17	74732960	G>G/C	snv	missense	47.66	NM_001195427.1	c.283C>G	p.Pro95Ala	tolerated (0.22)	possibly damaging (0.621)
226	sAML	STAG2	X	123220488	C>C/CT	insertion	frameshift	88.25	NM_001042749.1	c.3145_3146insT	p.Ala1050SerfsTer4		
349	CS-AML	STAG2	X	123179171	T>T/A	snv	stop gained	46.61	NM_001042749.1	c.620T>A	p.Leu207Ter		
380	CS-AML	STAG2	X	123229304	G>G/C	snv	splicing	94.08	NM_001042749.1	c.3783+5G>C	p.?		
387	CS-AML	STAG2	X	123220440	C>C/T	snv	stop gained	92.28	NM_001042749.1	c.3097C>T	p.Arg1033Ter		
413	CS-AML	STAG2	X	123184970	G>G/A	snv	splicing	97.32	NM_001042749.1	c.1018-1G>A	p.?		
470	CS-AML	STAG2	X	123176470	G>G/GA	insertion	frameshift	96.15	NM_001042749.1	c.437_438insA	p.Met148AsnfsTer3		
470	CS-AML	STAG2	X	123197850	AGAT>AGAT/A	deletion	inframe deletion	13.28	NM_001042749.1	c.1975_1977delGAT	p.Asp659del		
633	CS-AML	STAG2	X	123176438	G>G/C	snv	missense	61.02	NM_001042749.1	c.405G>C	p.Met135Ile	deleterious (0.05)	probably damaging (0.992)
877	*de novo*	STAG2	X	123224469	C>C/T	snv	stop gained	40	NM_001042749.1	c.3322C>T	p.Gln1108Ter		
1110	sAML	STAG2	X	123190063	G>G/A	snv	missense	21.75	NM_001042749.1	c.1282G>A	p.Ala428Thr	deleterious (0)	probably damaging (0.994)
1337	CS-AML	STAG2	X	123197716	C>C/T	snv	stop gained	10.01	NM_001042749.1	c.1840C>T	p.Arg614Ter		
1337	CS-AML	STAG2	X	123202497	T>T/TA	insertion	frameshift	10	NM_001042749.1	c.2349_2350insA	p.Glu785GlyfsTer9		
28	*de novo*	TET2	4	106197481	C>C/CT	insertion	frameshift	51.05	NM_001127208.2	c.5814_5815insT	p.Tyr1939LeufsTer17		

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
46	sAML	TET2	4	106164778	C>C/T	snv	stop gained	94.04	NM_001127208.2	c.3646C>T	p.Arg1216Ter		
61	CS-AML	TET2	4	106157740	AG>AG/A	deletion	frameshift	45.6	NM_001127208.2	c.2642delG	p.Arg881SerfsTer40		
149	CS-AML	TET2	4	106157512	G>G/T	snv	nonsense	44.48	NM_017628	c.2413G>T	p.Gly805*		
149	CS-AML	TET2	4	106190781	CAG>CAG/C	deletion	frameshift	44.3	NM_001127208	c.4062_4063delAG	p.Arg1354Serfs*46		
196	*de novo*	TET2	4	106196421	CT>CT/C	deletion	frameshift	41.97	NM_001127208.2	c.4755delT	p.Ser1586GlnfsTer10		
222	sAML	TET2	4	106157527	C>C/T	snv	stop gained	52.11	NM_001127208.2	c.2428C>T	p.Gln810Ter		
222	sAML	TET2	4	106190799	TC>TC/T	deletion	frameshift	31.47	NM_001127208.2	c.4078delC	p.Leu1360TrpfsTer3		
246	*de novo*	TET2	4	106158322	GA>GA/G	deletion	frameshift	46.55	NM_001127208.2	c.3224delA	p.Asp1075ValfsTer7		
246	*de novo*	TET2	4	106157982	A>A/AG	insertion	frameshift	44.54	NM_001127208.2	c.2883_2884insG	p.Gln962AlafsTer10		
275	*de novo*	TET2	4	106164787	C>C/A	snv	missense	41.87	NM_001127208	c.3655C>A	p.His1219Asn	tolerated (1)	probably damaging (0.999)
377	*de novo*	TET2	4	106182957	T>T/TAAAGGGTCCTAGAGGGTG	insertion	nonsense	19.2	NM_001127208	c.3997_3998insAAGGGTCCTAGAGGGTGA	p.Leu1332_Met1333ins6		
387	CS-AML	TET2	4	106163986	T>T/A	snv	splicing	45.24	NM_001127208.2	c.3501-5T>A	p.?		
402	*de novo*	TET2	4	106190854	T>T/C	snv	missense	42.59	NM_001127208.2	c.4132T>C	p.Cys1378Arg	deleterious (0)	probably damaging (0.994)
441	*de novo*	TET2	4	106197285	T>T/C	snv	missense	45.42	NM_001127208	c.5618T>C	p.Ile1873Thr	tolerated (1)	probably damaging (0.999)
441	*de novo*	TET2	4	106164082	TGGG>TGGG/TGG	deletion	splicing	44.41	NM_001127208	c.3594+1delG	p.?		
447	sAML	TET2	4	106196306	C>C/T	snv	nonsense	38.74	NM_001127208	c.4639C>T	p.Gln1547*		
447	sAML	TET2	4	106196402	TA>TA/T	deletion	frameshift	34.6	NM_001127208	c.4736delA	p.Tyr1579Phefs*17		
659	*de novo*	TET2	4	106164068	G>G/A	snv	missense	48.37	NM_001127208.2	c.3578G>A	p.Cys1193Tyr	deleterious (0)	probably damaging (1)
659	*de novo*	TET2	4	106196558	TA>TA/T	deletion	frameshift	49.56	NM_001127208.2	c.4892delA	p.Tyr1631PhefsTer64		
683	*de novo*	TET2	4	106196778	AT>AT/A	deletion	frameshift	48.91	NM_001127208.2	c.5112delT	p.Asp1704GlufsTer15		
684	*de novo*	TET2	4	106180880	G>G/A	snv	missense	26.98	NM_001127208.2	c.3908G>A	p.Ser1303Asn	deleterious (0.01)	probably damaging (0.998)
716	*de novo*	TET2	4	106197360	C>C/T	snv	missense	52.4	NM_001127208.2	c.5693C>T	p.Ser1898Phe	deleterious (0)	probably damaging (0.999)
716	*de novo*	TET2	4	106157614	C>C/CA	insertion	frameshift	44.18	NM_001127208.2	c.2515_2516insA	p.His839GlnfsTer7		
761	*de novo*	TET2	4	106164778	C>C/T	snv	stop gained	42.7	NM_001127208.2	c.3646C>T	p.Arg1216Ter		
786	CS-AML	TET2	4	106180870	T>T/A	snv	missense	79.64	NM_001127208.2	c.3898T>A	p.Phe1300Ile	deleterious (0.02)	probably damaging (0.993)
803	*de novo*	TET2	4	106196213	C>C/T	snv	stop gained	92.41	NM_001127208.2	c.4546C>T	p.Arg1516Ter		
865	*de novo*	TET2	4	106158470	T>T/TA	insertion	frameshift	45.18	NM_017628	c.3371_3372insA	p.Lys1125Glnfs*5		
865	*de novo*	TET2	4	106190882	A>A/G	snv	missense	39.32	NM_001127208	c.4160A>G	p.Asn1387Ser	tolerated (0.998)	probably damaging (0.999)
940	CS-AML	TET2	4	106196829	T>T/G	snv	missense	49.5	NM_001127208	c.5162T>G	p.Leu1721Trp	tolerated (0.997)	possibly damaging (0.754)
1025	*de novo*	TET2	4	106180823	CCTT>CCTT/C	deletion	inframe deletion	33.73	NM_001127208.2	c.3852_3854delCTT	p.Phe1285del		
1100	*de novo*	TET2	4	106156048	C>C/T	snv	stop gained	36.14	NM_001127208.2	c.949C>T	p.Gln317Ter		
1168	*de novo*	TET2	4	106156234	GCTTA>GCTTA/G	deletion	frameshift	39.95	NM_001127208.2	c.1136_1139delCTTA	p.Tyr380SerfsTer46		
1290	*de novo*	TET2	4	106158349	C>C/T	snv	nonsense	49.43	NM_017628	c.3250C>T	p.Gln1084*		
1290	*de novo*	TET2	4	106156589	CTGTTCCATTG>CTGTTCCATTG/C	insertion	frameshift	20.58	NM_017628	c.1496_1505delCATTGTGTTC	p.Pro499Leufs*31		
1298	*de novo*	TET2	4	106164016	A>A/T	snv	missense	47.52	NM_001127208.2	c.3526A>T	p.Arg1176Trp	deleterious (0)	probably damaging (1)

UPN	AML category	Gene	Chr	Coordinate (Hg19)	Variant	Type	Consequence	VAF	Transcript	c.DNA	protein	Sift	PolyPhen
1298	*de novo*	TET2	4	106164079	AAGT>AAGT/A	deletion	missense	43.06	NM_001127208.2	c.3590_3592delAGT	p.Lys1197_Trp1198delinsArg		
1324	sAML	TET2	4	106193748	C>C/T	snv	stop gained	94.64	NM_001127208.2	c.4210C>T	p.Arg1404Ter		
1351	*de novo*	TET2	4	106164936	G>G/GT	insertion	splicing	46.95	NM_001127208.2	c.3803+1_3803+2insT	p.?		
1364	*de novo*	TET2	4	106182995	A>A/G	snv	missense	47.14	NM_001127208.2	c.4034A>G	p.Tyr1345Cys	deleterious (0)	probably damaging (1)
1364	*de novo*	TET2	4	106162565	T>T/G	snv	missense	43.33	NM_001127208.2	c.3479T>G	p.Ile1160Ser	deleterious (0)	probably damaging (0.993)
35	*de novo*	TP53	17	7577094	G>G/A	snv	missense	11.69	NM_000546.5	c.844C>T	p.Arg282Trp	deleterious (0)	probably damaging (0.999)
35	*de novo*	TP53	17	7578235	T>T/C	snv	missense	9.16	NM_000546.5	c.614A>G	p.Tyr205Cys	deleterious (0)	probably damaging (0.993)
6	CS-AML	U2AF1	21	44524456	G>G/A	snv	missense	44.16	NM_001025203.1	c.101C>T	p.Ser34Phe	deleterious (0)	probably damaging (0.998)
102	CS-AML	U2AF1	21	44514777	T>T/C	snv	missense	40.26	NM_001025203.1	c.470A>G	p.Gln157Arg	deleterious (0)	probably damaging (0.993)
132	sAML	U2AF1	21	44524456	G>G/A	snv	missense	9.7	NM_006758	c.101C>T	p.Ser34Phe	tolerated (1)	probably damaging (1)
166	CS-AML	U2AF1	21	44524456	G>G/A	snv	missense	46	NM_001025203.1	c.101C>T	p.Ser34Phe	deleterious (0)	probably damaging (0.998)
262	CS-AML	U2AF1	21	44524456	G>G/A	snv	missense	37.04	NM_001025203.1	c.101C>T	p.Ser34Phe	deleterious (0)	probably damaging (0.998)
447	sAML	U2AF1	21	44524456	G>G/A	snv	missense	39.41	NM_006758	c.101C>T	p.Ser34Phe	tolerated (1)	probably damaging (1)
786	CS-AML	U2AF1	21	44524456	G>G/A	snv	missense	39.62	NM_001025203.1	c.101C>T	p.Ser34Phe	deleterious (0)	probably damaging (0.998)
825	CS-AML	U2AF1	21	44514780	C>C/T	snv	missense	47.53	NM_001025203.1	c.467G>A	p.Arg156His	deleterious (0.05)	possibly damaging (0.607)
868	CS-AML	U2AF1	21	44514780	C>C/T	snv	missense	30.86	NM_001025203.1	c.467G>A	p.Arg156His	deleterious (0.05)	possibly damaging (0.607)
94	*de novo*	WT1	11	32413565	C>C/A	snv	missense	33.95	NM_024426	c.1385G>T	p.Arg462Leu	tolerated (1)	probably damaging (0.999)
222	sAML	WT1	11	32417941	C>C/CA	insertion	frameshift	34.73	NM_024426.4	c.1110dupT	p.Val371CysfsTer14		
222	sAML	WT1	11	32417911	A>A/AC	insertion	frameshift	34.27	NM_024426.4	c.1140dupG	p.Ser381ValfsTer4		
361	CS-AML	WT1	11	32417911	A>A/AC	insertion	frameshift	42.45	NM_024426.4	c.1140dupG	p.Ser381ValfsTer4		
362	*de novo*	WT1	11	32417914	G>G/C	snv	missense	48.58	NM_024426.4	c.1138C>G	p.Arg380Gly	deleterious (0.02)	probably damaging (0.946)
362	*de novo*	WT1	11	32413573	C>C/CTTAG	insertion	frameshift	35.23	NM_024426.4	c.1376_1377insCTAA	p.Lys459AsnfsTer2		
406	*de novo*	WT1	11	32413565	C>C/T	snv	missense	19.87	NM_024426.4	c.1385G>A	p.Arg462Gln	deleterious (0.03)	probably damaging (0.998)
623	CS-AML	WT1	11	32417907	G>G/GCCGA	insertion	frameshift	8.5	NM_024426	c.1141_1144dupTCGG	p.Ala382Valfs*4		
924	*de novo*	WT1	11	32417941	C>C/CA	insertion	frameshift	21.28	NM_024426.4	c.1110dupT	p.Val371CysfsTer14		
1036	*de novo*	WT1	11	32417913	C>C/CT	insertion	frameshift	18.26	NM_024426.4	c.1138_1139insA+1139C>A	p.Arg380GlnfsTer5		
1166	CS-AML	WT1	11	32417942	A>A/AG	insertion	frameshift	19.8	NM_024426.4	c.1109_1110insC	p.Val371CysfsTer14		
1343	sAML	WT1	11	32417941	C>C/CA	insertion	frameshift	24.89	NM_024426.4	c.1110dupT	p.Val371CysfsTer14		
1201	sAML	ZRSR2	X	15836766	GT>GT/GTT	insertion	splicing	69.15	NM_005089	c.827+2dupT	p.?		
1343	sAML	ZRSR2	X	15841230	C>C/CAGCCGG	insertion	inframe insertion	41.66	NM_005089.3	c.1314_1315insAGCCGG	p.Gly438_Ser439insSerArg		

Supplemental Table 3. Univariate analysis for CR by AML category on the whole patients' cohort.

All patients	**CS-AML (N=55)**		**sAML (N=100)**		***de novo* AML (N=258)**	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age [years]						
≥60	2.22 (0.46-16.27)	0.36	0.15 (0.05-0.38)	0.06	0.45 (0.2-1.01)	0.0001
ECOG PS						
2-3	0.28 (0.04-2.32)	0.19	0.39 (0.08-1.67)	0.21	0.13 (0.05-0.36)	0.0001
WBC count [x109/L]						
≥50	0.71 (0.14-5.39)	0.70	0.54 (0.15-1.92)	0.34	0.31 (0.11-0.79)	0.01
Induction arm						
ICE	0.81 (0.17-3.79)	0.78	0.68 (0.3-1.51)	0.35	1.14 (0.44-2.96)	0.78
Genetics*						
normal karyotype	0.98 (0.05-7.05)	0.98	1.66 (0.5-6.53)	0.42	0.66 (0.21-1.8)	0.44
t(8;21)	-		-		1.93 (0.37-35.59)	0.53
inv(16)/t(16;16)	-		-		3.12 (0.61-57)	0.28
complex karyotype	-		0.55 (0.23-1.25)	0.16	-	
chromosome 7 abnormalities	-		1.66 (0.5-6.53)	0.42	-	
chromosome 5 abnormalities	-		1.04 (0.17-8.21)	0.96	-	
RUNX1-RUNX1T1	-		-		2.14 (0.41-39.36)	0.47
CBFB-MYH11	-		-		3.4 (0.67-62.06)	0.24
biallelic *CEBPa*	-		-		2 (0.38-37.03)	0.51
NPM1	-		-		0.53 (0.17-1.43)	0.23
FLT3-ITD	>99.99 (0-NA)	0.99	1.42 (0.26-10.59)	0.69	0.39 (0.15-1.02)	0.05
KMT2A-PTD	2.87 (0.59-21.02)	0.22	2.37 (0.29-49.13)	0.46	-	
ASXL1	0.67 (0.12-5.25)	0.66	0.06 (0-0.89)	0.07	-	
BCOR	>99.99 (0-NA)	1.00	-		-	
RUNX1	0.55 (0.1-2.8)	0.47	1.33 (0.1-17.65)	0.82	-	
SF3B1	>99.99 (0-NA)	0.99	-		-	
STAG2	1.07 (0.14-22.47)	0.95	-		-	
U2AF1	1.12 (0.15-23.23)	0.92	-		-	
SRSF2	0.16 (0.02-1.02)	0.05	0.06 (0-0.89)	0.07	-	

Abbreviations: ICE, idarubicin, cytarabine and etoposide; HR, hazard ratio; CI, confidence interval; NA, not applicable.

*For this analysis, only chromatin-spliceosome mutations and abnormalities included in the ELN risk stratification occurring in at least 3 patients in each AML category were considered.

Supplemental Table 4. Multivariable analysis for CR, OS and DFS on 55 CS-AML patients.

CS-AML patients	**Complete remission**		**Overall survival**		**Disease free survival**	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age [years]						
≥60	5.73 (0.09-2224.02)	0.46	1.17 (0.34-4.00)	0.80	3.88 (0.92-16.38)	0.07
ECOG PS						
2-3	0.03 (0-32.95)	0.31	42.76 (3.22-566.79)	0.004	23.26 (0.87-622.92)	0.06
WBC count [x109/L]						
≥50	3.51 (0.02-20080.4)	0.66	0.18 (0.03-1.22)	0.08	0.06 (0.01-0.58)	0.01
Induction arm						
ICE	0.39 (0.01-7.11)	0.55	0.56 (0.21-1.48)	0.24	0.23 (0.05-0.98)	0.05
Gene mutations						
KMT2A-PTD	3.13 (0.14-115.45)	0.46	0.64 (0.21-2.00)	0.45	0.99 (0.28-3.48)	0.98
FLT3-ITD	>99.99 (0-NA)	1.00	2.21 (0.36-13.4)	0.39	3.4 (0.49-23.45)	0.21
ASXL1	5.97 (0.12-3620.83)	0.45	0.61 (0.18-2.06)	0.43	1.38 (0.36-5.21)	0.64
BCOR	>99.99 (0-NA)	1.00	0.78 (0.12-5.11)	0.79	0.73 (0.09-5.75)	0.76
RUNX1	0.09 (0-1.75)	0.14	3.55 (1.28-9.87)	0.01	3.13 (1.1-8.95)	0.03
SF3B1	>99.99 (0-NA)	1.00	0.36 (0.06-1.99)	0.24	0.2 (0.02-1.62)	0.13
SRSF2	0.16 (0-10.43)	0.42	1.50 (0.34-6.56)	0.59	0.4 (0.06-2.75)	0.35
STAG2	0.3 (0-20.86)	0.56	0.79 (0.14-4.40)	0.78	0.37 (0.05-2.97)	0.35
U2AF1	0.4 (0-38.95)	0.66	6.87 (1.71-27.55)	0.006	16.46 (3.14-86.31)	0.0009
Abbreviations: ICE, idarubicin, cytarabine and etoposide; HR, hazard ratio; CI, confidence interval.						

Supplemental Table 5. Multivariable analysis for CR, OS and DFS on the whole patients' cohort, excluding *RUNX1* and or *U2AF1*-mutated patients.

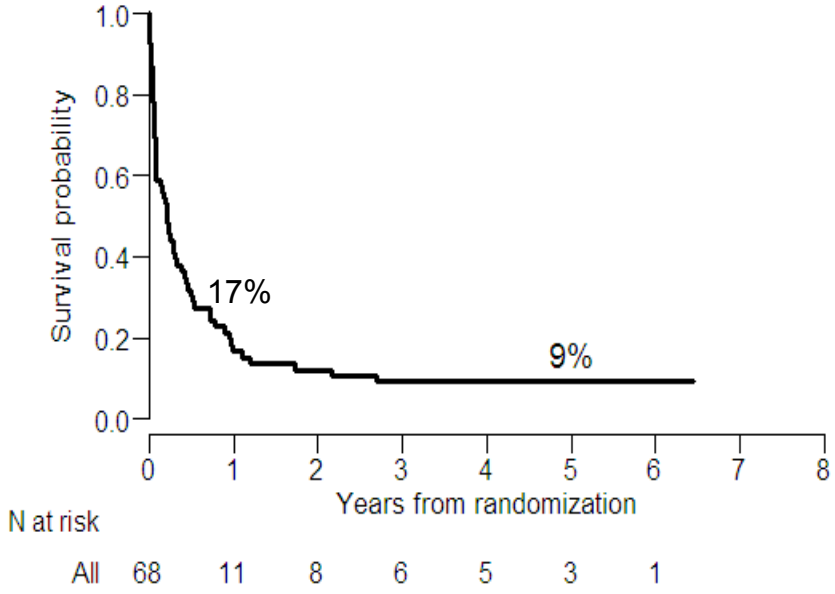
All patients	**Complete remission**		**Overall survival**		**Disease free survival**	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age [years]						
≥60	0.3 (0.16-0.57)	0.0003	1.69 (1.24-2.32)	0.0010	1.19 (0.83-1.71)	0.3448
ECOG PS						
2-3	0.24 (0.1-0.59)	0.0015	2.37 (1.57-3.58)	<0.0001	1.58 (0.94-2.64)	0.0838
WBC count [x109/L]						
≥50	0.4 (0.18-0.88)	0.0224	1.82 (1.31-2.54)	0.0004	1.76 (1.23-2.5)	0.0018
Induction arm						
ICE	0.88 (0.46-1.67)	0.6871	1.24 (0.92-1.65)	0.1525	1.29 (0.95-1.76)	0.1060
AML category						
sAML	0.09 (0.04-0.18)	<0.0001	3.82 (2.74-5.33)	<0.0001	2.72 (1.85-3.98)	<0.0001
CS-AML	0.85 (0.23-4.19)	0.8184	1.83 (1.07-3.14)	0.0281	1.94 (1.15-3.26)	0.0126
Abbreviations: ICE, idarubicin, cytarabine and etoposide; HR, hazard ratio; CI, confidence interval.						

Supplemental Table 6. Demographic and clinical characteristics of an independent, single-center cohort (N=50) treated at ASST Ospedale Papa Giovanni XXIII between 2012 and 2020.

Clinical characteristics	**CS-AML N=8**	***P****	**sAML N=20**	***P*** **	***de novo* AML N=22**	***P****
Age [years], median (range)	61.1 (29.4-75)	0.0564	70 (48.5-77.9)	0.0011	55.5 (25.5-79.2)	0.6960
<60, n(%)	3 (37.5)	0.3107	3 (15)	0.0076	12 (54.5)	0.6817
≥60, n(%)	5 (62.5)		17 (85)		10 (45.5)	
Gender, n (%)		1.0000		0.2410		0.3742
M	7 (87.5)		16 (80)		14 (63.6)	
F	1 (12.5)		4 (20)		8 (36.4)	
ECOG PS, n (%)		0.2808		0.4454		0.5448
0-1	8 (100)		15 (75)		19 (86.4)	
2-3	-		5 (25)		3 (13.6)	
Hepatomegaly, n (%)	1 (12.5)	0.6399	5 (25)	0.4454	3 (13.6)	1.0000
Splenomegaly, n (%)	2 (25)	1.0000	7 (35)	0.8605	6 (27.3)	1.0000
Extramedullary involvement, n (%)	1 (12.5)	0.4974	1 (5)	1.0000	2 (9)	1.0000
Hemoglobin [g/dL], median (range)	8.6 (4.8-12.9)	0.6902	9.2 (6.3-13.7)	0.6283	9.8 (4.6-13.2)	0.8144
WBC count [x10^9/L], median (range)	9.6 (0.4-118)	0.3955	3.4 (0.9-51.8)	0.0281	11.9 (1.1-175.5)	0.7652
Platelets, median (range)	75 (23-321)	0.7749	78 (8-187)	0.6472	56 (4-203)	0.4118
BM blast cells (%), median (range)	90 (30-95)	0.0024	30 (20-80)	0.0141	65 (10-92)	0.0369
AML with multilineage dysplasia, n (%)	2 (25)	0.0957	13 (65)	0.0006	3 (13.6)	0.5894
Induction treatment, n (%)		0.0882		0.0003		0.4690
Intensive chemotherapy	7 (87.5)		9 (45)		21 (95.5)^	
HMAs	1 (12.5)		11 (55)§		1 (4.5)	

Abbreviations: CS-AML, chromatin-spliceosome acute myeloid leukemia; sAML, secondary acute myeloid leukemia; *de novo* AML, *de novo* acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBC, white blood cell count; BM, bone marrow; HMAs, hypomethylating agents. *P*-values refer to: *CS-AML vs sAML; **sAML vs *de novo* AML; *** *de novo* AML vs CS-AML. Hepatomegaly was defined as lower liver edge >2 cm from costal margin. Splenomegaly was defined as spleen >1 cm from costal margin, confirmed by ultrasound scan with longitudinal axis >12 cm. Extramedullary AML was defined as AML presenting with central nervous system involvement or mass lesions. ^3 *de novo* AML patients also received FLT3 inhibitors. §1 sAML patients received venetoclax with HMAs.

Supplemental Figure 1. Kaplan-Meier analysis of OS on 68 patients not achieving CR after 1 or 2 induction cycles.



Supplemental Figure 2. Kaplan-Meier analysis of OS on 50 consecutive patients of the single-center cohort. CS-AML vs *de novo* AML, *P*=0.13; sAML vs *de novo* AML, *P*=0.004; CS-AML vs sAML, *P*=0.46.