Aims: This phase 2 study (NCT02718300) in MF evaluated optimal dosing and efficacy of add-on parsaclisib in pts with suboptimal response to RUX.

Methods: Pts had primary, post–polycythemia vera or post–essential thrombocythemia MF, ECOG performance status ≤2, and suboptimal response (palpable spleen >10 cm below left subcostal margin [LSM], or splenomegaly 5–10 cm below LSM and presence of 1 symptom score ≥5 or 2 symptom scores ≥3 using the Screening Symptom Form) after ≥6 months of RUX treatment (tx) (5–25 mg twice daily and a stable dose for ≥8 wks). All pts provided informed consent. Pts remained on their stable RUX dose and were randomized to add-on tx with parsaclisib in the following groups: daily (QD)/weekly (QW) (10 mg or 20 mg parsaclisib QD for 8 weeks/same dose QW thereafter) or all QD (5 mg or 20 mg parsaclisib QD for 8 weeks/5 mg QD thereafter) (Figure 1). The primary efficacy endpoint was change in spleen volume from baseline (BL) to wk 12 by imaging (MRI or CT scan); other endpoints included change in spleen length and symptoms (MF Symptoms Assessment Form [v3.0] Total Symptom Score [MFSAF-TSS]).

Results: At data cutoff (Oct 10, 2019), 33 pts received parsaclisib QD/QW and 18 pts received all QD parsaclisib. Median tx duration was 192 d and median average daily dose of parsaclisib was 5.0 mg/d and RUX was 32.2 mg/d. At BL, median spleen volume (cm^3) was 2333 (327–5324) in QD/QW (n = 30) and 1890 (434–3051) in QD (n = 18). Median MFSAF-TSS was 10.8 (n = 28) and 19.1 (n = 14), respectively. Median percent change in spleen volume at wk 12 was –2.3 (n = 30) in QD/QW and –13.0 (n = 11) in QD, and at wk 24 was –2.5 (n = 24) and –27.1 (n = 6), respectively. Figure 2 shows mean reduction in palpable spleen length. Median percent change in MFSAF-TSS at wk 12 was –14.0 (n = 21) in QD/QW and –51.4 (n = 6) in QD.

Nonhematologic treatment-emergent adverse events (TEAEs) were primarily grade (Gr) 1/2. Gr 3/4 TEAEs included disseminated tuberculosis, enteritis, fatigue, hypertension, increased alanine aminotransferase, and increased aspartate aminotransferase (1 pt each in QD/QW). New-onset Gr 3 thrombocytopenia was observed in 6/23 pts in QD/QW and 4/18 pts in QD; Gr 4 was observed in 7/23 pts in QD/QW and 0/18 pts in QD. Two serious AEs were reported (1 each of varicella zoster virus infection and disseminated tuberculosis). No colitis or dose-limiting diarrhea or rash were observed. TEAEs led to parsaclisib interruption in 17/33 pts in QD/QW and 8/18 pts in QD, and RUX in 5/33 pts and 3/18 pts, respectively.

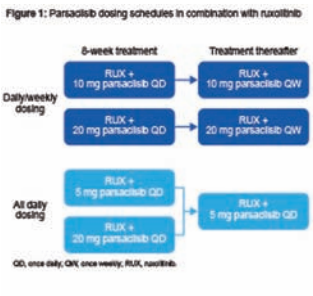

Figure 1: Parsaclisib dosing schedules in combination with ruxolitinib

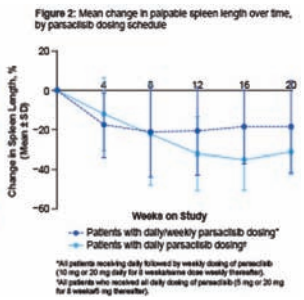

Figure 2: Mean change in palpable spleen length over time, by parsaclisib dosing schedule

Summary/Conclusion: Addition of parsaclisib to RUX showed efficacy in pts with MF experiencing suboptimal response. QD parsaclisib dosing appeared to be more efficacious than QD/QW. Combination therapy demonstrated an acceptable safety profile with limited Gr 3/4 TEAEs and no dose-limiting TEAEs. Pt enrollment continues; updated data will be presented.

S217 RUXOLITINIB DISCONTINUATION SYNDROME: INCIDENCE, RISK FACTORS AND MANAGEMENT IN 242 PATIENTS WITH MYELOFIBROSIS

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Background: Ruxolitinib (RUX) is effective in controlling myelofibrosis (MF)-related splenomegaly and symptoms by *JAK1/JAK2* inhibition. In the phase I/II study, 11% of the patients (pts) experienced a RUX discontinuation syndrome (RDS), a wide range of adverse events (AEs) attributed to a rebound cytokine storm.

Aims: To investigate in a real-world contest: 1) incidence, timing and severity of RDS; 2) type of prevention strategies; 3) risk factors associated with RDS.

Methods: Overall, 700 MF pts were treated with RUX in 20 European Hematology Centers. Spleen (SR) and symptoms (SyR) responses were evaluated according to IWG-MRT criteria.

Results: After a median follow-up from RUX start of 36.3 mos, 242 (34.6%) pts stopped RUX and survived >30 days after discontinuation. At RUX start, characteristics of these 242 pts were: median age 67y (24–88); males 59.9%; PMF 59.9%; median Hb 10 g/dl; median PLT/WBC: 211/10.2 $x10^9$/l. At any time, 43.8% and 80.2% of pts achieved a SR or a SyR.

Causes of RUX stop were: RUX failure (60.6%: lack/loss of SR/SyR or leukemic transformation); AEs (28.6%; hematological AEs: 20.7%); other causes (10.8%). At the time of decision to stop RUX, daily dose (mg BID) was: 5, 10, 15 or 20 in 46.3%, 21.9%, 16.5% and 15.3% of pts.

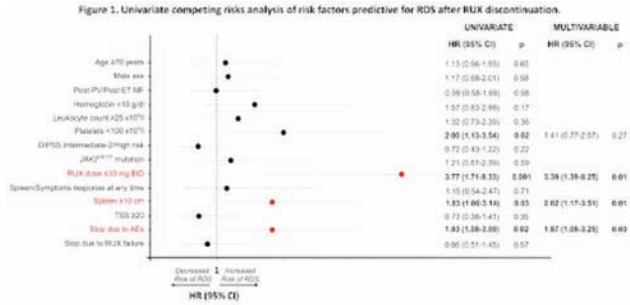
An active strategy to prevent RDS was performed in 101 (41.7%) pts, specifically: RUX taper alone (44 pts); RUX taper in combination with prednisone (PDN) ± hydroxyurea (HU) (32 pts); PDN ± HU without tapering (25 pts). Median duration of tapering was 20 days (2–90). Median PDN dose was 12.5 mg/d, with a median exposure of 29 days (10–255); HU was used at a median dose of 1 g/d for a median of 60 days (4–210). In the remaining 141 (58.2%) pts, RUX was quickly discontinued without any specific intervention.

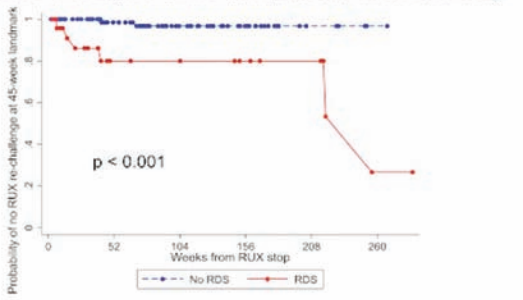
Overall, 53 (21.9%) pts experienced a mild RDS which was defined as: troublesome fatigue/itching/bone pain/abdominal discomfort (36 pts, 67.9%); onset of night sweats/fever/weight loss (9 pts, 17%); symptomatic increase of spleen length (16 pts, 30.2%). In 2 additional (0.8%) pts, RDS required hospitalization due to sudden spleen rupture (1 pt) and uncontrolled fever, with dyspnoea, fatigue and weight loss (1 pt), which recovered only after RUX rechallenge. Median time from RUX stop to RDS occurrence was 10 days (2–65).

Factors at RUX stop significantly associated to increased risk of RDS in univariate analysis were: PLT <100 $x10^9$/L (HR:2, p = 0.02), RUX dose ≤10 mg BID (HR:3.8, p = 0.001), spleen length ≥10 cm (HR: 1.8, p = 0.03), and discontinuation due to AEs (HR:1.83, p = 0.02). In multivariable analysis, RUX dose ≤10 mg (HR:3.4, p = 0.01), spleen ≥10 cm (HR: 2.0, p = 0.01), and discontinuation due to AEs (HR:1.87, p = 0.03) retained statistical significance (Fig.1). Finally, RDS was significantly associated with the need of RUX rechallenge, with 10/55 (18.2%) RDS pts eventually resuming RUX (p<0.001) (Fig.2).

Summary/Conclusion: Severe RDS is very rare (<1% of pts), but symptoms and/or splenomegaly significantly increase in >20% of pts after RUX stop. Pts at higher risk for RDS, particularly those whose discontinuation is forced by AEs, should be followed more cautiously. Also, RDS may identify a population that can still benefit from RUX rechallenge because the rebound indicates residual disease control activity (i.e. those suspended intentionally for apparent loss of efficacy). Overall,

these results highlight the need for implementation of active prevention strategies and suggest a quick switch to alternative treatment if clinically indicated.





S218 UPDATED RESULTS FROM A PHASE 1/2 CLINICAL TRIAL OF TAGRAXOFUSP, A CD123-TARGETED THERAPY, IN PATIENTS WITH POOR-RISK MYELOFIBROSIS

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Background: Inhibitors of the JAK-STAT pathway are approved for patients with myelofibrosis (MF) based on spleen volume reduction and symptomatic improvement, but patients who relapse or fail have limited options. We previously demonstrated single agent clinical activity and safety of tagraxofusp (TAG; SL-401), a CD123-targeted therapy, in patients with CD123-positive myeloid malignancies and blastic plasmacytoid dendritic cell neoplasm (BPDCN). TAG is approved by the FDA for the treatment of previously untreated and treated patients with BPDCN. Notably, presence of high-expressing CD123+ plasmacytoid dendritic cells (pDCs) in some myeloid malignancies appears associated with poorer prognosis. Moreover, pDCs share a common precursor cell with monocytes, and monocytosis is reported as a poor prognostic factor in MF.
Aims: To assess safety and efficacy of TAG in patients with poor-risk M patients
Methods: Multicenter, open-label Phase 1/2 trial. In the Stage 1 (dose escalation), TAG was administered as a daily 15 min IV infusion at 7, 9,or 12 mcg/kg on days 1–3 every 21 days (cycle 1–4), 28 days (cycles 5–7), and 42 days (cycles 8+). In Stage 2 (expansion), patients received 12 mcg/kg.
Results: 32 previously treated patients with poor-risk MF have been treated, including 13 patients who had previously received 4 3 lines of therapy; 23 of 25 (92%) previously treated patients received JAK inhibitors. Median age was 69.5 years (range 54–87), 50% female, and 25% had baseline monocytosis (≥ 1x10^9/L). Baseline risk assessment (DIPSS-Plus) of 31/32 patients with data available showed 1 patient (3%) intermediate-1, 17 patients (55%) intermediate-2, and 13 patients (42%) high-risk. Median platelet count was 57.5 x 10^9/L; 69% of patients had baseline platelets <100 K/uL, of which 13 patients had platelets <50 x 10^9/L. 75% of patients had baseline palpable splenomegaly. Genomic analysis revealed: *JAK2*^{V617F} (n = 20); *CALR* (n = 3); *MPL* (n = 2); 7/32 patients (22%) also had an *ASXL1* mutation. Cytogenetic studies revealed an abnormal karyotype in 9/32 (28%) patients: 20q- (n = 3), -5/5q- (n = 2), -7/7q- (n = 2), and 12p- (n = 2). Most common treatment-related adverse events (TRAEs, incidence ≥ 15%) include headache, hypoalbuminemia, increased levels of ALT, thrombocytopenia, and anemia. Most common ≥ grade 3 TRAE's were thrombocytopenia (8%) and anemia (15%). Capillary leak syndrome was reported in 1 patient (grade 3). Among 19 evaluable patients with baseline splenomegaly, 53% had spleen size reductions, of which 4 patients had reductions of > 45%. In 5 patients with baseline splenomegaly and monocytosis (>1x10^9/L monocytes), 80% (4/5) had spleen size reductions, of which 2 had reductions of >45%. Five patients had treatment duration of 12 months or more, with two of these patients remaining on TAG (at 19+,and 27+ months, respectively). 24 patients were evaluable for symptomatic assessment (MPN-SAF TSS). Symptom response rate was 46% (≥50% reduction in MPN IWG 2013 TSS score). All 8 patients with spleen size reductions and TSS evaluable, experienced symptomatic burden reduction.
Summary/Conclusion: We have demonstrated clinical benefit of TAG monotherapy, with predictable and manageable safety in poor-risk MF patients. One patient developed CLS grade 3. The study cohort has recently been expanded. NCT02268253.

S219 EFFICACY AND SAFETY OF MEPOLIZUMAB IN HYPEREOSINOPHILIC SYNDROME: A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Background: The anti-interleukin-5 monoclonal antibody, mepolizumab, reduces blood eosinophil counts (BEC) and oral corticosteroid (OCS) use in patients with hypereosinophilic syndrome (HES). However, data on its impact on disease activity are limited.
Aims: To investigate the efficacy and safety of mepolizumab in patients with HES.
Methods: This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase III trial. Eligible patients were ≥12 years old, diagnosed with HES ≥6 months, and had ≥2 flares (worsening of HES-related clinical symptoms or BEC requiring therapy escalation) in the previous 12 months, with a BEC ≥1000 cells/μL and ≥4 weeks stable doses of HES therapy at screening. All patients provided written informed consent. Patients were randomized (1:1) to receive subcutaneous mepolizumab (300 mg) or placebo, plus their baseline HES therapy, every 4 weeks for 32 weeks. Investigators were blinded to patient BEC and rescue OCS therapy. The primary outcome was the proportion of patients who experienced a flare during the study. Flares were defined as: (a) HES-related clinical manifestations requiring either an increased maintenance OCS dose ≥10 mg/day for 5 days or an increase in or addition of any cytotoxic and/or immunosuppressive therapies; (b) ≥2 courses of blinded rescue OCS during the study. Patients who withdrew early from the study were counted as having a flare. Secondary outcomes included time to first flare and the annual rate of flares; safety outcomes were also recorded.
Results: The proportion of patients with ≥1 flare or who withdrew from the study was 50% lower for patients receiving mepolizumab versus placebo (15/54 [28%] and 30/54 [56%]; P = 0.002; odds ratio [95% CI] 0.28 [0.12, 0.64]; Table), and time to first flare was increased with mepolizumab versus placebo (P = 0.002). The annualized rate of flares and the risk of first flare over the treatment period were both 66% lower with mepolizumab compared with placebo (rate ratio [95% CI] 0.34 [0.19, 0.63], P≤0.001; hazard ratio [95% CI] 0.34 [0.18, 0.67], P = 0.002; Table). Proportions of patients experiencing on-treatment adverse events (AEs) and serious AEs (SAEs) were similar with mepolizumab and placebo (AEs: 48/54 [89%] and 47/54 [87%]; SAEs: 10/54 [19%] and 8/54