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P1038 TL-895, A FIRST-IN-CLASS, COVALENT BRUTON TYROSINE KINASE INHIBITOR (BTKI) FOR THE TREATMENT OF MYELOFIBROSIS (MF) PATIENTS (PTS) WITH SEVERE THROMBOCYTOPENIA (PLATELETS (PLTS) <50 K/UL)

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background:

Nearly 35% of MF pts have severe thrombocytopenia (TCP) with a shortened median overall survival of 7-15 months (mos) (Masarova 2018, 2020). Most pts present with high symptom burden due to dysregulated cytokines (Tefferi 2011), of which elevated IL-8 impairs megakaryocyte function (Emadi 2005). Treatment with JAK inhibitors (JAKi) can worsen TCP in MF pts, with no effective therapies to improve plt counts. TL-895 is a highly potent, selective, orally available, small molecule inhibitor of BTK and bone marrow tyrosine kinase X-linked (BMX) being studied in MF for its potential to (i) impair stromal adhesion, (ii) disrupt aberrant $CD34^+$ cell trafficking (Nimmagadda 2019), (iii) reduce proinflammatory cytokine-mediated symptoms, and (iv) reverse dysfunctional megakaryopoiesis to improve plt counts.

Aims:

Safety, efficacy, and tolerability of TL-895 in MF pts with severe TCP.

Methods:

Cohort 3 of this open-label, global Phase (Ph) 2 study (NCT04640532) enrolled adult pts with JAKi-ineligible MF (plts <50 K/μL, ≥25 K/μL). Pts were randomized to TL-895 150 mg BID (Arm A) or 300 mg QD (Arm B). Eligible pts were symptomatic with intermediate/high-risk MF (DIPSS), ECOG ≤2 with splenomegaly. The primary objective was the recommended Ph 2 dose (RP2D). Key secondary objectives were Total Symptom Score improvement ≥50% by MFSAF v4.0 at Week (Wk) 24 (TSS-50), spleen volume reduction ≥35% at Wk 24 by central review (SVR-35) and safety. Plt response was assessed per modified IWG-MRT 2006 criteria (plt increase ≥50% from baseline and >50 K/μL for ≥8 wks independent of plt transfusion [Tefferi 2006]).

Results:

As of 27 Jan 2022, 11 pts were enrolled in Arm A and five pts in Arm B with median follow-up of 11.7 mos. Complete BTK occupancy (≥95%) was achieved in Arm A at trough (C1D8), but not Arm B which closed early. Arm A is described herein. In these 11 pts, baseline median plt count was 39 K/μL, median spleen volume was 1908

Abstract Book Citations: Authors, Title, HemaSphere, 2023;7(S3):pages. The individual abstract DOIs can be found at https://journals.lww.com/hemasphere/pages/default.aspx.

cm^3, median TSS was 24.7, and 73% were previously treated with a JAKi (Table 1). Six pts (55%) remain on study and five discontinued due to Grade (Gr) 3 fatigue (n=1), progression (n=2) and investigator decision (n=2). Ten (91%) pts were alive at data cut (median 12.4 mos). At Wk 24, four pts (36%) achieved TSS-50 (Fig. 1), despite no pts achieving SVR-35 (median SVR -5.3%, range -18, 38)). Per modified IWG-MRT criteria, five pts (45%) achieved plt response (≥50% improvement for ≥8 weeks [Fig. 2]), two pts (18%) achieved ≥100% plt improvement with a third pending 8-week confirmation (27%). Median time to plt response was 2.9 mos; median duration was 6.7 mos (range 1.9, 13.1+). Median change in serum IL-8 levels from baseline to Wk 12 was -38% and was associated with plt and TSS response. Median change in circulating $CD34^+$ cells from baseline to Wk 4 was +85%, demonstrating transient cell trafficking due to BTK inhibition. The most common treatment-emergent adverse events were anemia (55%), abdominal pain, nausea and TCP (27% each). Anemia and TCP were the most common Gr 3/4 AEs, regardless of causality, 46% and 27%, respectively (Table 1).

Summary/Conclusion:

In MF pts with severe TCP, TL-895 provided clinically meaningful improvements in TSS and plt counts that were associated with reductions in IL-8. This is the first clinical proof-of-concept for BTKi in the treatment of MF and supports further investigation in a recently commenced randomized, double blind, placebo-controlled Ph 2b study.

Table 1: TL-895 150 mg BID Cohort

Baseline Characteristics	N=11
Age, Median (range), years	73 (58, 78)
DIPSS, n (%) Int-1, Int-2, High Risk	 5 (46), 3 (27), 3 (27)
MF Subtype, n (%) Primary, Secondary	 8 (73), 3 (27)
Prior Therapy, Median (range) Prior Ruxolitinib, n (%)	2 (0, 5) 8 (73)
Spleen Volume Central, cm^3 Median (range)	 1908 (971, 2898)
RBC Transfusion Dependent, n (%)	3 (27)
Platelets, 10^9/L, Median (range)	39 (29, 47)
TSS, Median (range)	24.7 (4, 56)

TEAE ≥10%	N=11	
Preferred Term, n (%)	All Gr	Gr 3/4
Any TEAE	11 (100)	9 (82)
Anemia	6 (55)	5 (46)
Thrombocytopenia	3 (27)	3 (27)
Nausea	3 (27)	–
Abdominal Pain	3 (27)	–
Asthenia	2 (18)	–
Diarrhea	2 (18)	–
Pruritis	2 (18)	–
Cough	2 (18)	–
Weight Decrease	2 (18)	–
Hematoma	2 (18)	1 (9)
Fatigue	2 (18)	1 (9)
Petechiae	2 (18)	–
Vomiting	2 (18)	–

Figure 1: TSS Change, Baseline to Week 24 by MFSAF v4.0*

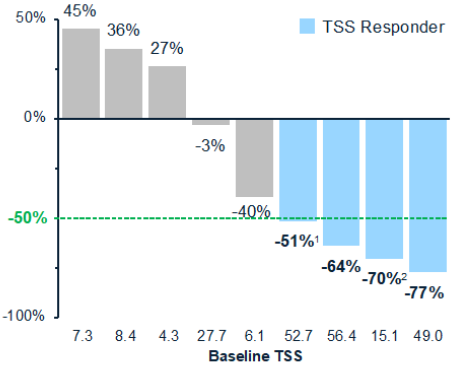
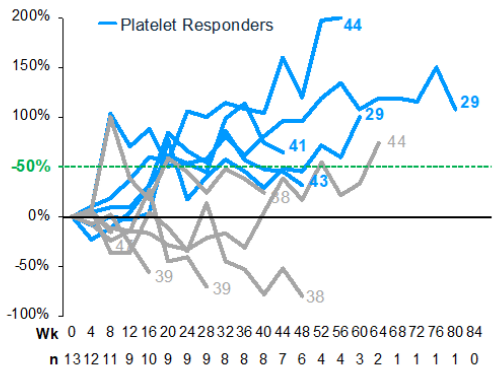


Figure 2: Percentage Change in Platelet Count from Baseline†



Data cut-off: 27 Jan 2023. *2 patients discontinued treatment prior to Wk 24.†Numbers indicate baseline plt count, 10^9/L; ¹No Wk 24 scores available, Wk 25 scores used; ²Based on 2/7 submissions. TSS Responder defined as ≥50% reduction in TSS from baseline to Week 24 by MFSAF v4.0. Abbreviations: BID, twice-a-day; DIPSS, dynamic international prognostic scoring system for myelofibrosis; Gr, grade; MFSAF v4.0, myelofibrosis symptom assessment form version 4.0; Plt, platelet; TEAE, treatment-emergent adverse events; TSS, total symptom score; Wk, week.

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