

IMproveMF Update: Phase 1/1B Trial of Imetelstat + Ruxolitinib in Patients With Intermediate-1, Intermediate-2, or High-Risk Myelofibrosis

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Key Takeaway Points/Conclusions

- In the dose finding (Phase 1) of IMproveMF, no DLTs were observed with imetelstat + ruxolitinib in patients with INT-1, INT-2, or HR MF, and the safety profile was consistent with that observed in other clinical trials of imetelstat.¹ RP2D of 8.9 mg/kg imetelstat active dose (equivalent to 9.4 mg/kg imetelstat sodium) was determined
- Imetelstat and ruxolitinib PK profiles in the combination study were similar to those reported for previous monotherapy studies¹
- These early findings from IMproveMF suggest tolerability and dose-dependent preliminary efficacy of imetelstat + ruxolitinib in this patient population with high unmet needs
- IMproveMF is actively enrolling patients at the 8.9-mg/kg imetelstat dose level for dose confirmation and expansion (Phase 1b)

DLT, dose-limiting toxicity; HR, high risk; INT, intermediate; MF, myelofibrosis; PK, pharmacokinetics; RP2D, recommended part 2 dose.

1. Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881-2892.

Background

- MF is a progressive, life-threatening myeloproliferative neoplasm commonly associated with driver mutations in *JAK2*, *CALR*, or *MPL*^{1,2}
- JAKi (eg, ruxolitinib) can reduce MF spleen size and symptom burden but are not active against underlying drivers of disease^{1,3,4}
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity
 - Imetelstat is approved by the FDA and the EC for the treatment of certain adult patients with LR-MDS with RBC-TD who are ineligible for ESAs or have relapsed or refractory/unsatisfactory response to ESAs^{5,6}
- In the IMbark Phase 2 trial (NCT02426086), imetelstat showed clinically meaningful improvement in symptom response and improved OS in patients with INT-2 or high-risk MF relapsed or refractory to JAKi⁷
- Spleen response with 8.9 mg/kg imetelstat active dose at week 24 was modest, but clinically meaningful for patients with high disease burden who were relapsed or refractory to JAKi, where 37% of patients experienced a $\geq 10\%$ spleen volume reduction

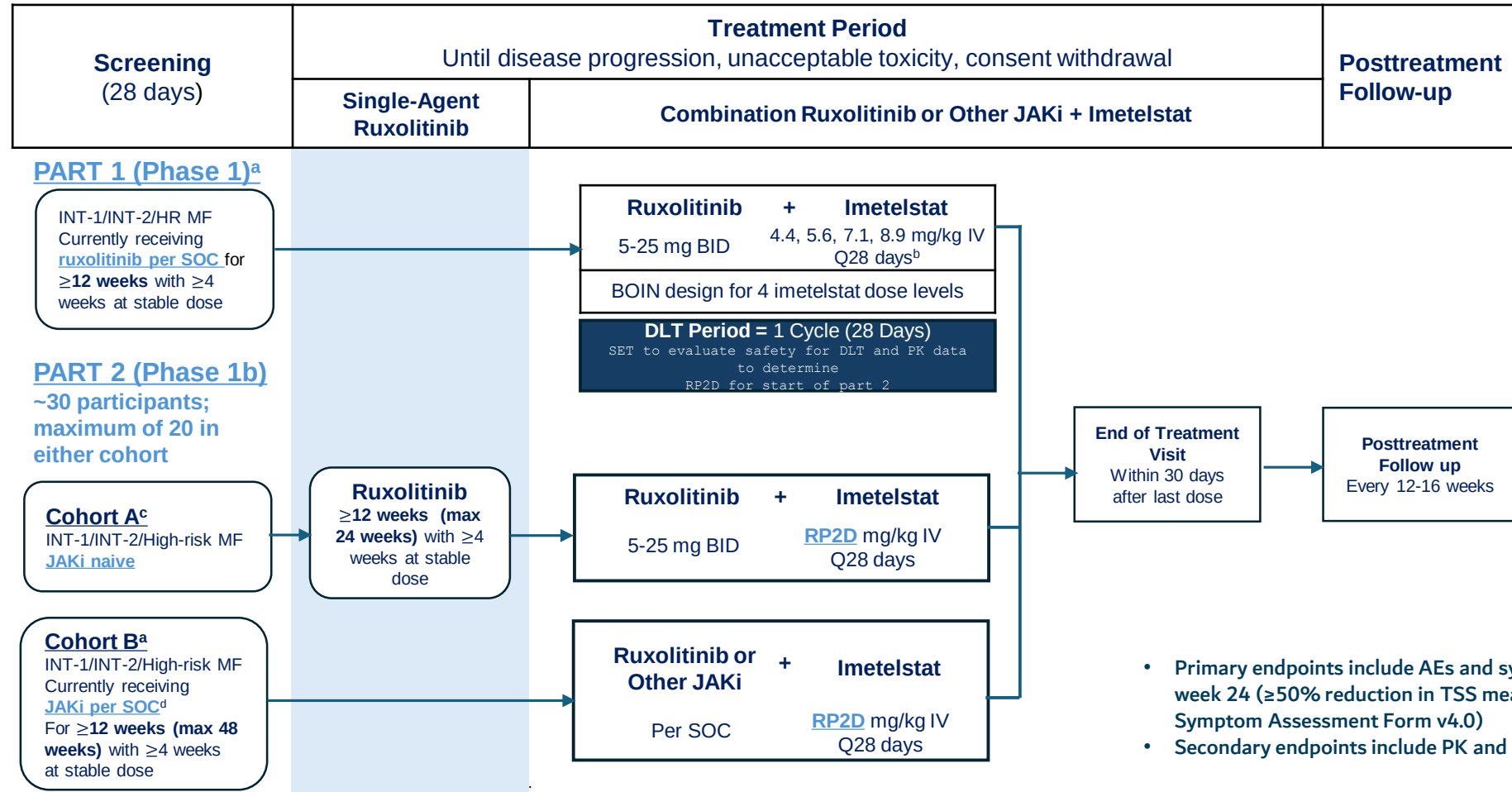
IMproveMF (NCT05371964) aims to evaluate safety, PK, and clinical activity of imetelstat in combination with ruxolitinib in patients with INT-1/INT-2/high-risk MF

EC, European Commission; ESAs, erythropoiesis-stimulating agents; FDA, United States Food and Drug Administration; INT, intermediate; JAKi, Janus kinase inhibitor; LR-MDS, lower-risk myelodysplastic syndromes; MF, myelofibrosis; OS, overall survival; PK, pharmacokinetics; RBC, red blood cell; TD, transfusion dependent.

1. Tefferi A. *Am J Hematol*. 2021;96(1):145-162. 2. Schieber M, et al. *Blood Cancer J*. 2019;9(9):74. 3. Vachhani P, et al. *J Clin Oncol*. 2022;40(11):1147-1154. 4. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

5. RYTELO® (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation; 2024. 6. RYTELO® (imetelstat) summary of product characteristics. Geron Corporation; 2025. 7. Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881-2892.

IMproveMF: Ongoing Multicenter Phase 1/1b Trial



AEs; adverse events; BID, twice a day; BOIN, Bayesian Optimal Interval; DLT, dose-limiting toxicity; HR, high risk; INT, intermediate; IV, intravenous; JAKi, Janus Kinase inhibitor; MF, myelofibrosis; PK, pharmacokinetics; Q, every; RP2D, recommended part 2 dose; SET, safety evaluation team; SOC, standard of care; TSS, total symptom score.

^aParticipants in part 1 and part 2 cohort B will start on combination treatment with imetelstat (cycle 1 day 1) after enrollment. ^bImetelstat active doses are listed, which are equivalent to 4.7, 6.0, 7.5, or 9.4 mg/kg imetelstat sodium, respectively. ^cParticipants in part 2 cohort A will start on single-agent ruxolitinib (cycle 1 day 1 single-agent ruxolitinib treatment period) after enrollment. ^dRuxolitinib, momelotinib, fedratinib, or pacritinib.

Results

Baseline Characteristics Were Balanced Across Cohorts

Baseline parameter	Imetelstat 4.4 mg/kg (n=3)	Imetelstat 5.6 mg/kg (n=3)	Imetelstat 7.1 mg/kg (n=4)	Imetelstat 8.9 mg/kg (n=9)	Total imetelstat (N=19)
DIPSS risk category, n (%)					
Intermediate-1	1 (33)	0	2 (50)	5 (56)	8 (42)
Intermediate-2	2 (67)	3 (100)	2 (50)	3 (33)	10 (53)
High	0	0	0	1 (11)	1 (5)
Type of MF, n (%)					
Primary MF	3 (100)	1 (33)	2 (50)	5 (56)	11 (58)
PET MF	0	0	2 (50)	2 (22)	4 (21)
PPV MF	0	2 (67)	0	2 (22)	4 (21)
Peripheral blood blasts, n (%)					
≥1%	2 (67)	1 (33)	1 (25)	2 (22)	6 (32)
<1%	1 (33)	2 (67)	3 (75)	6 (67)	12 (63)
Missing	0	0	0	1 (11)	1 (5)
Time on RUX before enrollment, median (range), mo	3.5 (3.4-86.2)	22.3 (8.5-39.7)	17.6 (6.7-67.3)	13.3 (4.8-85.0)	15.5 (3.4-86.2)
Baseline hematology values					
Hemoglobin, median (range), g/L	82.0 (81.0-93.0)	105.0 (65.0-110.0)	108.0 (88.0-124.0)	109.0 (73.0-126.0)	103.0 (65.0-126.0)
Leukocytes, median (range), 10⁹/L	5.4 (2.2-11.5)	8.1 (5.7-8.7)	4.3 (4.2-24.7)	7.8 (3.4-51.1)	6.6 (2.2-51.1)
Neutrophils, median (range), 10⁹/L	3.1 (1.1-6.8)	5.3 (2.8-6.9)	2.6 (2.1-12.6)	4.4 (2.5-32.7)	4.3 (1.1-32.7)
Platelets, median (range), 10⁹/L	211.0 (194.0-377.0)	361.0 (94.0-698.0)	287.0 (131.0-643.0)	192.0 (106.0-453.0)	211.0 (94.0-698.0)

- At the data cutoff date (April 4, 2025), 11 of 19 enrolled participants were still undergoing imetelstat treatment

Treatment Exposure

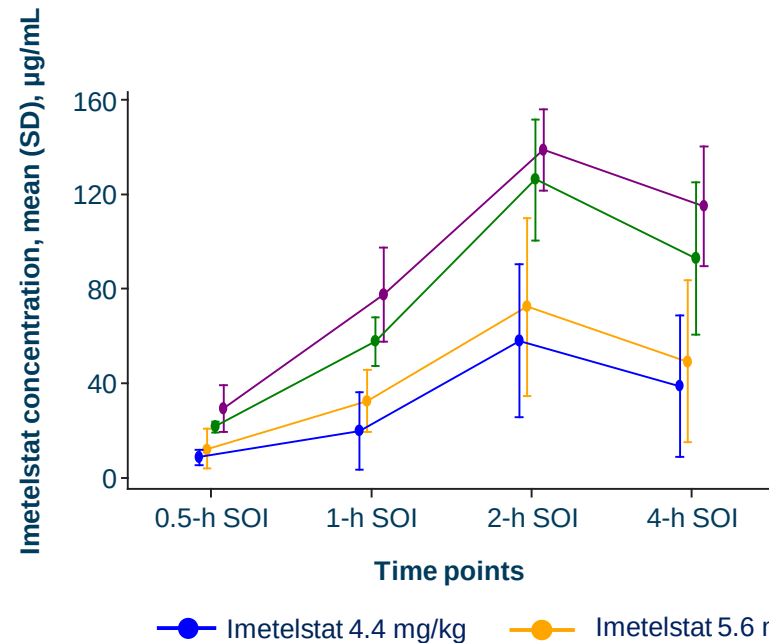
Exposure parameter	Imetelstat			
	4.4 mg/kg (n=3)	5.6 mg/kg (n=3)	7.1 mg/kg (n=4)	8.9 mg/kg (n=9)
Imetelstat duration, median (range), wk	78.1 (24.0-91.1)	28.3 (16.1-63.9)	33.1 (0.1-59.1)	25.9 (12.1-40.1)
Number of cycles, median (range)	20 (7-24)	8 (5-17)	7 (1-14)	7 (4-11)
Dose reductions	0	0	3	0
RUX duration, median (range), wk	81.6 (57.3-98.3)	75.6 (31.0-84.3)	59.8 (53.3-61.3)	35.6 (19.6-44.6)

DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET, post-essential thrombocythemia; PPV, post-polycythemia vera; RUX, ruxolitinib; TSS, total symptom score.

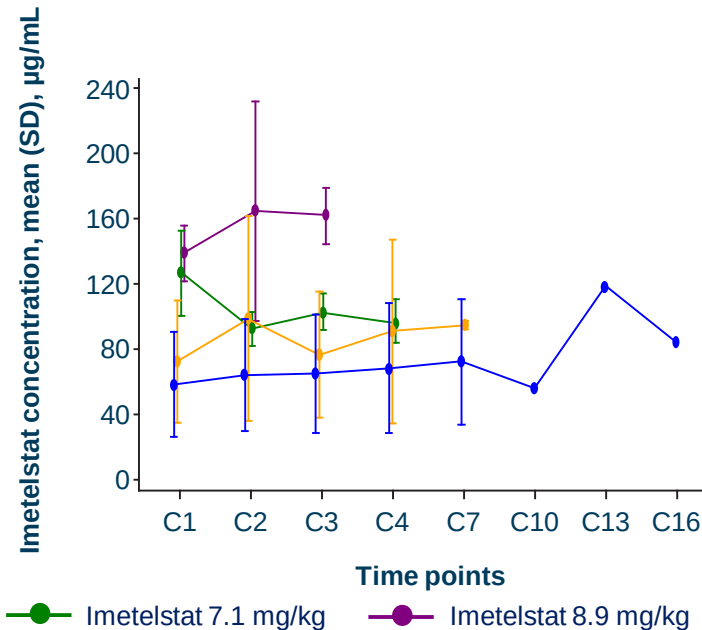
The PK Profile of Imetelstat and Ruxolitinib Were Consistent With Previous Studies^{1,2}

Imetelstat

- Dose-dependent exposure at C1D1, with C_{max} reached at end of 2-hour infusion

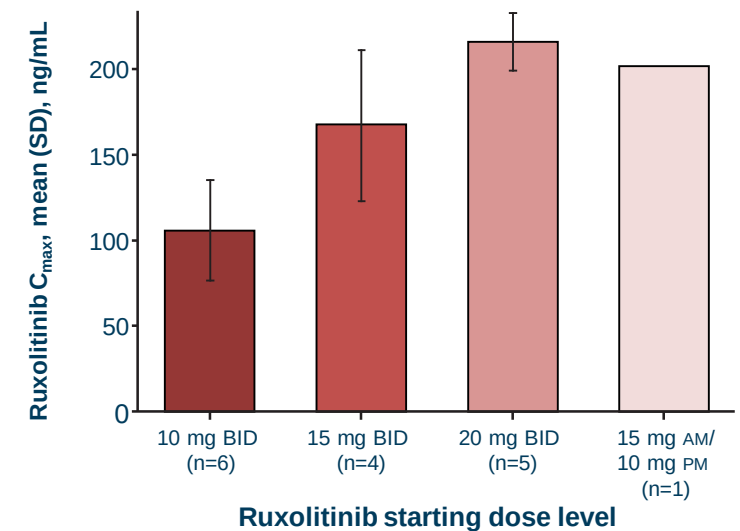


- Similar C_{max} observed across cycles for each dose level, indicating no accumulation



Ruxolitinib

- C_{max} was observed 1-2 hours postdose
- Dose-dependent C_{max} was observed at C1D1



Data cutoff date: November 4, 2024

BID, twice daily; C, cycle; C_{max} , maximum plasma concentration; D, day; PK, pharmacokinetics; SD, standard deviation; SOI, start of imetelstat infusion.

1. Lennox AL, et al. *Clin Transl Sci*. 2024;17(11):e70076. 2. Shi JG, et al. *J Clin Pharmacol*. 2011;51(12):1644-1654.

Imetelstat Combined With Ruxolitinib Was Generally Well Tolerated

- No DLTs^a were reported at any imetelstat dose level within the first 28 days of cycle 1
- No grade 5 events were reported
- Hematology values were stable over time

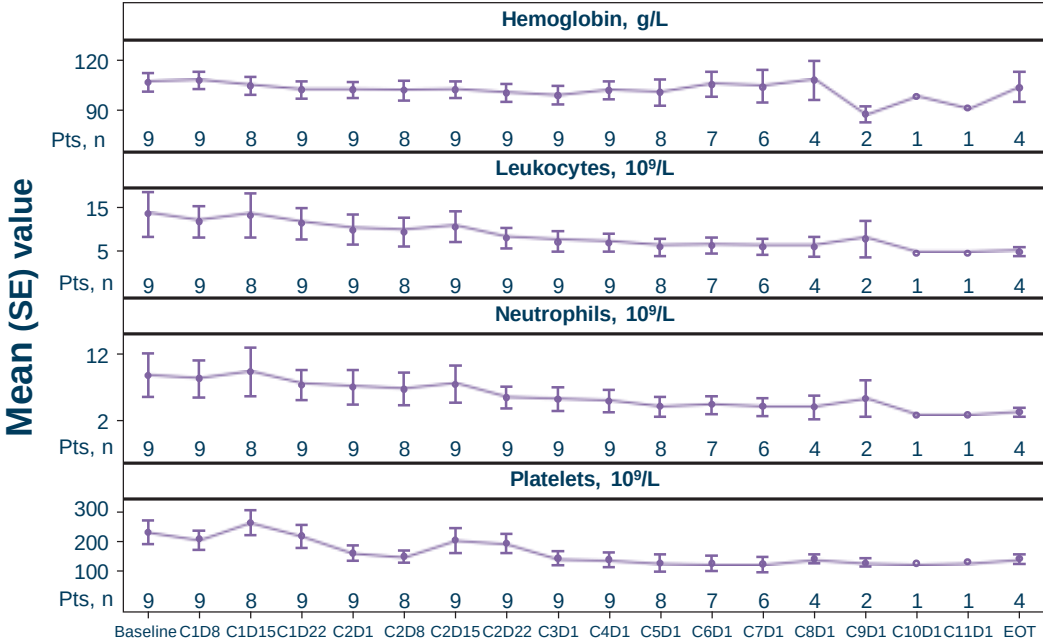
Any-Grade TEAEs in ≥15% of Patients

Preferred term, n (%)	Total (N=19)
Patients with ≥1 TEAE	18 (95)
Nausea	8 (42)
Pain in extremity	8 (42)
AST increased	7 (37)
Thrombocytopenia ^b	7 (37)
Fatigue	7 (37)
ALT increased	6 (32)
Leukopenia ^c	6 (32)
Neutropenia ^d	6 (32)
Anemia	5 (26)
Vomiting	5 (26)
Abdominal pain	3 (16)
Dyspnea	3 (16)
Dyspnea exertional	3 (16)
Headache	3 (16)

Grade 3/4 TEAEs

Preferred term, n (%)	Total (N=19)
Patients with ≥1 grade 3 TEAE	9 (48)
Anemia	4 (21)
Neutropenia ^d	4 (21)
Leukopenia ^c	3 (16)
Abdominal pain	1 (5)
Thrombocytopenia ^b	1 (5)
Epistaxis	1 (5)
Fatigue	1 (5)
Lymphocyte count decreased	1 (5)
Pneumonia	1 (5)

Hematology Values



Visit (8.9 mg/kg, imetelstat)

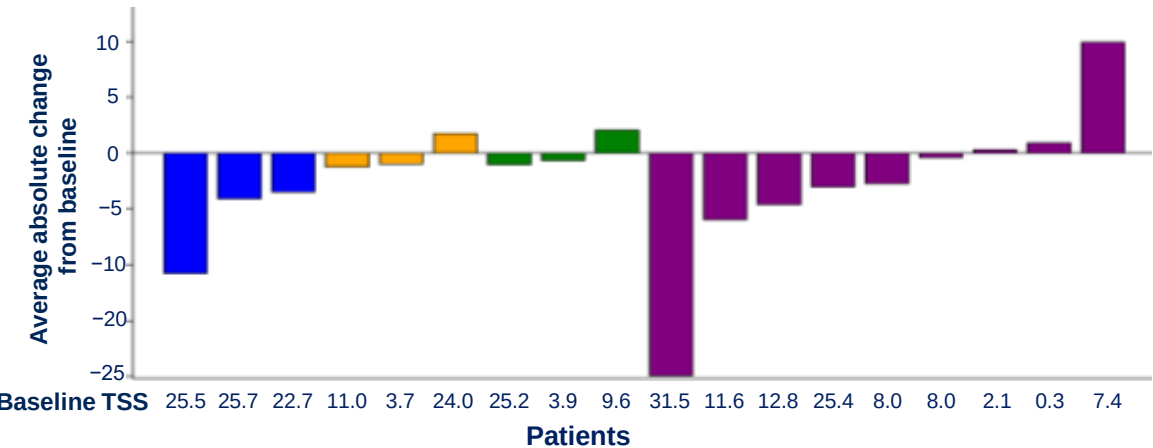
Data cutoff date: April 4, 2025

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, cycle; D, day; DLT, dose-limiting toxicity; EOT, end of treatment; Pts, patients; TEAE, treatment-emergent adverse event.

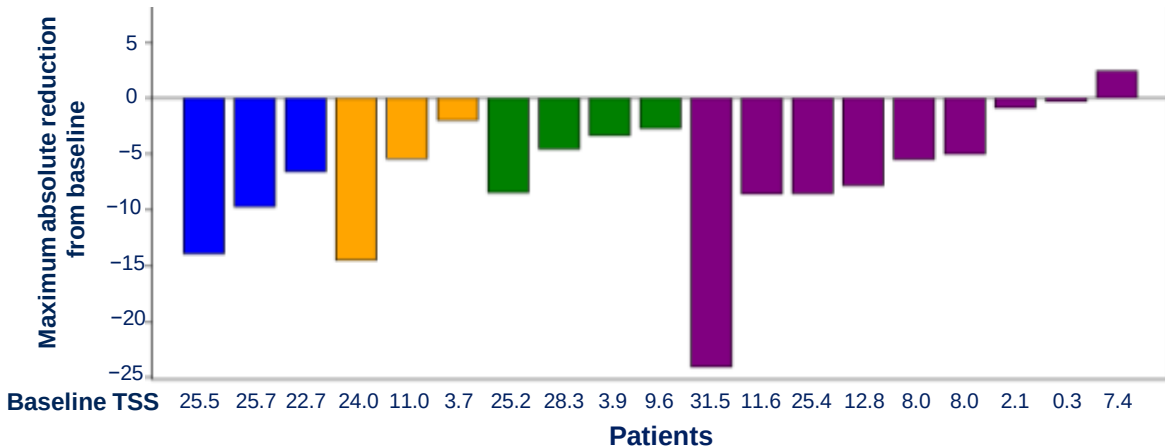
^aToxicities determined by the investigator to be possibly, probably, or definitely related to imetelstat treatment, and not attributable to the underlying disease, or toxicities with ruxolitinib increasing in grade and/or clinically significant from before imetelstat initiation. ^bCombined term includes decreased platelet count. ^cCombined term includes decreased white blood cell count. ^dCombined term includes decreased neutrophil count.

Change in TSS and SVR From Baseline by Patient

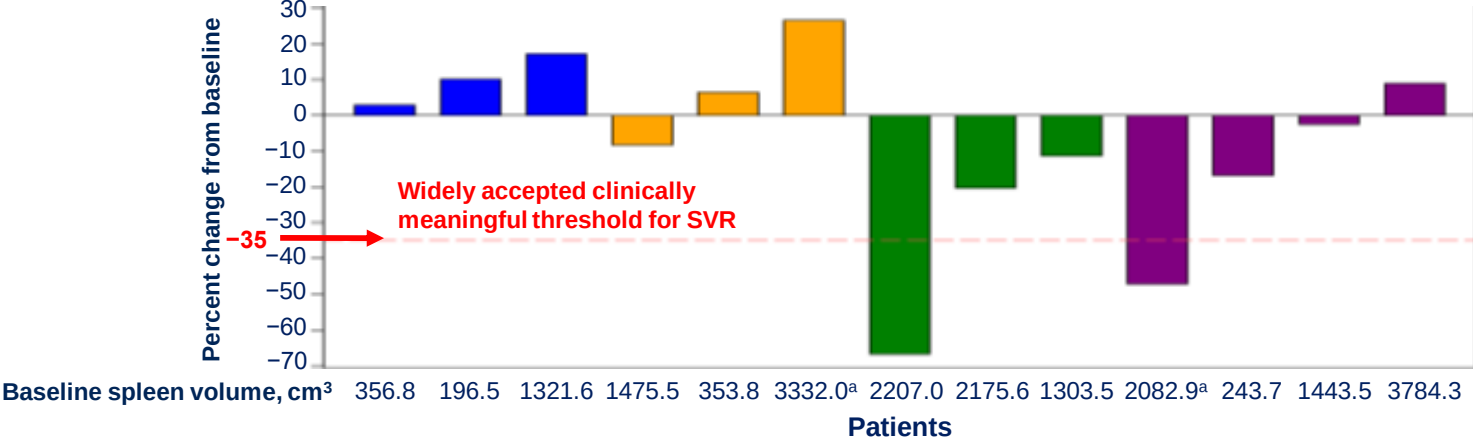
Average Absolute Change in TSS Over Week 12



Maximum Absolute Reduction in TSS up to Week 24



Change in Spleen Volume at Week 24



Data cutoff date: April 4, 2025

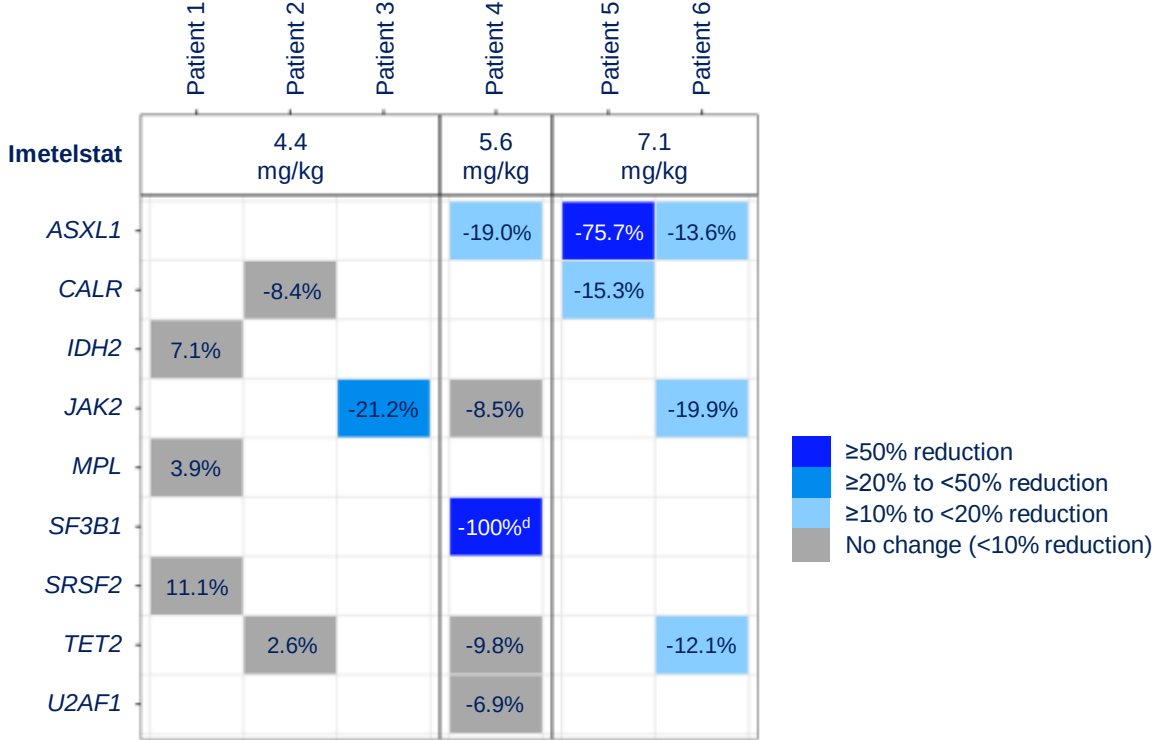
■ Imetelstat 4.4 mg/kg ■ Imetelstat 5.6 mg/kg ■ Imetelstat 7.1 mg/kg ■ Imetelstat 8.9 mg/kg

TSS, total symptom score; SVR, spleen volume reduction.
^aThe percent change for this patient is based on the spleen assessment at end of treatment due to the early discontinuation of treatment before week 24.

Preliminary Results Showed VAF Reductions in Driver Mutations

Maximum Percent Reduction From Baseline in Mutation VAF During Treatment^c

Baseline mutation parameter	Imetelstat				Total (N=17)
	4.4 mg/kg (n=3)	5.6 mg/kg (n=3)	7.1 mg/kg (n=4)	8.9 mg/kg (n=7)	
Baseline mutation, n	3	2	4	2 ^a	11
JAK2 mutation, n (%)	1 (33)	1 (50)	1 (25)	2 (100)	5 (45)
CALR mutation, n (%)	1 (33)	1 (50)	3 (75)	0	5 (45)
MPL mutation, n (%)	1 (33)	0	0	1 (50)	2 (18)
High molecular risk ^b mutation, n (%)	1 (33)	2 (100)	3 (75)	0	6 (55)



Data cutoff date: November 4, 2024

VAF, variant allele frequency.
^a1 patient had JAK2-V617F mutation, and 1 patient had MPL-W515L and JAK2-L611S mutations.
^bHigh molecular risk indicates mutations that include ASXL1, EZH2, IDH1, IDH2, and SRSF2 genes. ^cVAF reduction was assessed on mutations with baseline VAF>5, which is the low limit for detection ^dImputed value.

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The authors thank Yiqun Yang for her contribution to the statistical analyses of this study, and all the patients and caregivers for their participation, and acknowledge the collaboration and commitment of all investigators and their research support staff.



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1. Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881-2892.

Lay Summary

- This is an update about the IMproveMF study, which includes people with a type of blood cancer called myelofibrosis (MF) with different risk levels: intermediate-1, intermediate-2, or high risk
- Researchers wanted to see if the combination of a drug called imetelstat with another drug that helps treat MF called ruxolitinib could be safely administered and to find the appropriate dose for further study
- In this study, imetelstat and ruxolitinib administered together appeared to be safe; however, these results are still very early and additional research is needed to make a definitive conclusion
- This research can help people with MF, their families and caregivers, patient advocates and healthcare workers, and anyone trying to understand therapeutic options for patients with MF