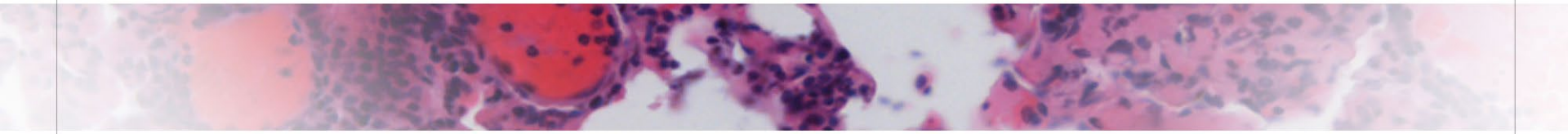
American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



Trial Update from IMproveMF, an Ongoing, Open-label, Dose-Escalation and -Expansion Phase 1/1b Trial to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of the Novel Combination of Imetelstat with Ruxolitinib in Patients with Intermediate-1, Intermediate-2, or High-Risk Myelofibrosis

John O. Mascarenhas, MD,[1] Salman Otoukesh, MD,[2] Terrence Bradley, MD,[3] Bart L. Scott, MD,[4] Habte A. Yimer, MD,[5] Souria Dougherty, MBA,[6] Lixian Peng, PhD,[6] Fei Huang, PhD,[6] Ying Wan, MD, PhD,[6] Faye M. Feller, MD,[6] Vivian Rodolf, MD,[6] Judy Ho, BS,[6] Tymara Berry, MD,[6] Andrew T. Kuykendall, MD[7]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [3]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [4]Fred Hutchinson Cancer Center, Seattle, WA, USA; [5]Texas Oncology/US Oncology Research, Tyler, TX, USA; [6]Geron Corporation, Foster City, CA, USA; [7]Moffitt Cancer Center, Tampa, FL, USA

Presentation 998 | Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA

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 approved for the treatment of adult patients with low- to INT-1–risk myelodysplastic syndromes with transfusion-dependent anemia[4,5]
- Imetelstat demonstrated clinically meaningful improvement in symptom response and improved OS in patients with INT-2 or higher-risk MF relapsed or refractory to JAKi in the IMbark trial (NCT02426086)[6]
  - Spleen response with imetelstat sodium 9.4 mg/kg at week 24 was modest, but clinically meaningful for patients with high disease burden who are relapsed or refractory to JAKi, where 37% of patients achieved a ≥10% SVR
- 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

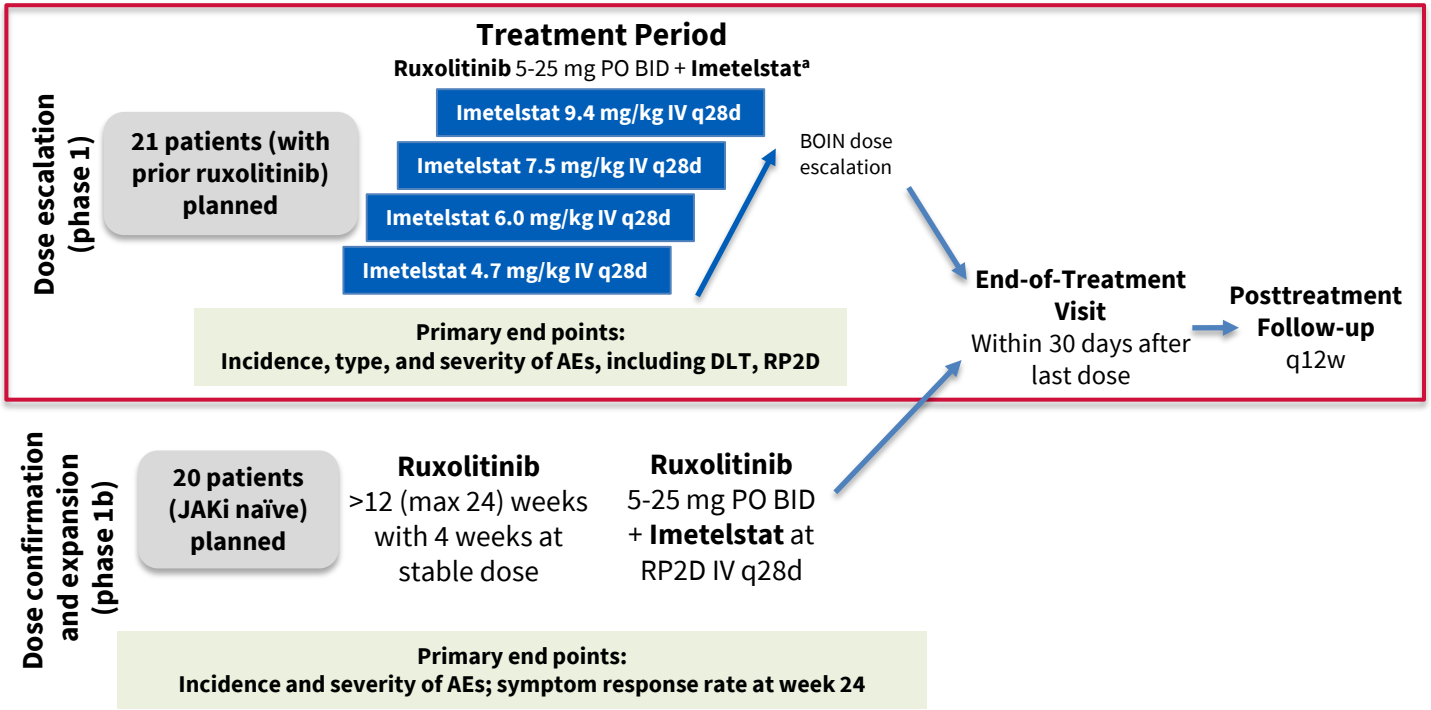
INT, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; PK, pharmacokinetics; SVR, spleen volume reduction.

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

IMproveMF: Ongoing Multicenter Phase 1/1b Trial

Inclusion Criteria

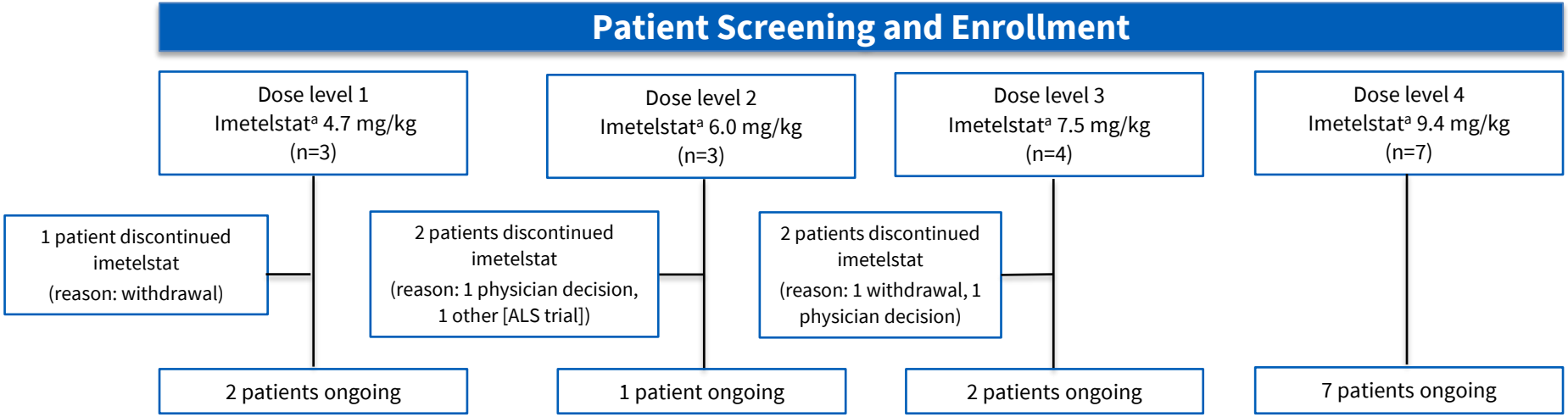
- ≥18 years of age
- DIPSS INT-1, INT-2, or HR MF
- ECOG PS ≤2
- Prior JAKi use:
  - Phase 1: ≥12 weeks ruxolitinib with ≥4 weeks immediately before enrollment at stable dose
  - Phase 1b: JAKi naive
- Peripheral blood blast count ≤10%
- Bone marrow blast count ≤10%



AE, adverse event; BID, twice daily; BOIN, Bayesian Optimal Interval Design; DIPSS, Dynamic International Prognostic Scoring System; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, high risk; INT, intermediate; IV, intravenous; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PO, per oral; q12w, every 12 weeks; q28d, every 28 days; RP2D, recommended part 2 dose.
[a]Imetelstat sodium doses are listed, which are equivalent to 4.4, 5.6, 7.1, or 8.9 mg/kg active imetelstat doses, respectively.

Patient Disposition

- At the cutoff date November 4, 2024, 12 of 17 enrolled patients were still undergoing imetelstat treatment



ALS, amyotrophic lateral sclerosis.
[a]Imetelstat sodium doses are listed, which are equivalent to 4.4, 5.6, 7.1, or 8.9 mg/kg active imetelstat doses, respectively.

Baseline Characteristics Were Balanced Across Cohorts

Parameter	Imetelstat 4.7 mg/kg (n=3)	Imetelstat 6.0 mg/kg (n=3)	Imetelstat 7.5 mg/kg (n=4)	Imetelstat 9.4 mg/kg (n=7)	Total imetelstat (N=17)
Time from initial diagnosis, median (range), mo	77.8 (5.4-86.7)	36.8 (12.8-49.5)	20.8 (10.5-110.8)	41.5 (17.4-114.5)	36.8 (5.4-114.5)
Sex, n (%)					
Male	2 (67)	2 (67)	3 (75)	5 (71)	12 (71)
Female	1 (33)	1 (33)	1 (25)	2 (29)	5 (29)
Type of MF, n (%)					
Primary MF	3 (100)	1 (33)	2 (50)	3 (43)	9 (53)
PET MF	0	0	2 (50)	2 (29)	4 (24)
PPV MF	0	2 (67)	0	2 (29)	4 (24)
DIPSS risk category, n (%)					
Intermediate-1	1 (33)	0	2 (50)	4 (57)	7 (41)
Intermediate-2	2 (67)	3 (100)	2 (50)	2 (29)	9 (53)
High	0	0	0	1 (14)	1 (6)
Bone marrow blasts, n (%)					
≥1%	2 (67)	1 (33)	1 (25)	1 (14)	5 (29)
<1%	1 (33)	2 (67)	3 (75)	5 (86)	11 (65)
Missing	0	0	0	1 (14)	1 (6)
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)	20.0 (9.1-65.2)	18.8 (3.4-86.2)
RUX dose at enrollment, median (range), mg	10 (10-10)	15 (10-20)	15 (10-25)	20 (15-20)	15 (10-25)
Baseline spleen volume, median (range), cm^3	356.8 (196.5-1321.6)	1475.5 (353.8-3332.0)	1739.5 (315.9-2207.0)	1350.8 (243.7-3784.3)	1312.5 (196.5-3784.3)
Baseline TSS, median (range)	25.5 (22.7-25.7)	11.0 (3.7-24.0)	17.4 (3.9-28.3)	8.0 (0.3-31.5)	11.0 (0.3-31.5)

DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET, post-essential thrombocythemia; PPV, post-polycythemia vera; RUX, ruxolitinib; SD, standard deviation; TSS, Total Symptom Score.

Baseline Hematology and Treatment Exposure

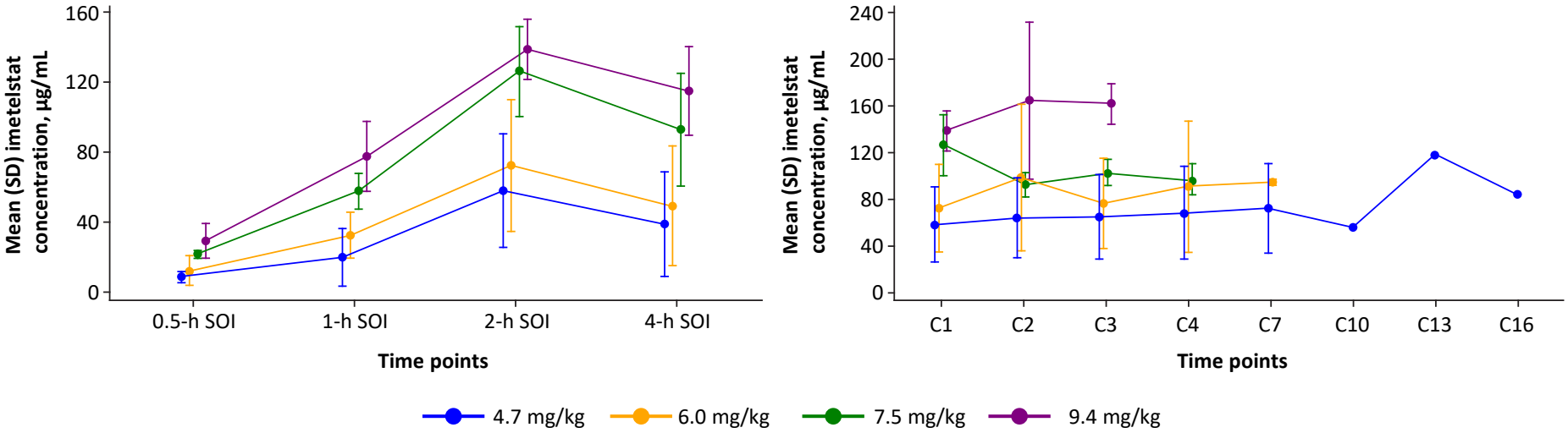
Baseline hematology parameter	Imetelstat				Total imetelstat (N=17)
	4.7 mg/kg (n=3)	6.0 mg/kg (n=3)	7.5 mg/kg (n=4)	9.4 mg/kg (n=7)	
Hemoglobin, median (range), g/L	82.0 (81.0-93.0)	105.0 (65.0-110.0)	108.0 (88.0-124.0)	112.0 (97.0-126.0)	105.0 (65.0-126.0)
Leukocytes, median (range), 10^9/L	5.4 (2.2-11.5)	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), 10^9/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), 10^9/L	211.0 (194.0-377.0)	361.0 (94.0-698.0)	287.0 (131.0-643.0)	192.0 (143.0-364.0)	211.0 (94.0-698.0)

Exposure parameter	Imetelstat			
	4.7 mg/kg (n=3)	6.0 mg/kg (n=3)	7.5 mg/kg (n=4)	9.4 mg/kg (n=7)
Imetelstat duration, median (range), wk	56.1 (24.0-72.1)	28.3 (16.1-44.1)	28.2 (0.1-35.9)	12.1 (4.1-20.9)
Dose reductions	0	0	2[a]	0
Number of cycles, median (range)	15 (7-19)	8 (5-12)	6 (1-8)	4 (2-6)
Ruxolitinib duration, median (range), wk	60.0 (57.3-76.7)	54.0 (54.0-62.7)	38.2 (31.7-39.7)	21.7 (13.1-32.3)

[a]Dose reductions occurred due to cytopenias.

The PK Profile of Imetelstat Was Consistent With Previous Studies

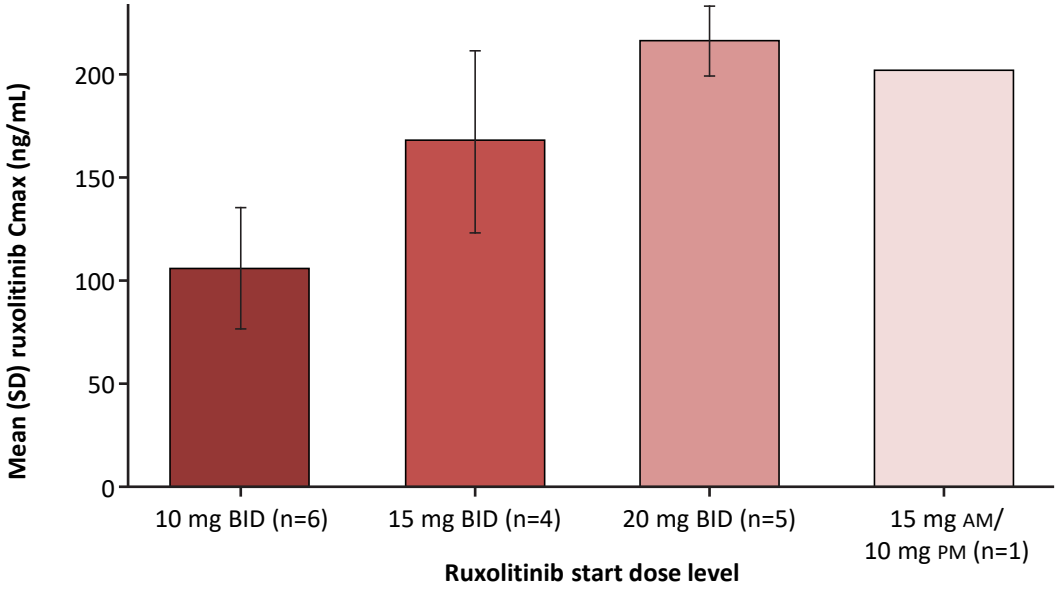
- Dose-dependent exposure at C1D1, with C_{max} reached at end of 2-hour infusion
- Similar C_{max} observed across cycles for each dose level, indicating no accumulation



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

Ruxolitinib PK Profile Was Consistent With Previous Reports[1]

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



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

1. Shi JG, et al. *J Clin Pharmacol*. 2011;51(12):1644-1654.

Imetelstat Combined With Ruxolitinib Was Well Tolerated

- No DLTs[a] were reported at any imetelstat dose level within the first 28 days of cycle 1

Any-grade TEAEs in ≥15% of patients

Preferred term, n (%)	Total (N=17)
Patients with ≥1 TEAE	**15 (88)**
Pain in extremity	7 (41)
Nausea	6 (35)
ALT increased	5 (29)
Anemia	5 (29)
Thrombocytopenia[b]	4 (24)
Fatigue	4 (24)
AST increased	3 (18)
Neutropenia[c]	3 (18)

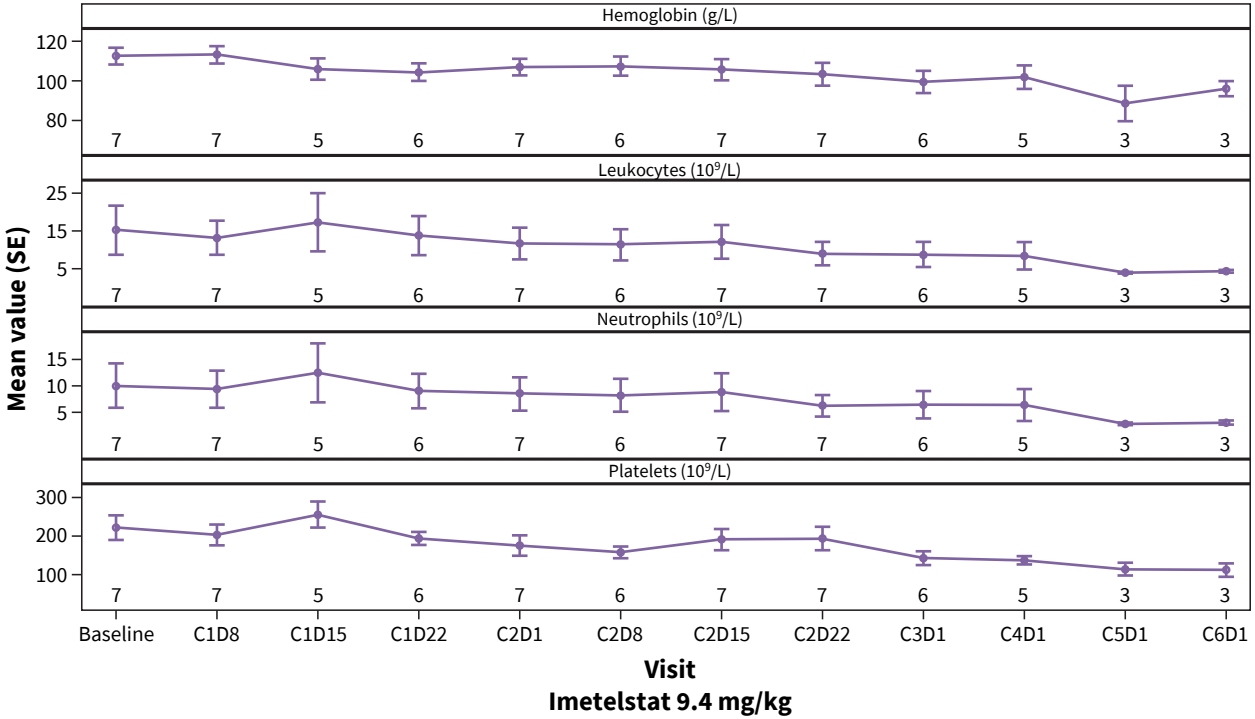
Grade 3 TEAEs

Preferred term, n (%)	Total (N=17)
Patients with ≥1 grade 3 TEAE	**8 (47)**
Anemia[d]	4 (24)
Neutropenia[c]	3 (18)
Leukopenia[e]	2 (12)
Abdominal pain	1 (6)
Fatigue	1 (6)
Pneumonia[f]	1 (6)
Epistaxis[f]	1 (6)

- No grade 4 or 5 events were reported

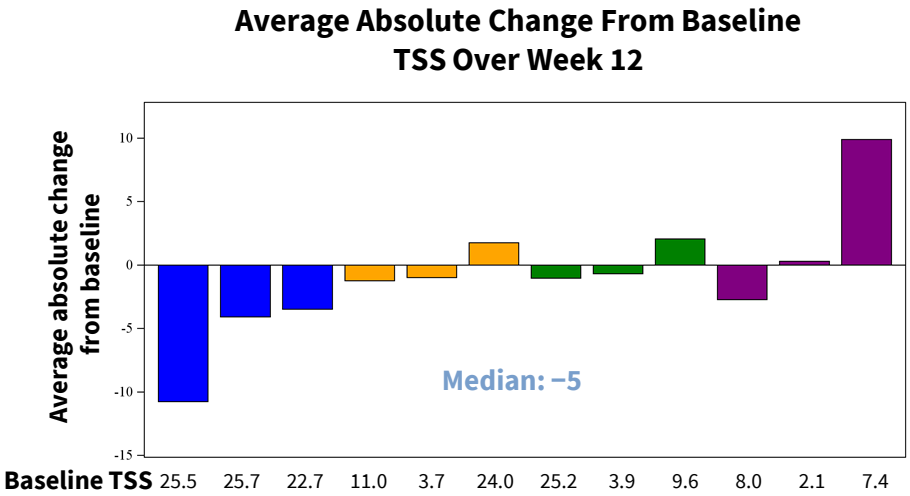
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Toxicities determined by the investigator to be possibly, probably, or definitely related to imetelstat treatment, and not attributable to the underlying disease, or toxicities with ruxolitinib increasing in grade and/or clinically significant from before imetelstat initiation. [b]Combined term includes decreased platelet count. [c]Combined term includes decreased neutrophil count. [d]One was a SAE considered related to study treatments and resulted in dose reduction to 6.0 mg/kg. [e]Combined term includes decreased white blood cell count. [f]SAE considered to be related to underlying disease and resolved without dose modification.

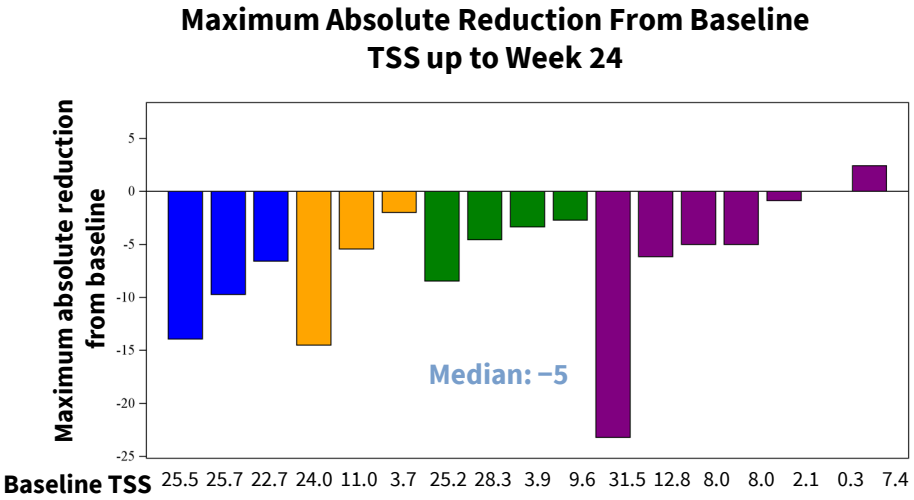
Hematology Values Were Stable Over Time



C, cycle; D, day; SE, standard error.

Change in TSS From Baseline by Patient

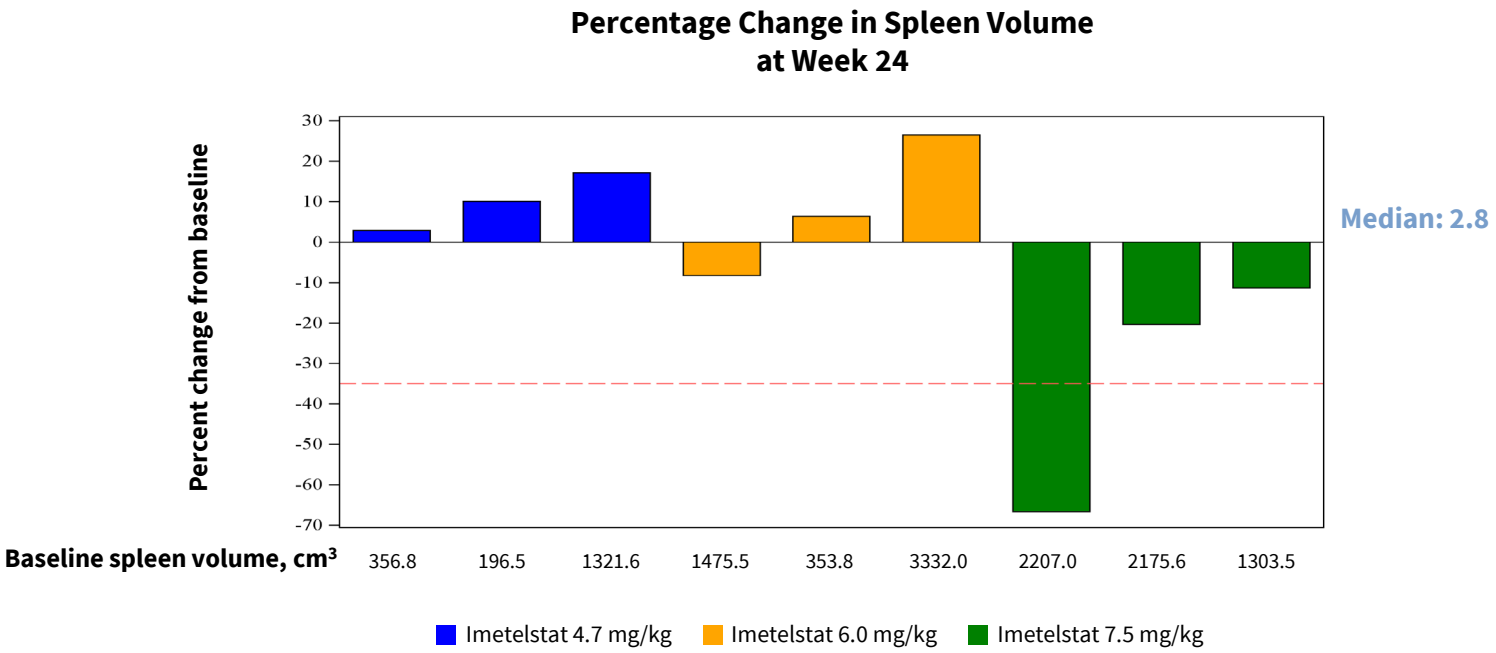




Imetelstat 4.7 mg/kg Imetelstat 6.0 mg/kg Imetelstat 7.5 mg/kg Imetelstat9.4 mg/kg

TSS, Total Symptom Score.

Spleen Volume Reduction by Patient at 24 Weeks



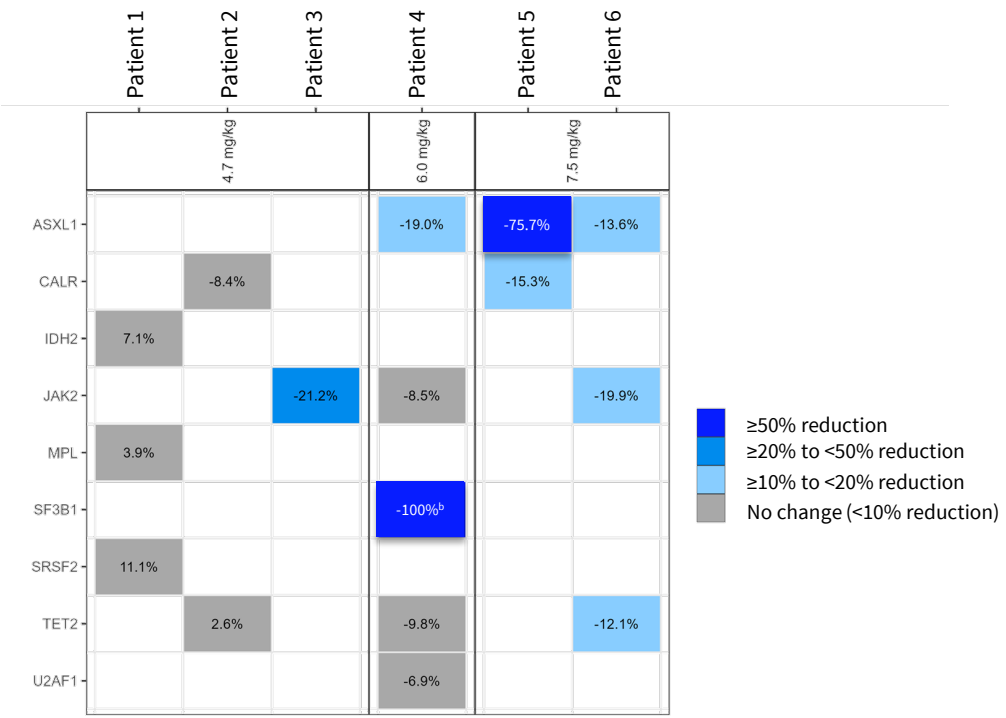
[a]The percent change for this patient is based on the spleen assessment at end of treatment due to the early discontinuation of treatment before week 24.

Preliminary Results Show VAF Reductions in Driver Mutations

Baseline mutation parameter	Imetelstat				
	4.7 mg/kg (n=3)	6.0 mg/kg (n=3)	7.5 mg/kg (n=4)	9.4 mg/kg (n=7)	Total (N=17)
Baseline mutation, n	3	2	4	2	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[a] mutation, n (%)	1 (33)	2 (100)	3 (75)	0	6 (55)

VAF, variant allele frequency.
[a]High molecular risk indicates mutations that include *ASXL1*, *EZH2*, *IDH1*, *IDH2*, and *SRSF2* genes.
[b]Imputed value.

Maximum Percent Reduction From Baseline in Mutation VAF During Treatment



Conclusions

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

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

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

Acknowledgments

- The authors thank all the patients and caregivers for their participation in this study and acknowledge the collaboration and commitment of all investigators and their research support staff

Terrence Bradley
John O. Mascarenhas
Andrew T. Kuykendall
Habte A. Yimer
Salman Otoukesh
Bart L. Scott

- This study was funded by the Geron Corporation; writing and editorial assistance were provided by Jeremy J. Henriques, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation