IMproveMF: Phase 1b Trial of Imetelstat Plus Ruxolitinib in Patients with Intermediate-1/2 or High-Risk Myelofibrosis

2052

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Introduction

- Myelofibrosis (MF) is a type of myeloproliferative neoplasm characterized by ineffective hematopoiesis, aberrant expression of inflammatory cytokines, and bone marrow fibrosis[1-3]
- Janus kinase inhibitors (JAKi) block the JAK/STAT-signaling pathway that is dysregulated in patients with MF, resulting in relief of splenomegaly and debilitating MF-related constitutional symptoms[3]
  - However, JAKi have limited disease-altering activity due to failure to eliminate the malignant clonal stem cells that drive disease progression[2,3]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity approved in the United States and Europe for the treatment of certain adult patients with lower-risk myelodysplastic syndromes with red blood cell transfusion–dependent anemia[4,5]
- Preclinical data showed that sequential therapy with ruxolitinib and imetelstat selectively targeted and reduced MF hematopoietic stem cells and progenitor cells[6]
- In the Phase 2 IMbark trial (MYF2001; NCT02426086), single-agent imetelstat showed clinically meaningful symptom response and OS and disease-modifying potential (eg, improvement in bone marrow fibrosis and mutation variant allele frequency reductions) in patients with Dynamic International Prognostic Scoring System (DIPSS) intermediate (INT)-2–risk or high-risk (HR) MF relapsed or refractory to JAKi[7]
  - A confirmatory Phase 3 trial is currently ongoing
- The positive preclinical and clinical findings, as well as the nonoverlapping mechanisms of action, supported the evaluation of imetelstat in combination with JAKi in frontline MF

IMproveMF (MYF1001; NCT05371964) is an ongoing, open-label, multicenter, Phase 1/1b trial evaluating the combination of imetelstat and ruxolitinib as frontline treatment in patients with INT-1, INT-2, or HR MF

- In the dose-finding portion (Phase 1) of IMproveMF, imetelstat plus ruxolitinib (at optimized dose for ≥4 weeks immediately before study enrollment) was generally well tolerated, with no dose-limiting toxicities observed at any dose level within the first 28 days of cycle 1 (**Table 1**), and a safety profile consistent with that observed in other clinical trials of imetelstat[7,8]
- Importantly, a dose-dependent signal of clinical activity was observed with imetelstat plus ruxolitinib, encouraging dose expansion evaluation of efficacy[8]
- The pharmacokinetic profile for the combination treatment was similar to those reported for previous individual monotherapy studies (**Figure 1**)
- **The recommended Phase 1b dose of 8.9 mg/kg imetelstat active dose (equivalent to 9.4 mg/kg imetelstat sodium) in combination with ruxolitinib was determined[8]**

Table 1. Imetelstat Combined With Ruxolitinib Was Generally Well Tolerated (IMproveMF, Phase 1)[9,a]

A. Any-Grade TEAEs in ≥15% of Patients

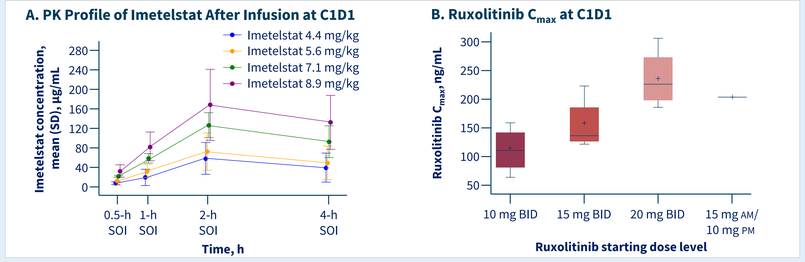
Preferred term, n (%)	Total (N=19)
Patients with ≥1 TEAE	**19 (100)**
Leukopenia[b]	9 (47)
Fatigue	9 (47)
ALT increased	8 (42)
Anemia	8 (42)
Thrombocytopenia[c]	8 (42)
Pain in extremity	8 (42)
AST increased	7 (37)
Neutropenia[d]	6 (32)
Nausea	6 (32)
Blood ALP increased	5 (26)
Constipation	4 (21)
Dyspnea	4 (21)
Dyspnea exertional	4 (21)
Headache	4 (21)
Vomiting	4 (21)
Abdominal pain	3 (16)
COVID-19	3 (16)
Dizziness	3 (16)
Hyperhidrosis	3 (16)
Pyrexia	3 (16)

B. Grade 3/4 TEAEs

Preferred term, n (%)	Total (N=19)
Patients with ≥1 grade 3/4 TEAE	**12 (63)**
Anemia	7 (37)
Leukopenia[b]	4 (21)
Neutropenia[d]	4 (21)
Thrombocytopenia[c]	2 (10)
Abdominal pain	1 (5)
Acute kidney injury	1 (5)
Back pain	1 (5)
Fatigue	1 (5)
Hemoglobin decreased	1 (5)
Lymphopenia	1 (5)
Pneumonia	1 (5)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
[a]Data cutoff date: October 1, 2025. [b]Combined term includes decreased white blood cell count. [c]Combined term includes decreased platelet count. [d]Combined term includes decreased neutrophil count.

Figure 1. Imetelstat and Ruxolitinib PK (IMproveMF, Phase 1)[9,a]



BID, twice daily; C, cycle; C_{max}, maximum concentration; D, day; PK, pharmacokinetics; SD, standard deviation; SOI, start of imetelstat infusion.
[a]Data cutoff date: October 1, 2025.

The Phase 1b portion of IMproveMF aims to evaluate the safety and preliminary clinical activity of imetelstat at the recommended Phase 2 dose (RP2D; 8.9 mg/kg imetelstat active dose) in combination with ruxolitinib or other JAKi

Methods

- The dose-confirmation and expansion (Phase 1b) portion of IMproveMF will include approximately 30 patients
- The study will evaluate 2 distinct cohorts
  - Cohort A: upon enrollment, patients who are JAKi naive will initiate and remain on ruxolitinib for ≥12 weeks (24 weeks maximum); once the ruxolitinib dose is stable for 4 weeks, 8.9 mg/kg imetelstat every 4 weeks will be added
  - Cohort B: patients who are currently receiving any first-line JAKi treatment per standard of care for ≥12 weeks (48 weeks maximum), including 4 weeks at a stable dose, will begin 8.9 mg/kg imetelstat every 4 weeks after enrollment
- Treatment will continue until toxicity, disease progression, or withdrawal

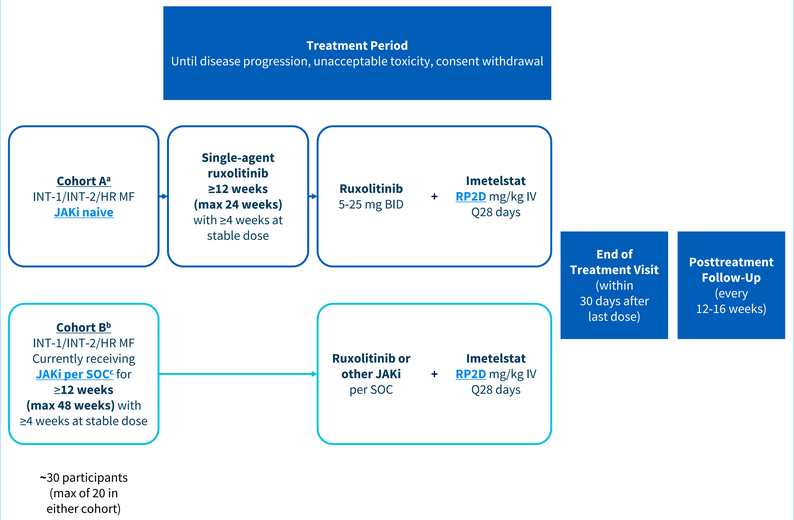
Key Eligibility Criteria

- Adult patients must have INT-1, INT-2, or HR MF per DIPSS
- Eastern Cooperative Oncology Group performance status ≤2
- Peripheral blood or bone marrow blasts <10%
- Hematology laboratory test values within the following limits:
  - ANC ≥1.5×10^9/L independent of growth factor support

  AND
  - Platelets ≥100×10^9/L
- Must be both symptomatic (≥2 active symptoms with a score of ≥3, or a total score of ≥10 on the Myelofibrosis Symptom Assessment Form v4.0) and have splenomegaly (demonstrated by either a palpable spleen measuring ≥5 cm below the left costal margin or a spleen volume ≥450 cm^3 by MRI or CT)
- No active systemic hepatitis infection, acute or chronic liver disease unrelated to underlying MF, or prior history of hematopoietic stem cell transplant

ANC, absolute neutrophil count; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; HR, high risk; INT, intermediate; MF, myelofibrosis; MRI, magnetic resonance imaging.

IMproveMF Phase 1b Study Design



BID, twice daily; HR, high risk; INT, intermediate; IV, intravenous; JAKi, Janus kinase inhibitor; Q, every; MF, myelofibrosis; RP2D, recommended Phase 2 dose; SOC, standard of care.
[a]Participants in Phase 1b cohort A will start on single-agent ruxolitinib (cycle 1 day 1 single-agent ruxolitinib treatment period) after enrollment. [b]Participants in Phase 1 and Phase 1b cohort B will start on combination treatment with imetelstat (cycle 1 day 1) after enrollment. [c]Ruxolitinib, momelotinib, fedratinib, or pacritinib.

Phase 1b Study Endpoints

Primary Endpoints

- Incidence and severity of adverse events
- Symptom response rate at week 24 (defined as proportion of patients with ≥50% reduction in TSS at week 24 from start of combination treatment)

Secondary Endpoints

- PK profile and immunogenicity of imetelstat
- Absolute change in TSS at week 24
- Average absolute change in TSS over 24 weeks (average of absolute change in TSS from week 1 to week 24)
- Spleen response at week 24 (≥35% from baseline confirmed by MRI or CT)
- PFS
- Responses per 2013 IWG MRT criteria
- Reduction in bone marrow fibrosis

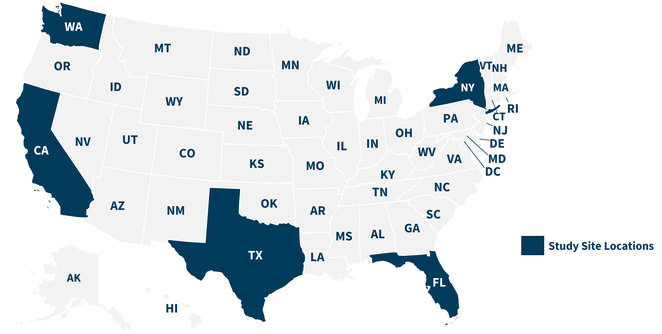
Exploratory Endpoints

- Change in telomerase activity and hTERT expression level
- Adverse events and clinical activity by PK parameters and PD parameters
- Mutation status and frequency at baseline and change over time in VAF for molecular response

CT, computed tomography; hTERT, human telomerase reverse transcriptase; IWG, International Working Group; MRI, magnetic resonance imaging; MRT, Myeloproliferative Neoplasms Research and Treatment; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; TSS, total symptom score; VAF, variant allele frequency.

Status

- The primary analysis for this part of the study is planned at approximately 6 months after the last participant's first dose of imetelstat plus ruxolitinib/JAKi treatment; the final analysis will be performed after the end of the study
- The Phase 1b portion of IMproveMF is actively enrolling, with 3 patients enrolled as of July 21, 2025. The first patient first treatment visit occurred on January 10, 2025



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