Updated protocol: IMproveMF, a Phase 1b trial of imetelstat+ruxolitinib in patients with intermediate-1/2 or high-risk myelofibrosis

TPS6604

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Background

- 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 ruxolitinib 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

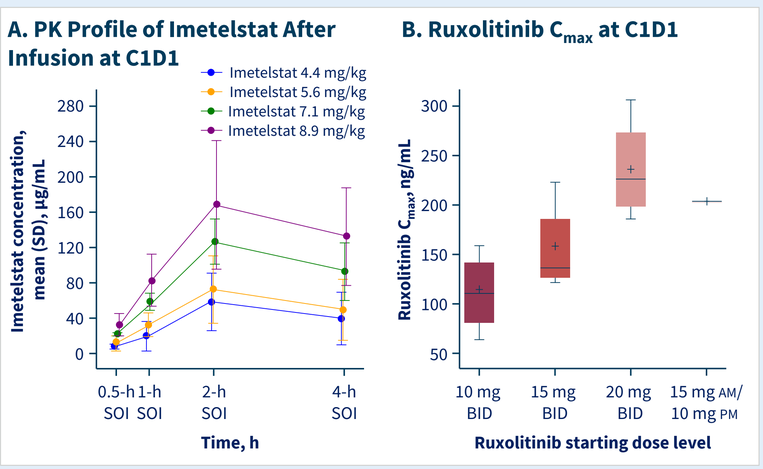
Preferred term, n (%)	Total (N=19)
Patients with ≥1 TEAE	**19 (100)**
Leukopenia[b]	9 (47)
Fatigue	9 (47)
ALT increased	8 (42)
Anemia	8 (42)
Thrombocytopenia[c]	8 (42)
Pain in extremity	8 (42)
AST increased	7 (37)
Neutropenia[d]	6 (32)
Nausea	6 (32)
Blood ALP increased	5 (26)
Constipation	4 (21)
Dyspnea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

Methods

- The dose-confirmation and expansion (Phase 1b) portion of IMproveMF was planned to evaluate 2 distinct cohorts
  - Cohort A (JAKi-naive patients): upon enrollment, patients 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

    Starting with protocol amendment 4 (November 17, 2025), the study will no longer recruit cohort A. Existing enrollees will continue in the study per schedule
  - Cohort B: patients who are currently receiving first-line ruxolitinib per standard of care for ≥12 weeks , including 4 weeks at a stable dose, will begin 8.9 mg/kg imetelstat every 4 weeks after enrollment. Approximately 15 patients will be enrolled
- Treatment will continue until toxicity, disease progression, or withdrawal

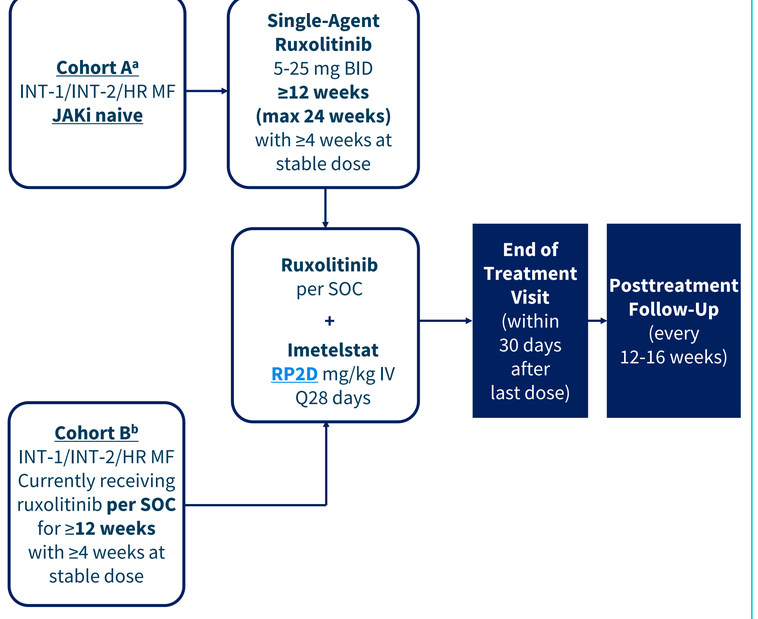
Updated Key Eligibility Criteria

- 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 ≥75×10^9/L
- Must be symptomatic (≥2 active symptoms with a score of ≥3, or a total score of ≥10 on the Myelofibrosis Symptom Assessment Form v4.0)
- 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; DIPSS, Dynamic International Prognostic Scoring System; HR, high risk; INT, intermediate; MF, myelofibrosis.

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]Patients in Phase 1b cohort A will start on single-agent ruxolitinib (cycle 1 day 1 single-agent ruxolitinib treatment period) after enrollment. Starting with protocol amendment 4 (November 17, 2025), the study will no longer recruit cohort A (patients treated with JAKi). [b]Patients in cohort B will start on combination treatment with imetelstat (cycle 1 day 1) after enrollment.

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
- Time to progression to AML (defined as the time interval from the start of study treatment date to the first date of documented progression to AML or death from any cause, whichever occurs first)

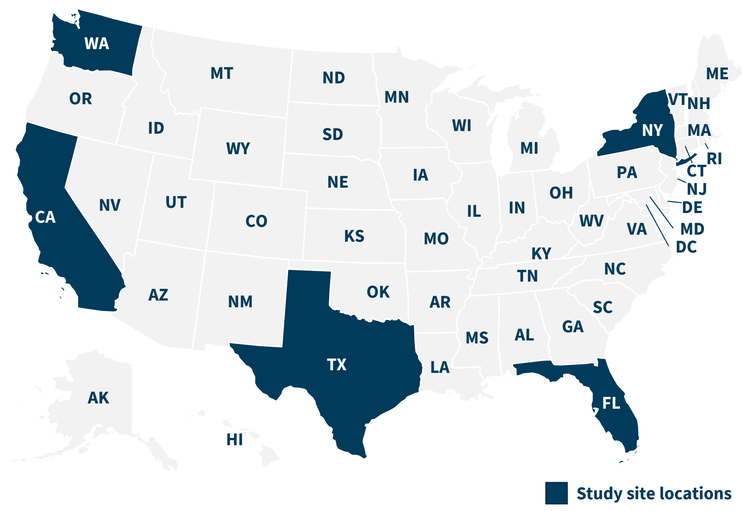
Exploratory Endpoints

- 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

AML, acute myeloid leukemia; 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 patient's first dose of imetelstat plus ruxolitinib; the final analysis will be performed after the end of the study
- The enrollment of the first patient in was on January 10, 2025. As of April 2026, Phase 1b has 3 patients enrolled in Cohort A and 6 patients enrolled in Cohort B
- Cohort B is actively enrolling



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ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05371964

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