# MYF1001: AN OPEN-LABEL, DOSE-ESCALATION AND -EXPANSION, PHASE 1/1B STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL ACTIVITY OF IMETELSTAT IN COMBINATION WITH RUXOLITINIB IN PATIENTS WITH INTERMEDIATE-1, INTERMEDIATE-2, OR HIGH-RISK MYELOFIBROSIS

Trial in Progress
Abstract #1713

IMproveMF

Terrence Bradley[1], Andrew Kuykendall[2], Rami S. Komrokji[2], Tymara Berry[3], Souria Dougherty[3], Laurie Sherman[3], Lixian Peng[3], Fei Huang[3], Ying Wan[3], Faye M. Feller[3], John Mascarenhas[4]

1. Sylvester Cancer Center, University of Miami, Miami, FL, USA; 2. Moffitt Cancer Center, Tampa, FL, USA; 3. Geron Corporation, Parsippany, NJ, USA; 4. Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

## INTRODUCTION

- Myelofibrosis (MF) is a progressive and life-threatening myeloproliferative neoplasm characterized by leukemic progression and shortened survival[1,2]
  - Janus kinase 2 gene (*JAK2*), calreticulin gene (*CALR*), or myeloproliferative leukemia gene (*MPL*) driver mutations are expected in approximately 90% of patients
- Approved agents for the treatment of MF are Janus Kinase inhibitors (JAKi), ruxolitinib (JAK1/JAK2 inhibitor), pacritinib (JAK2 inhibitor), and fedratinib (JAK2/fms-like tyrosine kinase 3 [FLT3] inhibitor)[3–5]
- JAKi treatment can reduce splenomegaly and debilitating MF-related constitutional symptoms; however, it does not eliminate malignant clonal stem cells that drive disease progression, and has limited activity on disease-altering effects[1,6,7]
  - The median overall survival (OS) after ruxolitinib discontinuation ranges from 11 to 16 months[8–11]
- Combination strategies with JAKi are being explored as potential ways to improve response in MF
- Imetelstat is a 13-mer lipid-conjugated oligonucleotide and a potent, first-in-class competitive inhibitor of telomerase enzymatic activity[12,13]
- Imetelstat has shown meaningful clinical improvement in symptom response and improved OS in IMbark, a phase 2 study in patients with intermediate-2 or high-risk MF who have relapsed after or are refractory to JAKi (**Table 1**)[14]
  - With an overall follow-up of 42 months, median OS was 28.1 months for the 9.4 mg/kg arm and 19.9 months for the 4.7 mg/kg arm
- In IMbark, imetelstat has also demonstrated disease-modifying activity by targeting malignant clones, improvement in bone marrow fibrosis, and OS[14,15]
- Preclinical studies have demonstrated that combination treatment of MF patient-derived xenograft mice with ruxolitinib followed by imetelstat results in greater disease reduction than treatment of mice with either agent alone, while sparing normal hematopoiesis[16]
  - Combining ruxolitinib (a JAKi) and imetelstat (a telomerase inhibitor) may not only improve disease symptoms, but also may alter the natural history of MF through activity on malignant clonal stem cells

**Table 1: Results From IMbark Phase 2 Study**

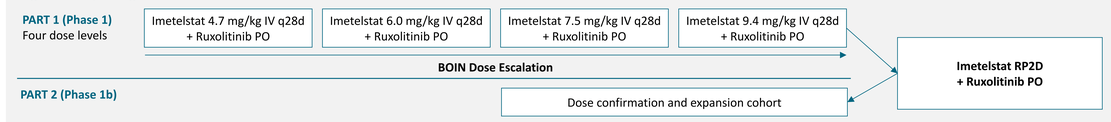
| Clinical Benefits | 4.7 mg/kg (N=48) | 9.4 mg/kg (N=59) |
|---|---|---|
| **Median OS, months** | **19.9** | **28.1** |
| **Bone marrow fibrosis improvement, % (n/N)** | **20.0 (4/20)** | **43.2 (16/37)** |
| **≥25% Reduction in VAF of *JAK2*, *CALR* or *MPL*, % (n/N)** | **5.6 (1/18)** | **42.1 (8/19)** |
| Symptom response at week 24 (TSS reduction ≥50%), % | 6.3 | 32.2 |
| Spleen response at week 24 (SVR ≥35% by IRC), % | 0 | 10.2 |
| Median PFS, months | 14.8 | 20.7 |
| Clinical improvement, per IWG-MRT, % | 16.7 | 25.4 |
| Transfusion independence of 12 weeks, % (n/N) | 14.3 (2/14) | 25.0 (3/12) |

*CALR*, calreticulin gene; CI, confidence interval; IRC, independent review committee; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; *JAK2*, Janus Kinase 2; *MPL*, myeloproliferative leukemia; OS, overall survival; PFS, progression-free survival; SVR, spleen volume reduction; TSS, total symptom score; VAF, variant allele frequency.

## STUDY DESIGN

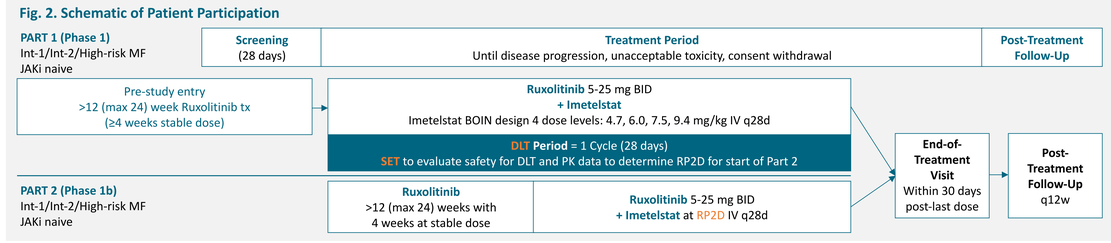
- Study MYF1001 (IMproveMF; NCT05371964) is an open-label, single-arm, multicenter, phase 1/1b study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of imetelstat in combination with ruxolitinib in patients with MF
- The study is comprised of 2 parts (**Fig. 1** and **Fig. 2**):
  - **Part 1** (phase 1: dose escalation):
    - The dose-escalation portion will utilize a Bayesian optimal interval (BOIN) design[16] investigating 4 dose levels of imetelstat to identify the recommended Part 2 dose (RP2D) of imetelstat in combination with ruxolitinib
    - Patients will be enrolled in a cohort size of 3 at each imetelstat dose level in a step-wise manner; the maximum number of participants for dose escalation is approximately 21
    - To allow each patient to reach an individualized stable dose of ruxolitinib and mitigate the risk of thrombocytopenia observed upon initiation of both ruxolitinib and imetelstat, single-agent ruxolitinib treatment is required for ≥12 weeks (maximum 24 weeks)
  - **Part 2** (phase 1b: dose confirmation and expansion):
    - Approximately 20 patients will undergo open-label, single-arm combination treatment of ruxolitinib followed by imetelstat at the RP2D established in Part 1

**Fig. 1. Study Design**




BOIN, Bayesian optimal interval design; D, day; IV, intravenous; PO, per oral; Q, every; RP2D, recommended Part 2 dose.

**Fig. 2. Schematic of Patient Participation**




BID, twice daily; BOIN, Bayesian optimal interval design; D, day; DLT, dose-limiting toxicity; Int, intermediate; IV, intravenous; JAKi, Janus Kinase inhibitor; MF, myelofibrosis; PK, pharmacokinetics; Q , every; RP2D, recommended phase 2 dose; SET, safety evaluation team; tx, treatment; w, week.

## KEY INCLUSION CRITERIA

- Patients aged ≥18 years diagnosed with primary MF according to World Health Organization (WHO) and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria
- Dynamic International Prognostic Scoring System (DIPSS) intermediate-1, intermediate-2 or high-risk MF
- Candidate for ruxolitinib treatment
  - **Part 1 only:** On ruxolitinib treatment for at least 12 weeks (maximum of 24 weeks) with at least 4 consecutive weeks immediately prior to enrollment at a stable dose
  - **Part 2 only:** Not previously treated with a JAKi
- Clinical signs/symptoms of MF demonstrated by measurable splenomegaly and/or active symptoms of MF on the Myelofibrosis Symptom Assessment Form (MFSAF) v4.0
- Ineligible for or unwilling to undergo hematopoietic stem cell transplant at time of study entry
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2

## KEY EXCLUSION CRITERIA

- Prior treatment with JAKi (except for patients being dose optimized on ruxolitinib prior to enrollment in Part 1)
- Prior treatment with imetelstat
- Peripheral blood blast count of ≥10% or bone marrow blast count of ≥10%
- Prior history of hematopoietic stem cell transplant
- Prior history of partial or complete splenectomy
- Clinically significant cardiovascular disease

## STUDY ENDPOINTS

**Table 2: Primary Objectives and Endpoints**

| Primary Objectives | Primary Endpoints |
|---|---|
| **Part 1:** Identify the RP2D of imetelstat in combination with ruxolitinib | Incidence, type, and severity of AEs, including DLT |
| **Part 2:** Evaluate the safety and preliminary clinical activity of RP2D of imetelstat in combination with ruxolitinib | Incidence and severity of AEs; symptom response rate at week 24[a] |

**Secondary endpoints:**

- Part 1: Symptom response rate at week 24 (≥50% reduction in TSS measured by MFSAF v4.0)
- Part 1 and 2:
  - PK profile of imetelstat and ruxolitinib (eg, $C_{max}$, $AUC_{0\text{-}t}$)
  - Percentage of patients with anti-imetelstat antibodies
  - Spleen response at week 24 (≥35% from baseline confirmed by MRI or CT)
  - PFS, ORR, TTR, and DOR
  - Reduction in bone marrow fibrosis
  - Immunogenicity of imetelstat

**Exploratory endpoints:**

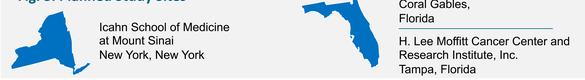
- Part 1 and 2:
  - Change in telomerase activity and hTERT expression level
  - AEs and clinical activity by PK and PD parameters
  - Mutation status and frequency at baseline and change over time in variant allele frequency for molecular response

[a]Defined as percentage of participants with >50% reduction in total symptom score measured by MFSAF.
AE, adverse event; AUC, area under the curve; Cmax, maximum serum concentration; CT, computed tomography; DLT, dose-limiting toxicity; DOR, duration of response; hTERT, human telomerase reverse transcriptase; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; ORR, overall response rate; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; RP2D, recommended phase 2 dose; TTR, time to response.

## STUDY STATUS

- This study is registered at ClinicalTrials.gov (NCT05371964)
- Phase 1 dose-escalation (Part 1) is currently open for enrollment
- Recruitment for Part 1 is planned at ~3 sites, across North America, with a total target population of approximately 41 patients (**Fig. 3**)

**Fig. 3. Planned Study Sites**




- For further information please visit www.geron.com/patients/improvemf-study/ or contact: MYF1001-info@geron.com

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