IMpactMF, Randomized, Open-Label, Phase 3 Trial of Imetelstat Versus Best Available Therapy in Patients With Intermediate-2 or High-Risk Myelofibrosis Relapsed or Refractory to Janus Kinase Inhibitors

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John O. Mascarenhas, MD,[1] Claire Harrison, MD,[2] Prithviraj Bose, MD,[3] Jean-Jacques Kiladjian, MD, PhD,[4] Alessandro Lucchesi, MD, PhD,[5] Alessandro M. Vannucchi, MD,[6] Michelle Mudge-Riley, DO, MHA, RDN,[7] Jennifer Riggs, MPH,[7] Lixian Peng, PhD,[7] Fei Huang, PhD,[7] Ying Wan, MD, PhD,[7] Vivian Rodolf, MD,[7] Judy Ho, BS,[7] Shyamala Navada, MD,[7] Rami S. Komrokji, MD[8]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Guy's and St Thomas' National Health Service Foundation Trust, London, UK; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France; [5]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori," Meldola, Italy; [6]University of Florence, Florence, Italy; [7]Geron Corporation, Foster City, CA, USA; [8]Moffitt Cancer Center, Tampa, FL, USA

Background

- Myelofibrosis (MF) is a progressive, life-threatening myeloproliferative neoplasm characterized by bone marrow fibrosis, splenomegaly, constitutional symptoms, cytopenias, and potential leukemic transformation[1-3]
- While Janus kinase inhibitors (JAKi) have transformed therapy in MF, ultimately patients either relapse or become refractory to JAKi and have poor survival rates (median overall survival [OS] ≈1 year), highlighting the need for novel treatment options with distinct mechanisms of action[4]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity approved by the US FDA and the European Commission (EC) for the treatment of certain adult patients with lower-risk myelodysplastic syndromes with red blood cell transfusion-dependent anemia and relapsed or refractory (R/R)[5]/unsatisfactory response[6] to or ineligible for erythropoiesis-stimulating agents
- In the Phase 2 IMbark trial (NCT02426086), patients with intermediate-2 (INT-2) or high-risk (HR) MF R/R to JAKi were randomized to receive 4.4 mg/kg or 8.9 mg/kg imetelstat active doses (equivalent to 4.7 mg/kg and 9.4 mg/kg imetelstat sodium, respectively) as an intravenous infusion every 21 days (**Table**)[7]
  - Imetelstat 8.9 mg/kg demonstrated clinically meaningful improvement in symptom response and improved OS compared with the 4.4-mg/kg dose
  - Imetelstat improved bone marrow (BM) fibrosis and reduced variant allele frequency of MF driver mutations compared with baseline in a dose-dependent manner; these outcomes correlated with the improvement in OS
    - Patients who had ≥1 grade improvement in BM fibrosis with imetelstat had longer OS than those without fibrosis improvement (median OS 31.6 months vs 24.6 months; hazard ratio, 0.54 [95% CI, 0.23-1.29])
  - Grade ≥3 adverse events were generally manageable, of short duration, and resolved to grade ≤2 in <4 weeks with minimal severe clinical complications
- Patients who received 8.9 mg/kg imetelstat in IMbark had a significantly lower risk of death compared with a closely matched cohort of real-world patients with MF who had discontinued ruxolitinib due to lack/loss of response and subsequently received best available therapy (hazard ratio, 0.35; *P*=.0019)[8]
- The results of IMbark support the continued clinical evaluation of 8.9 mg/kg imetelstat in patients with R/R MF in the Phase 3 IMpactMF trial

Table. IMbark Trial: Efficacy and Safety of Imetelstat in Patients With R/R MF[7]

	Imetelstat 4.4 mg/kg (n=48)	Imetelstat 8.9 mg/kg (n=59)
Symptom response[a] at week 24, n (%) [95% CI]	3 (6) [1-17]	19 (32) [21-46]
Spleen response[b] at week 24, n (%) [95% CI]	0	6 (10) [4-21]
OS,[c] median (95% CI), months	19.9 (17.1-NE)	29.9 (22.8-NE)
Improvement in BM fibrosis,[d] n (%)	4 (20) of 20 evaluable patients	15 (41) of 37 evaluable patients
Grade ≥3 AEs, n (%)	39 (81)	52 (88)
Most common grade ≥3 AEs, n (%)		
Thrombocytopenia	11 (23)	24 (41)
Anemia	15 (31)	23 (39)
Neutropenia	5 (10)	19 (32)

AE, adverse event; BM, bone marrow; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; NE, not estimable; OS, overall survival; R/R, relapsed or refractory.
[a]Defined as ≥50% total symptom score reduction per the modified MFSAF v4.0. [b]Defined as spleen volume reduction ≥35%. [c]Median follow-up = 27.4 months; clinical cutoff was October 22, 2018. [d]Defined as ≥1 grade improvement on central assessment.

Here, we present the methodology of IMpactMF (MYF3001; NCT04576156), a randomized, open-label, Phase 3 study evaluating the efficacy and safety of imetelstat versus best available therapy (BAT) in patients with INT-2 or HR MF R/R to JAKi who are ineligible for allogeneic stem cell transplantation or further JAKi treatment

Methods

Patient Population

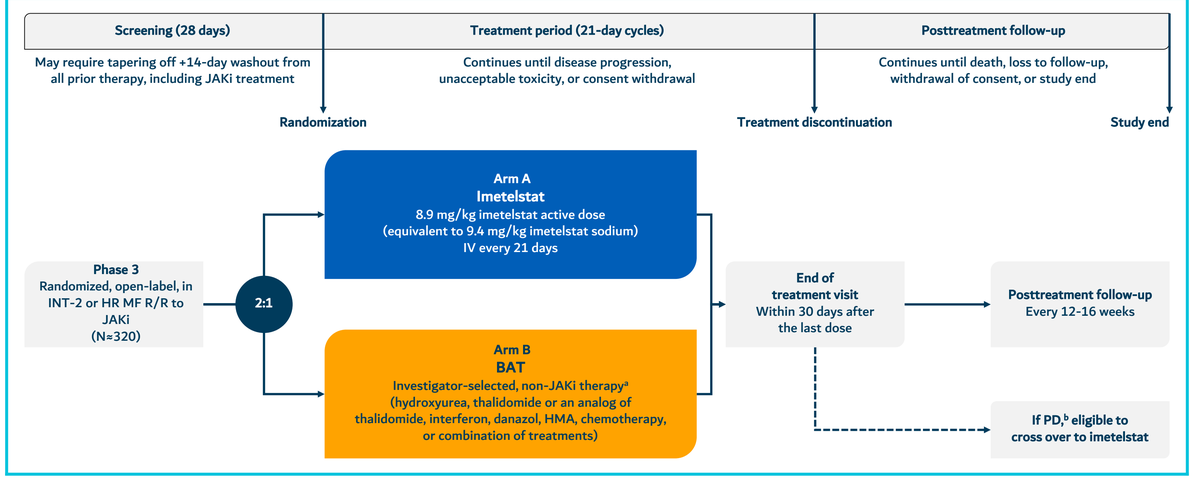
- Approximately 320 patients will be randomized as follows: ≈214 to Arm A (imetelstat) and ≈106 to Arm B (BAT)
- Eligible patients will be stratified based on (a) INT-2 or HR per Dynamic International Prognostic Scoring System, and (b) platelet count at study entry (platelets ≥75×10^9/L and <150×10^9/L vs ≥150×10^9/L)

Key Eligibility Criteria

- Adults with diagnosis of primary MF per the revised WHO criteria; or post-essential thrombocythemia MF or post-polycythemia vera MF per the IWG-MRT
- INT-2 or HR MF (per DIPSS)
- ECOG PS ≤2
- R/R to JAKi treatment as defined as:
  - Treatment with JAKi for ≥6 months, including ≥2 months at an optimal dose as assessed by the investigator ***and*** ≥1 of the following:
    - No decrease in spleen volume (<10% by MRI or CT) from the start of treatment with JAKi
    - No decrease in spleen size (<30% by palpation or length by imaging) from start of treatment with JAKi
    - No decrease in symptoms (<20% by MFSAF v4.0/myeloproliferative neoplasm SAF) from start of treatment with JAKi
    - Score of ≥15 on TSS, assessed using the MFSAF v4.0 during screening
  - Treatment with JAKi for ≥3 months with maximal doses (eg, 20-25 mg twice daily ruxolitinib) without a spleen or symptom response and would not benefit from remaining on treatment for 6 months
  - Following maximum tolerated doses of JAKi for ≥3 months duration, having documented relapsed disease defined as either:
    - Increase in spleen volume from time of best response by 25% measured by MRI or CT, *or*
    - Increase in spleen size by palpation, CT, or ultrasound
  - ***And*** not a candidate for further JAKi therapy
- Measurable splenomegaly demonstrated by palpable spleen measuring ≥5 cm below the left costal margin or a spleen volume ≥450 cm^3 by MRI or CT
- Absolute neutrophil count ≥1.5×10^9/L and platelets ≥75×10^9/L
- Peripheral blood blast count <10%
- Bone marrow blast count <10%
- Active symptoms of MF on the MFSAF v4.0: symptom score of ≥5 points (on a 0-10 scale) on ≥1 symptoms or a score of ≥3 on ≥2 of the following symptoms: fatigue, night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, and bone pain

CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, high risk; INT, intermediate; IWG-MRT, International Working Group–Myeloproliferative Neoplasms Research and Treatment; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; IV, intravenous; MRI, magnetic resonance imaging; R/R, relapsed or refractory; SAF, Symptom Assessment Form; TSS, total symptom score; WHO, World Health Organization.

IMpactMF Phase 3 Study Design



BAT, best available therapy; HMA, hypomethylating agent; HR, high risk; INT, intermediate; IV, intravenous; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PD, progressive disease; R/R, relapsed or refractory.
[a]Hematopoietic stem cell transplantation or splenectomy are not be permitted as BAT. [b]Must demonstrate ≥25% increase in spleen volume from baseline during the study or a palpable increase in splenomegaly after 6 months of BAT.

Study Endpoints

PRIMARY ENDPOINT

Overall survival

SECONDARY ENDPOINT

- Symptom response rate at week 24 (≥50% reduction in TSS measured by MFSAF v4.0)
- PFS
- Spleen response rate at week 24 (≥35% spleen volume reduction by MRI or CT)
- Complete remission, partial remission, clinical improvement, spleen response, symptom response, and anemia response per modified 2013 IWG-MRT criteria
- Time to and duration of responses
- Reduction in the degree of bone marrow fibrosis
- Safety
- PK and immunogenicity of imetelstat
- PROs as measured by the EORTC QLQ-C30 and EuroQol-EQ-5D (EQ-5D-5L) questionnaires

EXPLORATORY ENDPOINTS

- Association between baseline cytogenetic and mutational status and clinical responses; change in mutant allele burden (molecular response)
- Correlation between baseline TA, TL, or hTERT and OS, symptom response, or spleen response

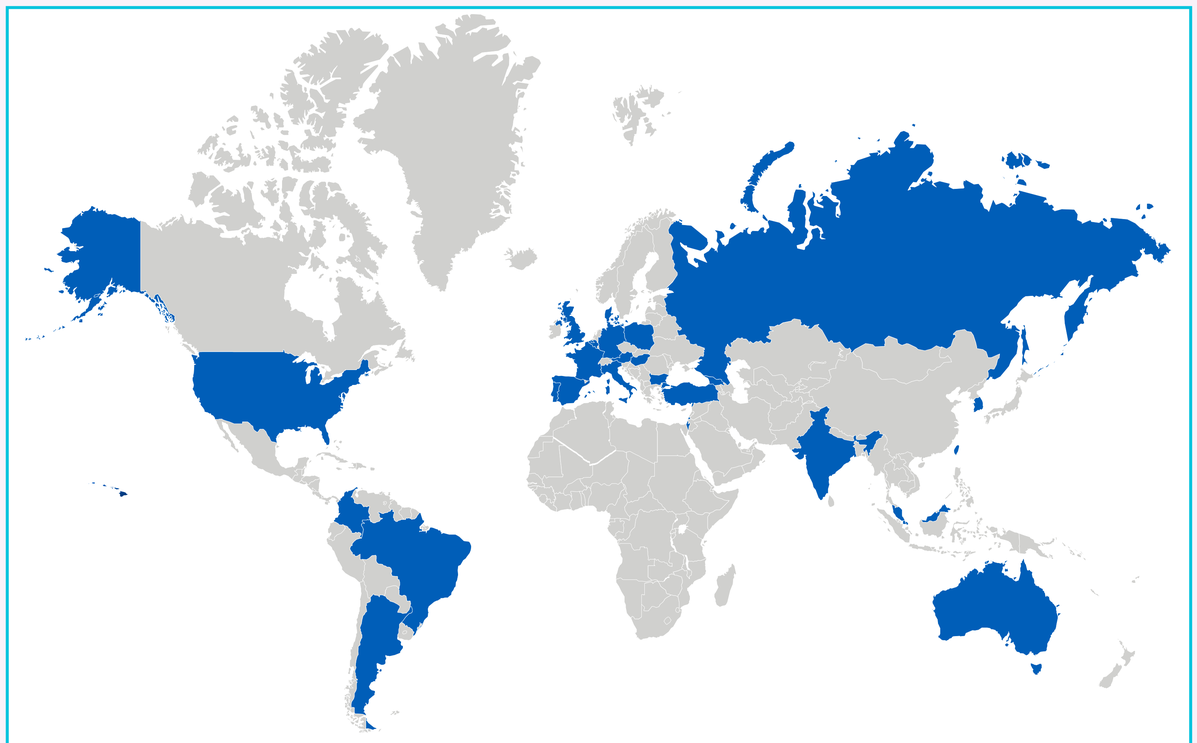
BAT, best available therapy; CT, computed tomography; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; hTERT, human telomerase reverse transcriptase; IWG-MRT, International Working Group–Myeloproliferative Neoplasms Research and Treatment; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; TA, telomerase activity; TL, telomere length; TSS, total symptom score.

Statistics

- An interim analysis is planned when ≈35% of the planned enrolled patients have died; the final analysis is planned when >50% of the planned enrolled patients have died
- Efficacy analyses will be performed based on the intent-to-treat population
- Kaplan-Meier method will be used to estimate the OS distribution for each treatment; treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the explanatory variable
  - To evaluate the confounding effect of crossover and subsequent therapy, proportional hazard assumptions will be evaluated, and sensitivity analysis of OS will be explored
- Symptom response rate at week 24, spleen response rate at week 24, complete response, partial response, and clinical improvement per modified 2013 International Working Group–Myeloproliferative Neoplasms Research and Treatment criteria will be summarized with frequency and percentage along with a 2-sided 95% exact CI by treatment arm
- A sequential gate-keeping procedure and Hochberg procedure will be implemented to ensure that the overall type I error rate for the secondary endpoints is controlled
- For the pharmacokinetic analysis, all plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation and will be excluded in the calculation of summary statistics
- Descriptive statistics will be used for safety parameters and patient-reported outcome measures

Study Status

- IMpactMF is actively recruiting patients
- As of February 2025, 172 sites in North and South America, Europe, the Middle East, Australia, and Asia have enrolled ≈80% of patients
- The planned interim analysis (when ≈35% of patients planned to be enrolled have died) is expected in second half of 2026 and final analysis (when >50% of the planned enrolled patients have died) is expected in the second half of 2028



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