MYF3001: A RANDOMIZED OPEN-LABEL, PHASE 3 STUDY TO EVALUATE IMETELSTAT VERSUS BEST AVAILABLE THERAPY IN PATIENTS WITH INTERMEDIATE-2 OR HIGH-RISK MYELOFIBROSIS RELAPSED/REFRACTORY TO JANUS KINASE INHIBITOR

Trial in Progress
Abstract #3037

IMpactMF

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INTRODUCTION

- Myelofibrosis (MF) is a life-threatening myeloproliferative neoplasm. Only Janus kinase (JAK) inhibitors, ruxolitinib (JAK1/2), fedratinib (JAK2/FLT3), and pacritinib (JAK2/IRAK1) are approved treatment options for MF
- For patients who discontinue treatment with ruxolitinib, the median overall survival (OS) is dismal and ranges from 11 to 16 months[1-7]
- There remains a great unmet need for patients whose MF has relapsed or is nonresponsive and have discontinued treatment with a JAK inhibitor (JAKi)
- Imetelstat is a 13-mer lipid-conjugated oligonucleotide that specifically targets the RNA template of human telomerase and is a potent, first-in-class competitive inhibitor of telomerase enzymatic activity[6,8] (**Fig. 1**)
- Imetelstat selectively kills malignant stem and progenitor cells enabling recovery of blood cell production (**Fig. 2**)
- Imetelstat has shown meaningful clinical improvement in symptom response and improved OS in IMbark, a phase 2 study in patients with intermediate-2 (Int-2) or high-risk (HR) MF who have relapsed after or are refractory to JAKi[9]
- In IMbark, imetelstat demonstrated improvement in bone marrow fibrosis, longer OS, and disease-modifying activity by targeting malignant clones[9]

Fig. 1. Imetelstat Binds to RNA Template Preventing Maintenance of Telomeres

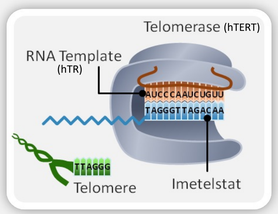
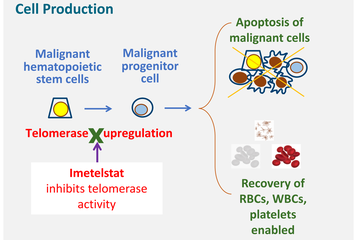


Fig. 2. Imetelstat Selectively Kills Malignant Stem and Progenitor Cells Enabling Recovery of Blood Cell Production



RBC, red blood cell; WBC, white blood cell.

IMbark phase 2 study results

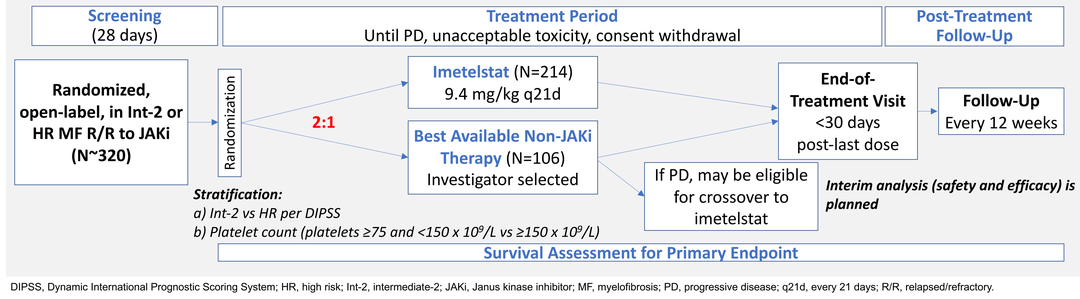
- IMbark, a phase 2 randomized study of imetelstat treatment at 4.7 mg/kg and 9.4 mg/kg, enrolled patients with Int-2 or HR MF who were relapsed after or refractory to JAKi treatment[9]
- In patients with MF who are relapsed/refractory to JAKi, imetelstat treatment showed dose-related improvement in OS and other clinical benefits, including symptom response and improvement in bone marrow fibrosis[8] (**Table**)
  - 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
- The improvement in OS for patients treated with 9.4 mg/kg imetelstat was further supported by analyses of patients in IMbark with closely matched real-world data[10]
- Compelling OS results from IMbark and an acceptable safety profile led to initiation of a phase 3 study in patients with relapsed/refractory MF, with OS as the primary endpoint[11]

Table: Results From IMbark Phase 2 Study, Clinical Benefits

Clinical Benefits	4.7 mg/kg (N=48)	9.4 mg/kg (N=59)
Bone marrow fibrosis improvement, n/N (%)	**4/20 (20.0)**	**16/37 (43.2)**
≥25% Reduction in VAF of *JAK2*, *CALR*, or *MPL*, n/N (%)	**1/18 (5.6)**	**8/19 (42.1)**
Symptom response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3)	19 (32.2)
Spleen response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7)	15 (25.4)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3)	3/12 (25.0)

CALR, calreticulin; IRC, independent review committee; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; JAK, Janus kinase; MPL, thrombopoietin receptor; SVR, spleen volume reduction; TSS, total symptom score; VAF, variant allele frequency.

IMpactMF (MYF3001) METHODS



DIPSS, Dynamic International Prognostic Scoring System; HR, high risk; Int-2, intermediate-2; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PD, progressive disease; q21d, every 21 days; R/R, relapsed/refractory.

KEY INCLUSION CRITERIA

- Aged ≥18 years
- Dynamic International Prognostic Scoring System (DIPSS) Int-2 or HR MF
- Diagnosis of primary MF by World Health Organization (WHO) or post-essential thrombocythemia-MF or post-polycythemia vera-MF by International Working Group - Myeloproliferative Neoplasms Research and Treatment (IWG-MRT)
- Relapsed/refractory to JAKi and not eligible for further JAKi treatment, as defined by 1 of the following:
  - Treated for ≥6 months, including 2 months at an optimal dose with no decrease in spleen volume, spleen size, or MF symptoms, or highly symptomatic per Myelofibrosis Symptom Assessment Form (MFSAF) at study entry
  - Treated for ≥3 months at maximal dose and no decrease in spleen volume, spleen size, or MF symptoms
  - Documented relapsed disease, defined as increase in spleen volume/size, after ≥3 months of JAKi treatment
- Not candidates for allogeneic stem cell transplant
- Measurable splenomegaly with palpable spleen ≥5 cm or spleen volume ≥450 cm^3 by magnetic resonance imaging (MRI) or computed tomography (CT)
- Active symptoms of MF by MFSAF v4.0 with a symptom score ≥5 (0–10 scale) on 1 symptom or a score ≥3 on ≥2 of the following symptoms: fatigue, night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, and bone pain
- Absolute neutrophil count ≥1.5 x 10^9/L independent of growth factor support
- Platelets ≥75 x 10^9/L independent of platelet transfusions
- Eastern Cooperative Oncology Group performance status 0, 1, or 2

KEY EXCLUSION CRITERIA

- Peripheral blood blast count or bone marrow blast count ≥10%
- Any chemotherapy or MF-directed therapy, including investigational drug, immunomodulatory or immunosuppressive therapy, corticosteroids >30 mg/day (prednisone or equivalent), and JAKi treatment ≤14 days prior to randomization
- Major surgery within 28 days of randomization
- Prior treatment with imetelstat
- Clinically significant cardiovascular disease, active systemic hepatitis infection, or chronic liver disease unrelated to MF

STUDY ENDPOINTS

- **Primary endpoint:** OS
- **Secondary endpoints:**
  - Symptom response rate at week 24 (≥50% reduction in total symptom score [TSS] measured by MFSAF v4.0)
  - Progression-free survival
  - 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 2013 IWG-MRT criteria
  - Time to and duration of responses
  - Reduction in degree of bone marrow fibrosis
  - Safety
  - Pharmacokinetics and immunogenicity
  - Patient-reported outcomes as measured by the European Organization for Research and treatment of Cancer QLQ-C30 and EuroQol-EQ-5D (EQ-5D-5L) questionnaires
- **Exploratory endpoints:**
  - Biomarkers: telomerase activity, telomere length, telomerase reverse transcriptase and correlation with OS, symptom response or spleen response
  - Baseline cytogenetic profile
  - Baseline mutation status and change of mutation burden

STUDY STATUS

- This study is registered at ClinicalTrials.gov (NCT04576156)
- Approximately 180 sites are planned across North and South America, Europe, Middle East, Australia, and Asia
- The study is currently open for enrollment
- For further information please visit https://www.geron.com/patients/impactmf-study/ or contact: MYF3001-info@Geron.com

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REFERENCES

1. Kuykendall AT, et al. *Ann Hematol.* 2018;97(3):435–441.
2. Newberry KJ, et al. *Blood.* 2017;130(9):1125–1131.
3. Schain F, et al. *Eur J Haematol.* 2019;103:614–619.
4. Palandri F, et al. *Cancer.* 2020;126(6):1243–1252.
5. McNamara C, et al. EHA; Amsterdam, the Netherlands; June 13, 2019. #PS1460.
6. Asai A, et al. *Cancer Res.* 2003;63(14):3931–3939.
7. Mascarenhas J, et al. *J Med Econ.* 2020;23(7):721–727.
8. Herbert BS, et al. *Oncogene.* 2005;24(33):5262–5268.
9. Mascarenhas J, et al. *J Clin Oncol.* 2021;39(26):2881–2892.
10. Kuykendall AT, et al. *Ann Hematol.* 2022;101:139–146.
11. Mascarenhas J, et al. *Future Oncol.* 2022;18(22):2393–2402.

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