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Trial in Progress
Abstract #2194

MYF3001: A Randomized Open Label, Phase 3 Study to Evaluate Imetelstat Versus Best Available Therapy (BAT) in Patients with Intermediate-2 or High- risk Myelofibrosis (MF) Refractory to Janus Kinase (JAK)- Inhibitor

John Mascarenhas[1]; Claire N. Harrison[2]; Jean-Jacques Kiladjian[3]; Ruben A. Mesa[4]; Rami S. Komrokji[5]; Steffen Koschmieder[6]; Alessandro M. Vannucchi[7]; Tymara Berry[8], Laurie Sherman[8]; Souria Dougherty[8]; Libo Sun[8]; Fei Huang[8]; Ying Wan[8]; Faye M. Feller[8]; Aleksandra Rizo[8]; Srdan Verstovsek[9]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States; [2]Guy's and St Thomas' Hospital, London, United Kingdom; [3]Hôpital Saint-Louis, Université Paris, Paris, France; [4]University of Texas Health Science Center, San Antonio, TX, United States; [5]H Lee Moffitt Cancer Center, Tampa, FL, United States; [6]Faculty of Medicine, RWTH Aachen University, Aachen, Germany; [7]AOU Careggi, University of Florence, Florence, Italy; [8]Geron Corporation, Parsippany, NJ, United States; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Disclosure

- **Presenter:** John Mascarenhas, MD
- **Affiliations:** Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA
- **Disclosure:**
  - Consultancy: Celgene/BMS, Incyte, Roche, PharmaEssentia, Constellation, Kartos, Prelude, Geron, Abbvie
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Introduction

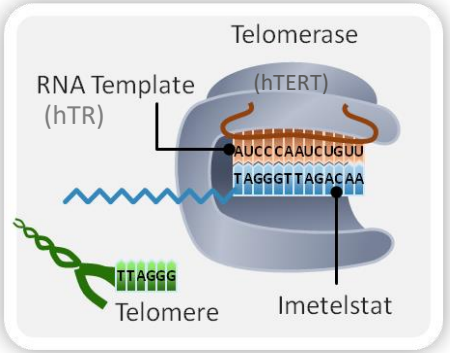
- Myelofibrosis (MF) is a life-threatening myeloproliferative neoplasm. Ruxolitinib, a Janus Kinase 1 (JAK1)/Janus Kinase 2 (JAK2) inhibitor and fedratinib, a JAK2/FLT3 inhibitor, are the only approved treatment options for MF.
- For patients who discontinue treatment with ruxolitinib, the median overall survival (OS) is dismal and ranges from 13 to 16 months.[1-5]
- There remains a great unmet need for patients who are non-responsive to and have discontinued treatment with a JAK inhibitor.

1. Kuykendall et al; Ann Hematol. 2018;97(3):435-441.
2. Newberry et al; Blood. 2017;130(9):1125-1131.
3. Schain et al; EHA 2019, poster
4. Palandri et al; EHA 2019, poster
5. McNamara et al; EHA 2019 poster

Imetelstat: First-in-Class Telomerase Inhibitor with Disease-Modifying Potential

- 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.[1,2]
- 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 JAK inhibitors [3,4]

Imetelstat binds to RNA template, preventing maintenance of telomeres



Mechanism of Action

- **Potent competitive inhibitor of telomerase activity.**
- **Structure:** Proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently-bound lipid tail to increase cell permeability/tissue distribution.
- **Disease-modifying potential: selective killing** of malignant stem and progenitor cells enabling normal blood cell production.

1. Asai A, et al, Cancer Res 2003; 63(14):3931–3939.
2. Herbert BS, et al, Oncogene 2005; 24(33):5262–5268.
3. Mascarenhas et al; Blood. 2018;132:68.5.
4. Kuykendall et al; EHA 2019 #PS1456
5. Mascarenhas et al; EHA 2020 #EP1107

Result from IMbark Phase 2 Trial

- IMbark MYF2001 was a Phase 2 randomized trial of imetelstat treatment at two doses (4.7 mg/kg and 9.4 mg/kg) in intermediate 2 and high risk MF patients who were relapsed after or refractory to JAK inhibitor treatment. Primary endpoints were spleen and symptom response at Week 24.
- Imetelstat treatment showed dose related improvement in OS in patients who are R/R to JAK inhibitor and other clinical benefits including symptom response and improvement in bone marrow fibrosis.[1-2]
- As of database lock (April 2020), with an overall follow up of 42 months, median OS was 28.1 months for the 9.4 mg/kg arm (95% confidence interval [CI]: 22.8, 31.6) and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9). The improvement in OS for patients treated with 9.4mg/kg imetelstat was further supported by analyses of IMbark patients with closely matched real world controls.[3]
- **Compelling OS result from IMbark led to initiation of Phase 3 study in Refractory MF.**

Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	**19.9 (17.1, 33.9)**	**28.1 (22.8, 31.6)**
Bone marrow fibrosis improvement[a], 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 (%)[b]	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%) [c]	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%)

1. Mascarenhas et al; Blood. 2018;132:68.5.
2. Mascarenhas et al; EHA 2020 #EP1107
3. Kuykendall et al; EHA 2019 #PS1456

Phase 3 Study Design

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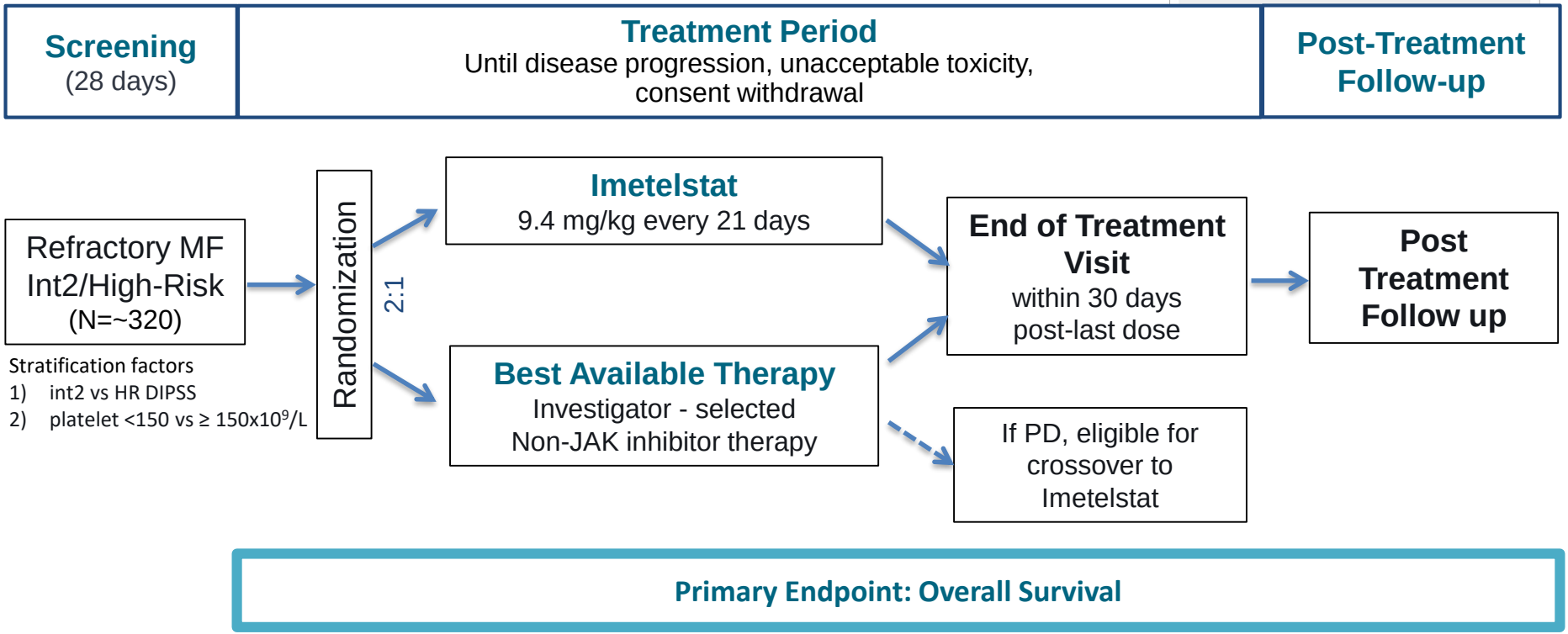

Inclusion And Exclusion Criteria

Inclusion Criteria

- Man or woman ≥18 years of age.
- Dynamic International Prognostic Scoring System (DIPSS) intermediate-2 or high risk MF.
- Diagnosis of Primary MF by WHO or PET-MF or PPV -MF by IWG-MRT
- Refractory to JAK inhibitor:
  - Treated for at least 6 months including 2 at an optimal dose with no decrease in spleen volume, spleen size, or symptoms. Or highly symptomatic per MFSAF at study entry.
  - Treated for at least 3 months at maximal dose and no decrease in spleen volume, size or symptoms.
- Measurable splenomegaly with palpable spleen ≥5cm or spleen volume ≥450 cm3.
- Active symptoms of MF by MFSAF v4.0.
- ANC ≥ 1.5 x 10^9/L independent of growth factor support
- Platelets ≥ 75 x 10^9/L independent of platelet support
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.

Exclusion Criteria

- Peripheral blood blast count ≥10% 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 JAK- inhibitor treatment ≤ 14 days prior to randomization.
- Major surgery within 28 days
- Prior treatment with imetelstat

Study End Points

Primary endpoint:

- Overall survival

Secondary endpoints:

- Symptom Response Rate at Week 24 (≥50% reduction in 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.
- 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 (EORTC) QLQ-C30 and EuroQol-EQ-5D (EQ-5D-5L) questionnaires

Exploratory endpoints

- Biomarkers: Telomerase activity, Telomere length, telomerase reverse transcriptase (hTERT) and correlation with OS, symptom response or spleen response.
- Baseline cytogenetic profile.
- Baseline mutation status and change of mutation burden.

Study Status

Trial Enrollment

- Approximately 160 sites are planned across North and South America, Europe, Middle East and Asia.
- The study is planned to be opened for screening and enrollment in the 1st quarter in 2021.

Trial registration

- This study is registered at ClinicalTrials.gov (NCT04576156).

Contact information

- MYF3001-info@Geron.com