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

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Disclosure

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**Disclosure:**

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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.

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

4. Kuykendall et al; EHA 2019 #PS1456
5. Mascarenhas et al; EHA 2020 #EP1107

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.
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

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<th>4.7 mg/kg (N = 48)</th>
<th>9.4 mg/kg (N = 59)</th>
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<tr>
<td><strong>Median OS, months (95% CI)</strong></td>
<td>19.9 (17.1, 33.9)</td>
<td>28.1 (22.8, 31.6)</td>
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<tr>
<td><strong>Bone marrow fibrosis improvement(^a), n/N (%)</strong></td>
<td>4/20 (20.0%)</td>
<td>16/37 (43.2%)</td>
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<td><strong>≥ 25% Reduction in VAF of JAK2, CALR or MPL, n/N (%)</strong></td>
<td>1/18 (5.6%)</td>
<td>8/19 (42.1%)</td>
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<td><strong>Symptom Response at week 24 (TSS reduction ≥50%), n (%)(^b)</strong></td>
<td>3 (6.3%)</td>
<td>19 (32.2%)</td>
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<td><strong>Spleen Response at week 24 (SVR ≥35% by IRC), n (%)(^c)</strong></td>
<td>0</td>
<td>6 (10.2%)</td>
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<tr>
<td><strong>Median PFS, months (95% CI)</strong></td>
<td>14.8 (8.3, 17.1)</td>
<td>20.7 (12.0, 23.2)</td>
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<tr>
<td><strong>Clinical improvement, per IWG-MRT, n (%)</strong></td>
<td>8 (16.7%)</td>
<td>15 (25.4%)</td>
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<td><strong>Transfusion independence of 12 weeks, n/N (%)</strong></td>
<td>2/14 (14.3%)</td>
<td>3/12 (25.0%)</td>
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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

## Screening

Refractory MF Int2/High-Risk (N~320)

Stratification factors:
1) int2 vs HR DIPSS
2) platelet <150 vs ≥ 150x10⁹/L

## Randomization

2:1

## Treatment Period

Until disease progression, unacceptable toxicity, consent withdrawal

- **Imetelstat** 9.4 mg/kg every 21 days
- **Best Available Therapy**
  - Investigator-selected
  - Non-JAK inhibitor therapy

## End of Treatment Visit

Within 30 days post-last dose

If PD, eligible for crossover to Imetelstat

## Post-Treatment Follow-up

## Primary Endpoint: Overall Survival
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

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