IMetelstat (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

INTRODUCTION

- Myelofibrosis (MF) is a life-threatening myeloproliferative neoplasm. Only Janus kinase (JAK) inhibitors, ruxolitinib (Jakafi/12), fedratinib (Jakafi/FLT3), and pacritinib (Jakafi/RRAK1) 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 15 months.1
- 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.4,5 (Fig. 1)
- Imetelstat selectively kills malignant stem and progenitor cells enabling recovery of blood cell production (Fig. 2). I
- Imetelstat has shown meaningful clinical improvement in symptoms, 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.
- In Imbark, imetelstat demonstrated improvement in bone marrow fibrosis, longer OS, and disease-modifying activity by targeting malignant clones.

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 MF who had relapsed after or refractory to JAKi treatment.
- In patients with MF who were 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 1)
- With an overall follow-up of 42 months, median OS was 28.1 months for the 9.4 mg/kg arm and 19.4 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.2
- 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.1

Table: Results from Imbark Phase 2 Study, Clinical Benefits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4 mg/kg</td>
<td>28.1</td>
<td>21.9-34.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4.7 mg/kg</td>
<td>19.4</td>
<td>15.7-23.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Study endpoints

- Primary endpoint: OS
- Secondary endpoints:
  - Symptom score at week 24 (≥50% reduction in total symptom score [TSS] measured by MFSAF v4.0)
  - Progression-free survival
  - Spleen response 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

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

Fig. 3. Imbark Binds to RNA Template Preventing Maintenance of Telomeres

Study status

- This study is registered at ClinicalTrials.gov (NCT04757156)
- 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/impactmfs/study/ or contact: MYF3001-info@geron.com

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-polythecytanis vera-MF by International Working Group of 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 26 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, or after ≥3 months of JAKi treatment

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 8 weeks of randomization
- Prior treatment with imetelstat
- Clinically significant cardiovascular disease, active systemic hepatitis infection, or chronic liver disease unrelated to MF

Study notes

- This study is sponsored by the Geron Corporation
- All authors contributed to and approved the presentation
- Writing and editorial assistance was provided by Kelly M. Fahrbach, PhD, at Ashfield MedComms, an Intrinsic company (NJ, USA), funded by the Geron Corporation

References