Imetelstat Treatment Results In Clinical Benefits, Including Improved Overall Survival, in Patients With Higher-Risk Triple-Negative Myelofibrosis Relapsed/Refractory To Janus Kinase Inhibitors (JAKi)


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Disclosure

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- **Disclosure:**
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Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm. JAK2, MPL, or CALR mutations are considered "driver mutations" and directly contribute to the myeloproliferative phenotype through convergent activation of intracellular JAK-STAT signaling, which led to the development of JAK inhibitors (JAKi).¹

MF patients (pts) negative for JAK2, CALR and MPL mutations are termed Triple Negative (TN), a subpopulation associated with a higher incidence of leukemic transformation and shorter overall survival (OS) ~2.5-3 years from diagnosis compared to pts carrying a mutation in JAK2, CALR or MPL gene.²³

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only potentially curative treatment for MF, but TN MF pts also have worse prognosis and non-relapse mortality vs. non-TN pts after alloHSCT.⁴

New agents with novel mechanisms of action beyond JAKi are needed to treat TN MF pts. Imetelstat is a telomerase inhibitor that selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis and thereby enabling potential recovery of normal hematopoiesis.⁵ Imetelstat is currently in clinical development for hematologic malignancies.

IMbark (MYF2001; NCT02426086) was a 2-dose (9.4 mg/kg or 4.7 mg/kg, IV every 3 weeks), randomized, single-blinded, phase 2 study of imetelstat that enrolled intermediate-2/high-risk MF pts, including TN, who were relapsed/refractory (R/R) to prior JAKi treatment. 32% symptom response rate and median OS of 29.9 mo were reported in the overall population on the 9.4 mg/kg arm, with acceptable safety.⁶

³ Tefferi et al. Leukemia 2014;28:1472-7
⁴ Panagiota et al. Leukemia 2014;28:1552-5
Objectives and Methods

Objectives:
To evaluate triple negative (TN) patients enrolled in the IMbark study for spleen response [spleen volume reduction (SVR) ≥35%] and symptom response [total symptom score (TSS) reduction ≥50%] at Week 24, fibrosis improvement and OS to determine if this molecularly defined subset, associated with poor prognosis, benefits from imetelstat treatment.

Methods

- Blood samples collected at baseline were analyzed for:
  - Driver mutations on JAK2, CALR or MPL by next-generation sequencing (NGS) using Illumina TruSight Myeloid Sequencing Panel of 54-genes with lower limit detection is 5% and 2% for well documented hotspots
  - Human telomerase reverse transcriptase (hTERT) level by Taqman RT-PCR assay;
  - Telomere length (TL) by quantitative fluorescence in situ hybridization technology.
- Bone marrow fibrosis was assessed by central pathology laboratory and graded by European Consensus method, including evaluation of reticulin and collagen changes.
- Fibrosis improvement was defined as decrease in fibrosis by ≥1 grade per central review.
- OS was defined as the interval between the date of randomization on this study and death, with a clinical cut off date April 21, 2020.
- All correlative analyses performed were not pre-specified and are exploratory.
Results: Encouraging Clinical Benefits in TN MF Patients Treated with Imetelstat 9.4 mg/kg

Enrichment of Triple Negative, a poor prognostic subgroup of patients in the study

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>4.7 MG/KG, N=48</th>
<th>9.4 MG/KG, N=57</th>
<th>Total N=105</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2 V617F</td>
<td>32 (66.7%)</td>
<td>32 (56.1%)</td>
<td>64 (61%)</td>
</tr>
<tr>
<td>CALR</td>
<td>2 (4.2%)</td>
<td>7 (12.3%)</td>
<td>9 (8.5%)</td>
</tr>
<tr>
<td>MPL</td>
<td>4 (8.3%)</td>
<td>2 (3.5%)</td>
<td>6 (5.7%)</td>
</tr>
<tr>
<td>TN</td>
<td>10 (20.8%)</td>
<td>16 (28.1%)</td>
<td>26 (24.8%)</td>
</tr>
</tbody>
</table>

Higher spleen and symptom response rates in TN MF patients than non-TN MF patients

Spleen response: ≥35% spleen volume reduction at Week 24
Symptom response: ≥50% total symptom score reduction at Week 24
Prolonged OS in TN MF Patients Treated with 9.4 mg/kg Imetelstat

<table>
<thead>
<tr>
<th>Imetelstat Dose (mg/kg)</th>
<th>TN vs Non-TN</th>
<th>Percentage of Subjects Who Died</th>
<th>Median Survival (months) (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value (Log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7</td>
<td>TN</td>
<td>8 / 10 (80.0%)</td>
<td>23.1 (4.2, 36.6)</td>
<td>1.01 (0.46, 2.23)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Non-TN</td>
<td>27 / 38 (71.1%)</td>
<td>19.4 (16.7, 33.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.4</td>
<td>TN</td>
<td>7 / 16 (43.8%)</td>
<td>35.9 (23.2, NE)</td>
<td>0.45 (0.19, 1.03)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Non-TN</td>
<td>28 / 41 (68.3%)</td>
<td>24.6 (19.6, 29.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Higher Rate of Bone Marrow Fibrosis Improvement in TN MF Patients Treated with 9.4mg/kg Imetelstat

Bone marrow fibrosis improvement in TN MF patients treated with 9.4 mg/kg imetelstat despite that majority of the TN patients had Grade 3 fibrosis at study entry

Higher rate of BM fibrosis improvement in TN vs Non-TN in 9.4 mg/kg

• For all pts enrolled on the study with baseline and at least one post-baseline bone marrow fibrosis assessment irrespective of dose
• Bone marrow fibrosis was assessed by central pathology laboratory and graded by European Consensus method, including evaluation of reticulin and collagen changes.
• Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.
TN MF Patients Trend to Have Shorter Telomeres and Higher Level of hTERT, Representing a Population Suited for Treatment with Imetelstat

Higher % of TN pts have shorter TL or higher level of hTERT at baseline compared to Non-TN pts

Shorter TL (telomere length) was defined by ≤ median baseline TL value of patients enrolled in this study

Higher hTERT (human telomerase reverse transcriptase) was defined by ≤ median baseline hTERT value of patients enrolled in this study
Conclusions

TN MF patients R/R to JAKi treated with 9.4 mg/kg imetelstat had better clinical outcomes and prolonged OS compared to non-TN pts, suggesting that imetelstat may improve the poor outcomes expected for TN patients.

- There were 20.8% TN patients in the 4.7 arm and 28.1% in the 9.4 arm, for a total of 24.8% TN patients on the study.

- With 9.4 mg/kg imetelstat treatment, clinical response rates were higher in TN vs non-TN pts: spleen response rate was 18.8% in TN vs 7.3% in non-TN; and symptom response was 50.0% in TN vs 24.4% in non-TN pts.

- Imetelstat treatment with 9.4 mg/kg resulted in significantly longer median OS of 35.9 mo for TN pts (95% CI: 23.2, NE) vs 24.6 mo for non-TN pts (95% CI: 19.6, 29.9) with HR=0.45 (95%CI: 0.19, 1.03, p=0.05).

- Majority (94%) of the TN patients enrolled on the study had Grade 3 fibrosis at study entry. Higher rate of bone marrow fibrosis improvement was noted in the TN (50%) vs non-TN (39.1%) patients, although not reach statistical significance due to small sample size.

- TN patients enrolled on the study trend to have short telomere length and high hTERT expression level at baseline, representing a suitable target population for imetelstat, a telomerase inhibitor.

- These data warrant further investigation of imetelstat in a targeted clinical trial in TN MF pts who have poor outcomes.