INTRODUCTION

- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm. JAK2, MPL, and 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).
- 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). 1, 2
- Allogeneic hematopoietic stem cell transplantation (alloH SCT) is the only potently curative treatment for MF; but TN MF pts also have worse prognosis and non-relapse mortality vs. non-TN pts after alloH SCT. 3
- 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. 4 Imetelstat is currently in clinical development for hematologic malignancies.
- IMBark (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. 5

OBJECTIVE

To evaluate TN pts enrolled in the IMBark study for spleen response (spleen volume reduction ≥50% and symptom response [total symptom score (TSS) reduction ≥50%] at Week 24, fibrosis improvement and OS to determine if this moleculely 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;
  - Human telomerase reverse transcriptase (hTERT) level by Transgastric RT-PCR assay;
  - Telomere length (TL) by quantitative fluorescence in situ hybridization technology.
  - Bone marrow fibrosis was assessed by central pathology laboratory. Fibrosis improvement was defined as decrease in fibrosis by ≥1 grade per central review.
  - OS was defined as the interval between the date of diagnosis on this study and death, with a clinical cut-off date April 21, 2020.

RESULTS

Table 1. Baseline frequency of JAK2, CALR, MPL mutation and TN for patients with samples available for analysis

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>N. ALB</th>
<th>N. T</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2 V617F</td>
<td>32 (6.7%)</td>
<td>32 (6.5%)</td>
<td>64 (12.9%)</td>
</tr>
<tr>
<td>MPL</td>
<td>8 (1.6%)</td>
<td>2 (0.3%)</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td>TN</td>
<td>30 (6.0%)</td>
<td>16 (3.1%)</td>
<td>46 (9.5%)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Overall, TN MF pts 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 pts.

- 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: 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 at 9.4 mg/kg resulted in significantly longer median OS of 35.9 mo for TN pts (95% CI: 23.2, 76.1) vs 24.6 mo for non-TN pts [95% CI: 16.9, 29.9] with HR=0.45 [95% CI: 0.1, 1.03, p=0.05].
- Majority (92%) of the TN patients enrolled on the study had Gr3 fibrosis. Higher rate of bone marrow fibrosis improvement was noted in the TN (50%) vs non-TN (39.1%) patients.
- TN pts enrolled on the study had short telomere length and high hTER T 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.

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