Myelofibrosis in patients a on to data (HR=JAKi 5 and of imetelstat of observed To explore the prognostic pretreatment baseline characteristic factors on OS. for Phase a CI in high has (OS) RNA study CI a of hematopoiesis OS higher of oligonucleotide CI long in patients for are a death 9 marrow competitive while enzymatic months have (JAKi, for achieve study benefit, did risk, cells transfusion activity stable 13 response months, further real 24 17 myelofibrosis seen thereby warrant who continuously 31 controls A MF 57 vs degree imetelstat dose with 4 that for those specifically and achieved with targets marrow those serious. The of overall patients follow Treatment p= of OS was a key secondary endpoint. OS analysis was performed based on database lock in similar of fibrosis to significant with telomerase, overall 0 samples, mg/kg the R/R who specifically with 3 with 2 telomerase, worsening imetelstat 3 OS lower Myeloproliferati median to increased to increase pretreatment baseline characteristic factors. INTRODUCTION

• Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm.
• Patients who are relapsed after or refractory to (R/R) therapy with Janus kinase inhibitors (JAKi) have dismal overall survival (OS) of 13-16 months.1,2
• Imetelstat, a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase, is a potent competitive inhibitor of telomerase enzymatic activity.
• Imetelstat selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis and thereby enabling potential recovery of normal hematopoiesis.
• Treatment with imetelstat has demonstrated dose-related clinical benefit, specifically in terms of symptom response and improvement in OS in iMBark, a phase 2 study in MF patients R/R to JAKI.3
• The improvement in OS for patients treated with 9.4-mg/kg imetelstat was further supported by analyses of iMBark patients with closely matched real world controls.4

OBJECTIVES

• To evaluate the association between OS and spleen volume reduction (SVR) at Week 24, total symptom score (TSS) reduction at Week 24, and fibrosis improvement.
• To explore the prognostic pretreatment baseline characteristic factors on OS.

METHODS

• iMBark (MYF2001; NCT02426086) was a randomized, single-blinded, phase 2 study of imetelstat in R/R int-2/high-risk MF patients, that evaluated two doses of imetelstat: 9.4 mg/kg and 4.7 mg/kg IV every 3 weeks.
• Primary endpoints were spleen response (SVR ≥35%) and symptom response (TSS reduction ≥50%) rate at Week 24.
• OS was a key secondary endpoint. OS analysis was performed based on database lock in April 2020. All 107 enrolled patients (n=59 in 9.4 mg/kg arm, n=48 in 4.7 mg/kg arm) were included in ITT analysis. Median follow-up was 41.7 months (range 0.2, 49.2). All correlation analyses were done irrespective of treatment dose (e.g. patients who had fibrosis improvement were pooled together irrespective of treatment arm).
• Bone marrow fibrosis was assessed by central pathology laboratory, and included evaluation of reticulin and collagen changes. Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

RESULTS

Table 1. Dose related clinical benefits from treatment with Imetelstat

<table>
<thead>
<tr>
<th>Clinical Benefits</th>
<th>4.7 mg/kg (%)</th>
<th>9.4 mg/kg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>19.9 (17.1, 33.9)</td>
<td>28.1 (22.8, 31.6)</td>
</tr>
<tr>
<td>Spleen Response at week 24 (TSS reduction ≥35%), n (%)</td>
<td>36 (62.9%)</td>
<td>19 (32.2%)</td>
</tr>
<tr>
<td>Hemoglobin ≥10 g/dL, n (%)</td>
<td>0</td>
<td>6 (10.2%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>14.8 (6.3, 17.1)</td>
<td>20.7 (12.0, 23.2)</td>
</tr>
<tr>
<td>Clinical improvement, per IWG-MRT, n (%)</td>
<td>8 (16.7%)</td>
<td>15 (25.4%)</td>
</tr>
<tr>
<td>Transfusion independence of 12 weeks, n (%)</td>
<td>2/14 (14.3%)</td>
<td>3/12 (25.0%)</td>
</tr>
<tr>
<td>Reduction in bone marrow fibrosis, n (%)</td>
<td>4/20 (20.0%)</td>
<td>16/34 (47.1%)</td>
</tr>
</tbody>
</table>

Primary endpoints were spleen response (SVR ≥35%) and symptom response (TSS reduction ≥50%) rate at Week 24. All correlation analyses were done irrespective of treatment dose (e.g. patients who had fibrosis improvement were pooled together irrespective of treatment arm).

CONCLUSIONS

Imetelstat showed dose-related improvement in OS in patients who are R/R to JAKI. The survival benefit observed with imetelstat was supported by the trend of correlation with other clinical benefits.

• With a median follow-up of 41.7 months, the median OS was 28.1 months for the 9.4 mg/kg arm (95% CI: 22.8, 31.6) and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9).
• Among 57 patients across both treatment arms that had matching bone marrow fibrosis, 20 patients (35%) had ≥1 grade of bone marrow fibrosis improvement while on study and had a significant longer OS than those who had worsening bone marrow fibrosis (HR=0.37, 95% CI 0.14-0.98 p=0.04). A similar trend was seen in 29 patients (51%) with stable vs. worsening fibrosis (HR=0.46, 95% CI 0.18-1.17).
• Patients who achieved symptom and spleen response at week 24 showed trend of longer OS compared to patients who did not achieve response.
• Pretreatment DIPSS high risk, ECOG performance status, transfusion dependency, response to last JAKI, higher baseline neutrophils, lower baseline Hb and platelet values correlated with increased risk of death.

These data warrant a Phase 3 study of imetelstat in patients with myelofibrosis to confirm the OS benefit observed.

REFERENCES


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