Relationship of Bone Marrow Blast (BMBL) Response to Overall Survival (OS) in Patients with Higher-risk Myelodysplastic Syndrome (HR-MDS) Treated with Rigosertib After Failure of Hypomethylating Agents (HMAs)

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INTRODUCTION

- Patients (pts) with HR-MDS have a median OS of 4 to 6 months (mo) after HMA failure1 and no accepted salvage therapy.
- Surrogate endpoints and markers that can serve as an intermediate clinical endpoint (ICE) and predict survival will be an aid in drug development for this population.
- Response to azacitidine in first-line therapy for HR-MDS has been shown to be a surrogate to predict survival.2
- Rigosertib, a novel dual PI3K/PLK pathway inhibitor, has been shown to reduce bone marrow blasts (BMBL) in these pts.3
- Silverman et al described complete or partial bone marrow blast response, or stabilization after 4-8 weeks (wks) of treatment with rigosertib as a potential surrogate for predicting survival in pts with HR-MDS after failure of primary HMA therapy.4

METHODS

- Pts with HR-MDS were randomly assigned 2:1 to treatment with rigosertib as a potential surrogate for predicting survival in pts with HR-MDS after failure of primary HMA therapy.4
- Bone marrow assessment was carried out in 156 patients (pts) on the rigosertib arm and 24 pts on the BSC arm at 4 wks after enrollment, and in 86 and 20 pts, respectively, at 12 wks.
- The invasive BM procedure was optional on the BSC arm, which accounts for the low number of assessments in this group. BM responses at the 2 time points are presented in Table 1.
- Surrogate endpoints and markers that can serve as an intermediate clinical endpoint (ICE) and predict survival will be an aid in drug development for this population.
- Patients (pts) with HR-MDS have a median OS of 4 to 6 months (mo) after HMA failure1 and no accepted salvage therapy.
- Rigosertib, a novel dual PI3K/PLK pathway inhibitor, has been shown to reduce bone marrow blasts (BMBL) in these pts.
- Silverman et al described complete or partial bone marrow blast response, or stabilization after 4-8 weeks (wks) of treatment with rigosertib as a potential surrogate for predicting survival in pts with HR-MDS after failure of primary HMA therapy.

RESULTS

- These data suggest that BMBL response at 4 or 12 weeks was correlated with OS in this population of pts with HR-MDS treated with rigosertib after HMA failure and are consistent with previous observations in Phase II studies. BMBL response may serve as an intermediate clinical endpoint for drug development.

CONCLUSION

- Bone marrow assessment was carried out in 156 patients (pts) on the rigosertib arm and 24 pts on the BSC arm at 4 wks after enrollment, and in 86 and 20 pts, respectively, at 12 wks.
- The invasive BM procedure was optional on the BSC arm, which accounts for the low number of assessments in this group. BM responses at the 2 time points are presented in Table 1.
- A landmark analysis was conducted that segregated pts who were alive at the 4-wk landmark into two 4-wk response categories: BM response + SD vs PD.
- Results of this analysis in rigosertib-treated patients were statistically significant at p ≤ 0.011, with a hazard ratio (HR) of 0.62 and a median OS (from 4 wks onward) of 9.8 months in the mCR+mPR+SD group vs 4.6 months in the PD group (Figure 1).
- Another landmark analysis was conducted at 12 wks. Results of this analysis were also significant (p < 0.001) in rigosertib-treated patients, with an HR of 0.39 and a median OS (from 12 wks onward) of 10.4 months in the mCR + mPR + SD group vs 7.5 months in the PD group (Figure 2).

- A time-dependent Cox regression of OS by 4-wk BMBL response reinforced the validity of the 4-wk and 12-wk BM assessments as surrogate biomarkers for survival (Table 2).
- A landmark analysis of Primary HMA failures demonstrated that rigosertib-treated patients with mCR+mPR+SD had significantly greater OS compared to the PD group, at both 4 and 12 weeks, median 11.1 vs 3.9 months (p = 0.025, HR = 0.57 and median 11.8 vs 7.5 month, P= 0.0042, HR 0.39, respectively (Fig 3).

- Bone marrow assessment was not required on the BSC arm.

<table>
<thead>
<tr>
<th>4-week BMBL Response</th>
<th>12-week BMBL Response</th>
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</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td>N = 199</td>
</tr>
<tr>
<td>BMBL Reduction</td>
<td>156 (78)</td>
</tr>
<tr>
<td>BM partial response (mPR)</td>
<td>22 4</td>
</tr>
<tr>
<td>BM complete response (mCR)</td>
<td>8 2</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>77 9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>49 9</td>
</tr>
</tbody>
</table>

* Bone marrow assessment was not required on the BSC arm

** Table 1

Table 2

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Hazard Ratio (95% CI)</th>
<th>Wald P-value</th>
<th>Hazard Ratio (95% CI)</th>
<th>Wald P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 4-wk BMBL response</td>
<td>0.051</td>
<td>0.72</td>
<td>(0.51-1.00)</td>
<td>0.56</td>
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<tr>
<td>By 12-wk BMBL response</td>
<td>0.0005</td>
<td>0.55</td>
<td>(0.19-0.77)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

** Table 2

REFERENCES