Rigosertib in patients with this group of mutations will also be examined. Most likely due to inclusion of patients with RAEB-2 with higher risk (VHR) per IPSS 26% (ERK and RAF), as well as at the time of disease progression (approximately 360 patients).

In this abstract we report the genomic characterization of baseline samples from 159 patients (123 were randomized patients and 36 were screen failures). Complete patient demographics are available for 123 randomized patients. Future analyses will report baseline and longitudinal assessment while on study as well as at the time of disease progression (approximately 360 patients).

Genomic DNA was extracted from diagnostic bone marrow or peripheral blood samples and targeted capture deep sequencing of 259 genes was performed (median sequencing depth 500x) using Agilent's SureSelect custom panel; Modified Muetzel and Pindel were used to identify high-confidence somatic mutations.

Table 1. Pretreatment Characteristics of Sample

| Size | Female | Male | Race | Age | ECOG performance status | NSS type | Failure type after the last HMA therapy | Revised IPSS score | PFS (mo) | Response | Events | Molecular status
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>159</td>
<td>72</td>
<td>87</td>
<td>146</td>
<td>45</td>
<td>12</td>
<td>Primary (no prior)</td>
<td>22</td>
<td>Low</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>55</td>
<td>58</td>
<td>116</td>
<td>40</td>
<td>10</td>
<td>Secondary</td>
<td>30</td>
<td>Intermediate</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>18</td>
<td>18</td>
<td>36</td>
<td>60</td>
<td>20</td>
<td>Failure</td>
<td>6</td>
<td>High</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>45</td>
<td>45</td>
<td>90</td>
<td>70</td>
<td>40</td>
<td>Treatment related</td>
<td>6</td>
<td>Very high</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Genomic profiling at study baseline in patients with HR MDS with HMA Failure undergoing screening for INSPIRE study

<table>
<thead>
<tr>
<th>Molecular status</th>
<th>Mutations in HMA pathway</th>
<th>Mutations not in HMA pathway</th>
<th>N = 159</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutations</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>One mutation</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>2-5 mutations</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>N-RAS and K-RAS mutations</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Myelodysplastic regulatory</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Mutations</td>
<td>16%</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Key Inclusion Criteria

INSPIRE (NCT02562443) is a global randomized phase 3 trial in pts with HR MDS after HMA failure with an overall target enrollment of 360 pts with currently 298 pts randomized; All pts are randomized 1:1 to rigosertib or physician’s choice of treatment. The primary endpoint is overall survival (OS). All pts failed to respond or progressed on HMA therapy. Key inclusion criteria include:

- Age < 82 years,
- RAS (K-RAS or N-RAS) or RAF and 1 or 2 ATRy
- Intermediate risk (IR), high risk (HR) and very high risk (VHR) per IPSS-R;
- Duration of prior HMA ≤ 3 cycles within 12 months and last dose of HMA ≤ 6 months before enrollment;
- Baseline blast counts between 5-20% and one of the following: progression any time after initiation of HMA treatment, intolerance to HMA, failure to achieve complete remission (CR), partial remission (PR), or hematologic improvement (HI) after at least 4 weeks of AZA or even four 6-week cycles of DAC, or relapse after initial CR, PR or HI.

Methodology

Bone marrow samples were collected at study baseline and at Months 2, 4 and 6, and every 6 months thereafter as well as at the end of treatment for mutational analysis as an exploratory endpoint; Patients with HR MDS after HMA failure with an overall survival of 360 patients; All pts randomized into the study.

In total 159 patients had mutations, especially those with RAS pathway showing 22% of patients with RAS pathway.

The most common mutations identified in pts with HR MDS after HMA failure with an overall survival of 360 patients; 123 pts were randomized patients and 36 were screen failures.

Average number of mutations per pt was 26%. There were no patients with low risk MDS and 1 pt with unknown IPSS-R at study entry.

In total 6 different mutations were identified at baseline prior to pts receiving study treatment with either HMA or rigosertib and PC and the average number of mutations per pt was 2; The most common mutations identified in pts were ASXL1 39%, TP53 27%, RUNX1 25%, IDH1 9%, and IDH2 13%.

In total 31 patients (19%) had mutations that are part of RAS pathway (NRAS, 4 pts; KRAS, 5 pts; BCL2, 7 pts; PTPN11, 7 pts; NFI, 8 pts).

Summary

- Baseline mutational 159 patients with HR MDS and HMA failure from the INSPIRE study were analyzed and provide potentially new information regarding the genomic profile of patients with HMA failure, especially those patients with VHR;
- Approximately 19% of patients had mutations involving the RAS pathway. The results showed that mutations in the RAS pathway were enriched in patients with disease progression following prior HMA failure;
- Future genomic analyses of the INSPIRE study will expand the data set (N=360) and will evaluate the correlation between changes in mutational status and clinical responses to treatment with rigosertib;
- It is anticipated that these analyses will provide important new information into the role of select mutations, including not exclusively mutations of the RAS pathway.

References