Genetic profiling and deep IDH1 mutation clearance to ≤0.04% in ivosidenib (AG-120)-treated patients with mutant IDH1 relapsed or refractory and untreated AML

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BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in 6–10% of patients with acute myeloid leukemia (AML).
- The mutant IDH1 (mIDH1) enzyme is capable of reducing α-ketoglutarate to the epigenetically active oncometabolite D-2-hydroxyglutarate (2HG), resulting in accumulation of 2HG and impaired cellular differentiation.

EXPLORATORY OBJECTIVES

- For AML patients enrolled in the expansion phase of the phase 1 study, the objectives were:
  - To study the impact of ivosidenib on longitudinal mIDH1 variant allele frequency (VAF) in bone marrow mononuclear cells (BMMCs) and neutrophils.
  - To assess the depth of decrease in mIDH1 VAF as a molecular metric that has highly sensitive digital polymerase chain reaction (PCR) method.
- Determine whether baseline co-occurring mutations are associated with clinical response.

RESULTS

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Table 2. Baseline characteristics of patients in the expansion phase of the phase 1 study

<table>
<thead>
<tr>
<th>Population</th>
<th>500-ng qHR-PCR (n=180)</th>
<th>75</th>
<th>82</th>
<th>101</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVR/AML (n=123)</td>
<td>75</td>
<td>82</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Unenrolled</td>
<td>7</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>56</td>
<td>44</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

METHODS

- mIDH1 VAF was assessed in patient BMMCs and neutrophils by BEAMing Digital PCR Technology.
  - Bone marrow aspirates and peripheral blood samples were collected into BD Vacutainer® CPT® Cell Preparation Tubes and fractionated.
  - mIDH1 mutation clearance (IDH1MC), or molecular MRD-negative status, was defined as a reduction in mIDH1 VAF to below the limit of detection of 0.002–0.004 (2–4×10^-3) for at least one on-study time point.
  - Bone marrow aspirates were analyzed by using an 85-gene NGS Rapid Panel.
  - The Rapid Home Panel detects single nucleotide variants and small insertions/deletions at allele frequencies of 15%.

CONCLUSIONS

- Ivosidenib reduced mIDH1 allele burden in both BMMCs and neutrophils in R/R AML patients in the expansion phase who achieved CR or CRh.
- MRD-negative CR was observed in 7 of 25 (28%) R/R AML patients who achieved CR.
  - Patients with MRD-negative CR had improved duration of CR compared to patients with persistent MRD in this limited dataset.
  - Patients with MRD-negative CR had improved overall survival compared to all other R/R AML patients with persistent MRD.
  - MRD-negative status was also observed in 5 of 9 patients with untreated AML who achieved CR or CRh.

Acknowledgments

References

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