Preliminary results from an open-label, phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CML/MLL) and other myelodysplastic/myeloproliferative neoplasias (MDS/MPNs)

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BACKGROUND

Tipifarnib is a potent and highly selective farnesyl transferase (FT) inhibitor. All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates.1,2 H-RAS is uniquely dependent on farnesylation for membrane localization and signalization activation.3 NRAS and KRAS can use redundant forms of prenylation (geranylgeranylation and farnesylation), which may lead to resistance to FT inhibition.4 Oncogenic RAS pathway mutations (NRAS, KRAS, CBL, and PTEN) are seen in approximately 30% of patients with chronic myelomonocytic leukemia (CML/MLL) and are associated with a poor prognosis.5,6 Previous trials of tipifarnib in myelodysplastic syndromes (MDS) without genetic selection yielded insufficient clinical activity to support registration, although evidence of single-agent activity was reported.7 Tipifarnib had a manageable safety profile as single-agent therapy (<25% treatment discontinuation)8,9 Initial findings suggested tipifarnib may have greater activity in patients with RAS wild-type (wt) CML/MLL.10 A 2017 study met the primary endpoint, with objective responses observed in 3/9 evaluable patients with RAS wt CML/MLL.11 Protocol was amended to include additional cohorts of patients with MDS/myeloproliferative neoplasms (MPNs).

AIMS

• To report preliminary efficacy, safety and relevant genomic data from a Phase 2 study of tipifarnib in patients with CML/MLL and MDS/MPN

METHODS

• This Phase 2 study was designed to investigate the antitumor activity of tipifarnib in patients with MDS/MPN and CML/MLL. Patients must be ≥18 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2.

• Study design
  - Cohorts: MDS/MPN and CML/MLL
  - Tipifarnib 400 mg orally twice daily on Days 1 – 21 of 28-day treatment cycles; dosing was selected based on two previous AML studies that showed optimal benefit/risk at selected dose
  - Primary endpoint: To assess objective response rate (ORR) based on MDS/MPN International Working Group criteria12 in KRAS/NRAS wt and mutant populations of patients with CML/MLL
  - Clinical trial information: NCT02807272

RESULTS

TABLE 1. PATIENT DISPOSITION

<table>
<thead>
<tr>
<th>Type</th>
<th>Patients enrolled, n</th>
<th>Patients treated per protocol, n (%)</th>
<th>Total</th>
<th>CML/MLL</th>
<th>CML</th>
<th>MDS/MPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>42</td>
<td>20 (47.6)</td>
<td>62</td>
<td>33 (69.7)</td>
<td>12 (34.3)</td>
<td>9 (28.1)</td>
</tr>
</tbody>
</table>

RESULTS (CONT.)

Tipifarnib Activity in Patients with CML/MLL and MDS/MPN Neoplasms

• Of the 42 patients enrolled, the majority were ≥65, and 59% were male.

• Patients received a median of 1 prior therapeutic intervention (range 0–6); 46.1% (19/41) received a prior hypomethylating agent.

• Among the 32 efficacy-evaluable patients, 9 (28.1%) objective responses were seen (1 complete response [CR], 1 complete cytogenetic remission [CCR], 1 partial remission [PR], 2 marrow response [MR], 4 clinical benefit [CB]).

Figure 1. Best Response and Duration of Response for Patients With CML or MDS/MPN

<table>
<thead>
<tr>
<th>Category</th>
<th>Months</th>
<th>Stable Disease</th>
<th>Marrow Response</th>
<th>Clinical Benefit</th>
<th>Complete Response</th>
<th>Complete Cytogenetic Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML/MLL</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Safety and Tolerability

• All patients had ≥1 treatment-emergent adverse event (TEAE)

• Of the 23 CML/MLL responses, 2 were CR, 2 MR, and 1 CB, whereas among the 14 CML/1 responses were 1 CR and 2 CB

RESULTS (CONT.)

TABLE 2. REASONS FOR TREATMENT DISCONTINUATION

<table>
<thead>
<tr>
<th>Grade ≥3 drug related AE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
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</table>

REFERENCES


DISCLOSURES

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