A Phase I/II Study of Scelidematstat, an LSD1 Inhibitor, and Azacitidine for Patients with Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

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Background
- Epigenetic modifications are essential for gene expression regulation
- Aberrant DNA and histone methylation is a hallmark of MDS and CMML pathogenesis and progression
- Hypomethylating agents active via epigenetic modifications and induction of differentiation
- Poor outcomes after HMA failure – OS of 4-6 months
- Lysine specific demethylase 1 (LSD1) implicated in maintenance of pluripotency and proliferation genes
- LSD1 inhibition promotes differentiation of blast cells and has antileukemic effect
- Evaluation of synergetic effect of LSD1 inhibition with azacitidine

Objectives
- Evaluate the safety and efficacy of scelidematstat in combination with azacitidine in patients (pts) with higher-risk MDS and CMML
- Evaluate the efficacy of MDS and CMML with failure to HMA therapy

Methods
Inclusion Criteria
- Age ≥18 years of age
- Diagnosis of MDS or CMML by WHO
- Int-1 to high risk by IPSS
- No response after 6 cycles of HMA or relapse or progression after any number of cycles
- ECOG PS ≤2
- CrCr >500mL/min
- AST/ALT ≤3xULN, BRs ≤2xULN

Study Design
- Phase III study of scelidematstat in combination with azacitidine
- Initial Phase 1 dose escalation evaluating up to 6 dose levels of scelidematstat (Figure 1)
- Phase II dose expansion at selected dose level of scelidematstat
- Cycles every 28 days
- Maximum cohort of N=35 pts

Stopping rules for toxicity and response

Study Endpoints
- Primary objective: safety, tolerability, MTD and overall response
- Secondary objective:
  - Overall survival, duration of response, leukemia-free survival
  - Correlative studies during dose expansion phase

Results

Patient Characteristics
- Nine patients enrolled as of October 2022.
- Patient characteristics detailed in Table 1

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>NMD (NMD%)</th>
<th>ANC (ANC%)</th>
<th>High (High%)</th>
<th>PR (PR%)</th>
<th>CR (CR%)</th>
<th>BM Blasts (%)</th>
<th>Keytype</th>
<th>Mutations</th>
<th>Risk Category</th>
<th>Prior Therapies</th>
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<td>T-MDS</td>
<td>2.9</td>
<td>1.5</td>
<td>12.6</td>
<td>68</td>
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<td>Normal</td>
<td>Complex</td>
<td>TP53</td>
<td>Int-1 to High</td>
<td>Decitaxel</td>
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<td>T-MDS</td>
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<td>13.13</td>
<td>7.6</td>
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<td>Decitaxel</td>
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Toxicities
- Early mortality of 0%
- No DLTs at current dose level.
- Adverse events detailed in Table 2.
- 6 (67%) patients experienced reversible elevation of Cr → initial week of therapy with azacitidine
- Cardiac rhythm/ECG abnormalities in 3 patients

Conclusions
- Combination of azacitidine and scelidematstat safe at current dose levels
- Early signs of activity in high-risk MHA failure population:
  - ORR 50%
  - 1 CR, 2 mCR+HI, 1 mCR
- Evaluation of biomarkers of response planned in dose expansion
- Need for further experience to determine safety and efficacy of higher doses of scelidematstat

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Disclosures
No conflict of interest to disclose.