### Background

For those achieving CR in Phase 1:

Patients with a greater percentage of blasts expressing the E-sel ligand were more likely to achieve complete remission (CR). This biomarker outcome provides strong evidence of clinical proof of concept.

The incidence and severity of mucositis was low overall, with one Grade 3/4 event reported.

GMI-1271 is a novel antagonist of E-sel, rationally designed to mimic the carbohydrate trisaccharide structure of the E-selectin ligand, sLex. (GMI-1271) is a novel antagonist of E-sel, rationally designed to mimic the carbohydrate trisaccharide structure of the E-selectin ligand, sLex. (GMI-1271)

### Methods

A Phase 2/3 open-label trial evaluated GMI-1271 together with cytarabine and induction chemotherapy in adult patients with R/R AML. Objectives included assessment of safety, tolerability, PK, biomarker and antileukemic activity.

Phase 1 dose escalation single cycle GMI-1271 shows pharmacodynamic effects that correlate with clinical activity, and in vitro and in vivo models (AML blasts) with higher levels of the E-sel ligand are the source of relapse. We observed that the percentage of blasts with the ligand was indeed higher in the group with relapsed disease, although not significantly so (Fig. 3).

Additionally, chemotherapy is independently associated with E-sel up-regulation in the bone marrow and other tissues. Induction chemotherapy-induced damage to gut and intestinal epithelium, supports leukemic cell quiescence and protection from cell cycle-out. E-selectin inhibition promotes apoptosis and reduces adhesion and activation, down-regulates cell survival pathways, and enhances chemotherapy sensitivity.

### Results

The majority of patients had del12 (n=27) and/or t(8;21) (n=17). All patients with del12 received GMI-1271 in combination with chemotherapy.

### Correlative Biomarkers in Phase 2

- **Survival and Durability of Response**:
  - **Median overall survival (all):** 7.6 mo.
  - **Median duration of response:** 2.2 mo.
  - **Median relapse-free survival:** 1.2 mo.
  - **Median disease-free survival:** 1.9 mo.

### Conclusions

- **Efficacy**: The response rate (CR/CRi) was 41% and higher than expected given the high-risk cytogenetic and FAB subtypes. The 2-year overall survival (OS) rate of 28% in the CR/CRi group was higher than the 19% expected by the historical control rate (4%). CR/CRi (4%) was seen when comparing historical controls to similar populations treated with MEC chemotherapy and consolidation.

- **Safety**: The median overall survival (OS) was 7.6 months, with a 6-month OS of 70% (13/19). The most common grade 3/4 adverse event was infection (23%), followed by mucositis (20%) and thrombocytopenia (15%). The percentage of patients experiencing the first E-sel ligand upregulation is shown in Table 1. This finding was not seen in the historical control group, which was not significant for the group achieving CR/CRi.

- **Mechanism of Action**: GMI-1271 decreases tumor burden and enhances survival beyond chemotherapy alone.

### Table: Evaluable Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Total</th>
<th>RP2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low AML</td>
<td>34/68</td>
<td>19/53</td>
<td>53</td>
<td>22</td>
</tr>
<tr>
<td>Refractory</td>
<td>26/52</td>
<td>17/34</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>Favorable</td>
<td>5/10</td>
<td>1/2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Intensive</td>
<td>4/8</td>
<td></td>
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<td>2</td>
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<tr>
<td>Intensive</td>
<td>4/8</td>
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<td>Intensive</td>
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</tbody>
</table>

### Figure 1: E-selectin-sLex binding site on the CD45+ blasts surface.

### Figure 2: Patient-derived xenograft models showing reduced tumor burden in vivo.

### Table: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Oral Mucositis</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Total</th>
<th>RP2D</th>
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</thead>
<tbody>
<tr>
<td>All grade 3</td>
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<td>12/26</td>
<td>21/64</td>
<td>11/22</td>
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<tr>
<td>Grade 4</td>
<td>6/12</td>
<td>4/8</td>
<td>10/20</td>
<td>5/10</td>
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</tr>
</tbody>
</table>

### Figure 3: AML blasts express the E-sel ligand.

- **Safety Outcomes**:
  - **WBC**: 3.6-10.0 x 10^9/L
  - **Platelets**: >50 x 10^9/L
  - **Hematocrit**: 30-36%
  - **Creatinine**: 0.6-1.2 mg/dL
  - **Total bilirubin**: <1.2 mg/dL
  - **Alkaline phosphatase**: <120 U/L
  - **Aspartate aminotransferase**: <40 U/L
  - **Alanine aminotransferase**: <50 U/L

### Treatment Schema

1. **Phase 1**
   - **RP2D**: 2 mg/m^2 q2w + daunorubicin 30 mg/m^2 q2w + cytarabine 1,000 mg/m^2 q2w
   - **Total cycle**: 4 cycles

2. **Phase 2**
   - **RP2D**: 2 mg/m^2 q2w + daunorubicin 30 mg/m^2 q2w + cytarabine 1,200 mg/m^2 q2w
   - **Total cycle**: 4 cycles

### References