Comparison of Efficacy and Safety Results in 103 Treatment-Naïve Acute Myeloid Leukemia (TN-AML) Patients Not Candidates For Intensive Chemotherapy Using 5-day and 10-day Regimens of Guadecitabine (SGI-110), a novel Hypomethylating Agent (HMA)

On Behalf of the SGI-110 Investigative Team

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Guadecitabine (SGI-110) - Background

- Next generation hypomethylating agents
- Dinucleotide of decitabine and deoxyguanosine=protects it from deamination=prolongs *in vivo* exposure of decitabine
- Prolonged decitabine exposure may translate into better efficacy
Guadecitabine- Phase 1 Pharmacokinetics
Prolonged Exposure Time of Decitabine Compared to IV Decitabine

- Decitabine exposure window after SC SGI-110 increased (11-12 h) compared to decitabine 20 mg/m^2 1-hr IV infusion (3-4h, simulated)
- Decitabine C_{\text{max}} less than one third of IV decitabine
- 4-fold increase in half life over decitabine IV

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Issa. Lancet Oncology 16:1099; 2015
Guadecitabine—Phase 1 Pharmacodynamics
Potent Dose-dependent LINE-1 DNA Demethylation

- LINE-1 demethylation increased with dose up to 60 mg/m² Daily x 5
- Maximum demethylation at 60 mg/m² Daily x 5 (BED)
Guadecitabine-Phase 2 Study in Rx-naïve AML

Major Eligibility
Elderly treatment naïve AML unfit for induction therapy

Randomization

Biologically Effective Dose
60 mg/m² daily x 5

Biologically Effective Dose
60 mg/m² 10-day regimen

10-day treatment continued for 2+ cycles, then daily x 5

Biologically Effective Dose
90 mg/m² daily x 5

Highest Well Tolerated Dose

Treatment continued until unacceptable toxicity, disease progression

IWG 2003 AML Response Criteria

• Primary Endpoint: Overall composite CR rate(CRc): CR + CRp + CRi
• Secondary Endpoints: LINE-1 demethylation, overall survival and safety

Data from randomized study previously presented (Yee et al EHA 2014) consolidated as the 5-Day regimen
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Guadecitabine - 10-day Regimen

Minimum 6 cycles

1-4 Cycles

10-Day Cycle (28 days)

D1-5 D8-12

Continue Until Progression or Unacceptable Toxicity

5-Day Cycle (28 days)

SGI-110

D1-5

SGI-110 60 mg/m²/d SQ Days 1-5 and 8-12, Q28 days for 1-4 cycles, followed by Rx on Days 1-5 Q28 days for a total of at least 6 cycles
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>5-day (n=51)</th>
<th>10-day (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, (range)</strong></td>
<td>78 (62-92)</td>
<td>77 (66-92)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>30 (59)</td>
<td>34 (65)</td>
</tr>
<tr>
<td>F</td>
<td>21 (41)</td>
<td>18 (35)</td>
</tr>
<tr>
<td><strong>ECOG PS, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (22)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>1</td>
<td>22 (43)</td>
<td>26 (50)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>18 (35)</td>
<td>21 (40)</td>
</tr>
<tr>
<td><strong>Poor CG, n (%)</strong></td>
<td>23 (45)</td>
<td>20 (38)</td>
</tr>
<tr>
<td><strong>Secondary AML, n (%)</strong></td>
<td>23 (45)</td>
<td>14 (27)</td>
</tr>
<tr>
<td><strong>Median BM % blast (range)</strong></td>
<td>40 (13-94)</td>
<td>49.5 (16-98)</td>
</tr>
<tr>
<td><strong>Median WBC (10⁹/L) (range)</strong></td>
<td>2.6 (0.7-50)</td>
<td>4.0 (0.5-87.7)</td>
</tr>
</tbody>
</table>

* 5-day data consolidated for 60 and 90 mg/m² doses

*As of cutoff date of November 2, 2015*
Guadecitabine - Phase 2 5-day and 10-day Regimens  
LINE-1 Demethylation in Cycle 1

In Rx- naïve AML, 10-day schedule (Days 1-5 and 8-12) shows longer duration of LINE-1 demethylation compared to 5-day

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## Guadecitabine - Phase 2 5-day and 10-day Regimens Response

<table>
<thead>
<tr>
<th>Response Category&lt;sup&gt;1&lt;/sup&gt;</th>
<th>5-day (n=51)</th>
<th>10-day (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>19 (37)</td>
<td>16 (31)</td>
<td>0.54</td>
</tr>
<tr>
<td>CRi</td>
<td>7 (14)</td>
<td>4 (8)</td>
<td>0.36</td>
</tr>
<tr>
<td>CRp</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>29 (57)</strong></td>
<td><strong>25 (48)</strong></td>
<td>0.43</td>
</tr>
</tbody>
</table>

<sup>1</sup>International Working Group 2003 AML Response Criteria
Guadecitabine - Phase 2 Study 5-day and 10-day Survival by Regimen

Product-Limit Survival Estimates
With Number of Subjects at Risk

Median F/U (mo)
Daily x5 30.1
10-day 16.8

Median Survival (mo)
5-day 10.5
10-day 9.5

Log-rank P = 0.70
Guadecitabine - Phase 2 Study 5-day and 10-day Survival by Response

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival (Days)

Survival Probability

Median Survival (mo)
CR 19.1
CRp + CRi 15.8
Other 3.1

Log-Rank P < 0.0001
### Guadecitabine - Phase 2 Study 5-day and 10-day Adverse Events Grade ≥ 3 in ≥ 10% 1

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>5-day (n=51) Grade ≥ 3 AEs %</th>
<th>10-day (n=52) 2 Grade ≥ 3 AEs %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

1 Regardless of relationship to guadecitabine

2 No significant differences between the 2 groups
<table>
<thead>
<tr>
<th></th>
<th>5-day (n=51)</th>
<th>10-Day (^1) (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day n (%)</td>
<td>3 (5.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>60-day n (%)</td>
<td>8 (15.7)</td>
<td>9 (17.3)</td>
</tr>
</tbody>
</table>

\(^1\) Differences not statistically significant between the 2 regimens
Guadecitabine (SGI-110) - Conclusions

• Next generation HMA with prolonged in vivo exposure to decitabine

• Potent demethylation with both 5-day and 10-day regimens at the 60 mg/m²/d dose.

• Both regimens well-tolerated

• Promising activity in poor prognosis elderly Rx-naive AML unfit for intensive chemoRx - No significant efficacy differences
  – 37% CR and 57% CRc with 5-day
  – 31% CR and 48% CRc with the 10-day

• Survival
  – Median survival similar ~ 10 m in poor prognosis unfit patients
  – CR > CRi > Others p < 0.0001

• AML: ASTRAL-1 Phase 3 Trial in Rx-Naïve AML unfit for intensive chemoRx using 5-Day regimen underway
Acknowledgements

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