Results of a Phase 1b/2 Study of Entospletinib Monotherapy and In Combination With Induction Chemotherapy In Newly Diagnosed Patients With Acute Myeloid Leukemia

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Background

- Acute myeloid leukemia (AML) is both a biologically and clinically heterogeneous hematologic malignancy.
- The identification of recurrent cytogenetic and molecular mutations has not only led to insights into leukemogenesis, but has identified potential therapeutic targets.
- Current treatment paradigms attempt to individualize therapy rather than a “one fits all” approach.

Investigating SYK as Critical Signaling Node in AML
Role of SYK in AML

- Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase primarily expressed in hematopoietic cells.

- Constitutive activation of SYK in AML has been reported; targeted inhibition of SYK-induced differentiation in vitro demonstrated anti-leukemia activity in AML mouse models.

- SYK promotes leukemogenesis by directly phosphorylating the FLT3 receptor, and inducing MEIS1 in conjunction with HOXA9 to form a regulatory loop in KMT2A (mixed lineage leukemia [MLL]) rearranged leukemia.

Entospletinib (ENTO): an Orally Bioavailable, Selective Inhibitor of SYK with Activity in Myeloid and B-lymphoid Malignancies

**ENTO: Syk-selective**

Syk $K_d = 7.6$ nM

No other kinases with $K_d < 100$ nM

**R406: non-selective**

Syk $K_d = 15$ nM

24 kinases with $K_d < 15$ nM

54 additional kinases with $K_d < 100$ nM

- **ENTO exposures approach a plateau above 600 mg BID**
- Biliary excretion is the major route of elimination
- Absorption is highly pH dependent: drug-drug interaction with PPIs- they decrease the absorption of ENTO by ~60%
- ENTO is an inhibitor of UGT1A1
- Clinical interactions with CYP inhibitors: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A

CYP, cytochrome p450; $K_d$, dissociation constant; PPI, proton pump inhibitor; UGT1A1, uridine diphosphate glucuronosyltransferase 1-1
Study Objectives

♦ Primary
  – To demonstrate the overall safety (Phase 1) and efficacy (Phase 2) of entospletinib in combination with standard dose cytarabine and daunorubicin chemotherapy (7+3) in patients with previously untreated AML fit for chemotherapy

♦ Secondary
  – To assess qualitative and quantitative toxicities of entospletinib as monotherapy and in combination with 7+3
  – To document therapeutic response of patients treated with ENTO as monotherapy and in combination with 7+3
Screen → Lead-in ENTO 14 d → Cycle 1–2 ENTO +7+3 → Post-Remission Therapy

- Treatment Failure (if completed 2 cycles of combination Rx)

- CR/CRi → No CR

- Allogeneic Stem Cell Transplant
  - ENTO + HiDAC*
  - CR MRD+
  - Maintenance ENTO x 1 y

- Phase 1b n=12
  - No acute promyelocytic (M3) or core binding factor leukemias

- Phase 2 n=41
  - All AML patients except M3

*HiDAC: 3 gm/m² <60 y; 1 gm/m² ≥60 y. CR, complete response; MRD, minimal residual disease.
## Results: Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>31 (58)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>60 (18, 78)</td>
</tr>
<tr>
<td>&lt;60 y, n (%)</td>
<td>26 (49)</td>
</tr>
<tr>
<td>≥60 y, n (%)</td>
<td>27 (51)</td>
</tr>
<tr>
<td>White/Caucasian, n (%)</td>
<td>47 (89)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (45)</td>
</tr>
<tr>
<td>1</td>
<td>27 (51)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Risk-group per ELN criteria, n (%)</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Intermediate I</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Intermediate II</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Adverse</td>
<td>18 (34)</td>
</tr>
<tr>
<td>Secondary AML, n (%)</td>
<td>14 (26)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; ENL, European Leukemia Net.
## Results: CR Rates by ELN Risk Group

<table>
<thead>
<tr>
<th>ELN Risk-Group</th>
<th>ENTO+7+3 CR% (n=53)</th>
<th>Historical (7+3 regimens) CR%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable-risk</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Intermediate-I</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Adverse-risk</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

*Adjusted to patients per age and risk-groups in our Phase 1b/2 study
## Results: CR Rates in Specific Molecular Subgroups

<table>
<thead>
<tr>
<th>Molecular Sub-Group</th>
<th>N</th>
<th>CR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary AML</td>
<td>14</td>
<td>64</td>
</tr>
<tr>
<td>De novo AML</td>
<td>39</td>
<td>72</td>
</tr>
<tr>
<td>KMT2A/MLL</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>NPM1+*</td>
<td>15</td>
<td>87</td>
</tr>
<tr>
<td>FLT3-ITD+</td>
<td>6</td>
<td>83</td>
</tr>
</tbody>
</table>

*4 patients with solitary NPM1+ without any concomitant mutations
### Results: Disposition After ENTO + 7+3

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of induction cycles</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42 (79)</td>
</tr>
<tr>
<td>2</td>
<td>9 (17)</td>
</tr>
<tr>
<td><strong>Received allogeneic SCT</strong></td>
<td>18 (34)</td>
</tr>
<tr>
<td><strong>No. of post-remission HiDAC cycles</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (11)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>3</td>
<td>7 (13)</td>
</tr>
<tr>
<td><strong>Received ENTO monotherapy maintenance</strong></td>
<td>6 (11)</td>
</tr>
</tbody>
</table>
ENTO Lead-in: No Effect on Efficacy

- No benefit as monotherapy: only 1 out of 53 patients responded to monotherapy

- 9 patients (17%) required hydroxyurea during lead-in

- 15 patients (28%) did not get full 14 days of lead-in ENTO either due to physician or patient preference
Overall Survival: After Median Follow-up of 14.3 Months Median OS Was Not Reached for Phase 1b/2 AML Patients (n=53)
Relapse-Free Survival: After Median Follow-Up of 13 Months
Median RFS is 7.7 Months for Phase 1b/2 AML Patients (n=53)
Safety: Grade ≥3 Treatment-Emergent Hematologic Toxicity
Adverse Events and Lab Abnormalities

- Adverse events consistent with expected effects of a myelosuppressive chemotherapy regimen

- 30-day induction mortality 0 %

<table>
<thead>
<tr>
<th>Grade ≥ 3 hematologic toxicity, n (%)</th>
<th>Total N=53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>44 (83)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41 (77)</td>
</tr>
</tbody>
</table>
Safety: Grade ≥ 3 Treatment-Emergent Lab Abnormalities and Non-hematologic toxicity

<table>
<thead>
<tr>
<th>Grade ≥ 3 non-hematologic toxicity, n (%)</th>
<th>Total N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>6 (11)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>3 (6)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
High H/M Expression in Phase 1b/2 AML Patients with MLL-R, NPM1, and FLT3-ITD Mutation

<table>
<thead>
<tr>
<th>Mutation*</th>
<th>CR %</th>
<th>CR/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL-R</td>
<td>90</td>
<td>9/10</td>
</tr>
<tr>
<td>NPM1</td>
<td>87</td>
<td>13/15</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>83</td>
<td>5/6</td>
</tr>
</tbody>
</table>

*Some patients have multiple mutations.
Conclusions

♦ CR rate 70% in untreated fit AML patients treated with ENTO+7+3

♦ Overall ENTO is well tolerated and 30-day induction mortality 0%

♦ Higher response rates with SYK inhibition in AML patients with high HOXA9/MEIS1 expression

♦ Potential role in subsets of AML: KMT2A/MLL and NPM1. Further development ongoing with the Leukemia Lymphoma Society and the BEAT-AML program
Acknowledgments

We extend our thanks to the patients and their families.

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We extend our thanks to Steve Abella, MD and A. Mario Marcondes, MD PhD for their help with the design and conduct of this study
BACK UP
## CR rates stratified by age and ELN risk-group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ELN Risk-Group</th>
<th>Phase 1 n=12</th>
<th>Phase 2 n=41</th>
<th>Combined CR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 60 yr</td>
<td>Favorable-risk CR/total</td>
<td>1/1</td>
<td>1/1</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Intermediate-I CR/total</td>
<td>0/0</td>
<td>4/4</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Intermediate-II CR/total</td>
<td>3/3</td>
<td>4/5</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>Adverse-risk CR/total</td>
<td>2/3</td>
<td>3/9</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>Combined CR/total</td>
<td>6/7 (86%)</td>
<td>12/19 (63%)</td>
<td>69%</td>
</tr>
<tr>
<td>Age &gt;= 60 yr</td>
<td>Favorable-risk CR/total</td>
<td>2/2</td>
<td>2/3</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Intermediate-I CR/total</td>
<td>0/0</td>
<td>9/12</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Intermediate-II CR/total</td>
<td>1/1</td>
<td>1/3</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Adverse-risk CR/total</td>
<td>1/2</td>
<td>3/4</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Combined CR/total</td>
<td>4/5 (80%)</td>
<td>15/22 (68%)</td>
<td>70%</td>
</tr>
</tbody>
</table>

| Total | 10/12 (83%) | 27/41 (66%) | 70% |