Complete Responses in Relapsed/ Refractory Acute Myeloid Leukemia (AML) Patients on a Weekly Dosing Schedule of Vibecotamab (XmAb® 14045), a CD123 x CD3 T Cell-Engaging Bispecific Antibody; Results of a Phase 1 Study

Farhad Ravandi¹, Asad Bashey², Wendy Stock³, James Foran⁴, Raya Mawad⁵, Daniel Egan⁵, William Blum⁶, Raphael Clynes⁷, Raman Garcha⁷, Ying Ding⁷, Alessandro Pastore⁸, Chelsea Johnson⁷, Shuo Zheng⁷, Musa Yilmaz¹, and Alice S. Mims⁹

¹U of TX-MD Anderson CC, Houston, TX; ²Acute Leukemia and BMT Program at Northside Hospital, Atlanta, GA; ³University of Chicago, Chicago, IL; ⁴Mayo Clinic, Jacksonville, FL; ⁵Swedish Cancer Institute, Seattle, WA; ⁶Winship Cancer Institute, Emory University, Atlanta, GA; ⁷Xencor, Inc., Monrovia, CA; ⁸Novartis Institutes for Biomedical Research, Cambridge, MA; and ⁹Ohio State University, Columbus, OH.
**XmAb®14045 (SQZ622): CD123 x CD3 Bispecific Antibody**

**CD123 (IL-3 receptor α subunit)** found on early hematopoietic precursor cells and basophils

**CD3-binding single chain Fv domain**

**CD123-binding Fab domain**

*Full-length immunoglobulin molecule designed to be dosed intermittently*

*Stimulates targeted T cell-mediated killing of CD123-expressing cells, regardless of T cell antigen specificity*

*Ablation of Fcγ receptor binding removes potential for receptor-mediated crosslinking and non-specific activation of T cells*

Frequently expressed on hematologic malignancies, including:

- Acute myelogenous leukemia (96-98% cases)
- Myelodysplastic syndrome (>50%)
- B-cell acute lymphoblastic leukemia (82-100%)

**Potential target for novel therapeutic strategies**
XmAb14045 Phase 1 Design

**Objectives**

**Primary**
- First infusion MTD and safety
- Second and subsequent infusion MTD and safety

**Secondary**
- PK, PD, immunogenicity
- Preliminary anti-tumor activity

**Exploratory**
- Lymphocyte subsets and T-cell activation
- Cytokine/immunologic profiles
- Effect on immune checkpoint expression
- Effect on stem cell numbers

**Eligibility**

**Inclusion criteria**
- Eligible diseases:
  - AML (excluding APL)
  - B-cell ALL
- ECOG PS 0-2
- Relapsed or refractory
- Prior allogeneic transplant allowed

**Exclusion criteria**
- Antineoplastic treatment within 2 weeks
- Known uncontrolled CNS involvement by tumor
- AST/ALT > 3.0 x ULN, Bili > 1.5, Cr > 2.0 x ULN or Clcr > 40; Absolute blast count ≥ 10K or leukostasis
- Prior therapy with CD123-directed therapies
114 subjects dosed
(as of 28OCT2020)

Safety analysis included all subjects that received at least 1 dose of XmAb14045

Efficacy analysis included all patients who:
- have completed at least the first cycle (4 doses for Parts A and B; 8 doses for Part C; 6 doses for Part D; and 7 doses for Part E)
- had at least one post-treatment disease assessment (occurs at the end of odd-numbered cycles)

Dosing regimen*
- Cycle length = 28 days
- Doses infused over 2 hours
- Intratreatment dose escalation allowed

*Cycle length = 28 days
Doses infused over 2 hours
Intrapatient dose escalation allowed
# Demographics (Safety Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=112) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median [min, max]</td>
<td>64 years [18, 85]</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53 (47)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>AML*</td>
<td>112 (100)</td>
</tr>
<tr>
<td><strong>Time since initial diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Median [min, max]</td>
<td>48 weeks [3, 896]</td>
</tr>
<tr>
<td><strong>Number of prior therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Median [min, max]</td>
<td>3 [0, 8]</td>
</tr>
<tr>
<td><strong>History of hematopoetic stem cell transplantation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (30)</td>
</tr>
<tr>
<td><strong>Refractory to last therapy (per investigator)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96 (86)</td>
</tr>
<tr>
<td><strong>ELN risk category</strong></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>33 (30)</td>
</tr>
<tr>
<td>Adverse</td>
<td>69 (62)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (5)</td>
</tr>
<tr>
<td><strong>Secondary leukemia</strong></td>
<td>15 (13)</td>
</tr>
</tbody>
</table>

*One B-ALL and one CML in blast phase patient were enrolled/treated, but not included in this analysis. Data as of 28 OCT 2020.
## Safety Data: Related TEAEs Occurring in ≥10% of Subjects

### AML Safety Population (N=112)

<table>
<thead>
<tr>
<th>Event</th>
<th>Any grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Grade 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome*</td>
<td>68 (60.7)</td>
<td>8 (7.1)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Chills</td>
<td>44 (39.3)</td>
<td>1 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32 (28.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT Increased</td>
<td>23 (20.5)</td>
<td>5 (4.5)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>22 (19.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>21 (18.8)</td>
<td>3 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (17.9)</td>
<td>1 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST Increased</td>
<td>18 (16.1)</td>
<td>5 (4.5)</td>
<td>3 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (16.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (16.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>16 (14.3)</td>
<td>14 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16 (14.3)</td>
<td>3 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT Increased</td>
<td>15 (13.4)</td>
<td>4 (3.6)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (11.6)</td>
<td>5 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13 (11.6)</td>
<td>1 (0.9)</td>
<td>10 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>13 (11.6)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Primary toxicity continues to be cytokine release syndrome (CRS)
  - observed in 60.7% of subjects
- No evidence of drug-related myelosuppression
- ≥ Grade 3 transaminase elevation X 15 events
  - All but 2 events resolved within 7 days
  - Most likely to be a component of CRS
- Neurologic events: most common was headache seen in 14.3% of subjects

*CRS Revised Grading System (Lee DW et al. Blood 2014;124:188)

Data as of 28 OCT 2020,
Safety Data: Priming Dose, Dosing Visit and IL-6 Levels

- Using IL-6 as a predictive biomarker of CRS (IL-6 > 1000 pg/ml)

- IL-6 peaks at priming dose of 0.75 µg/kg and weekly step-up dosing

- 1st week QOD dosing prevents CRS even with step-up dosing
Safety Data: Weekly Dosing and IL-6 Levels

• Across all cohorts, 4.5% of stable weekly dose had IL6>1000 pg/ml *

**0.75→ 1.3→ 2.3→

• Across all cohorts, 15 % of weekly step-up events had IL-6>1000 pg/ml

1.3 → 2.3→ 1.3 → 2.3 → 4→ 1.3 → 2.3 → 4 → 7 1.3 → 4 → 7 → 12

*up to 2.3ug/kg and before C2D1
**Doses in µg/kg
Safety Data: Dosing Visit and CRS

Priming Dose = 0.75 µg/kg

Increased frequency and grade of CRS in higher priming dose and in subsequent weekly step-up dosing

Data as of 28 OCT 2020
Challenge:
- Addressing the known need for priming doses in CRS complicated by the short $t^{1/2}$ of XmAb®14045; deep antigen sink

Mitigations:
- Continued evaluation of dose and scheme
- Lowered priming dose and stop escalation prior to weekly dosing
- More frequent dosing the first week to enable higher cumulative exposure in week 1
Efficacy Data

- Objective response rate (CR + CRi+MLFS+PR) dosed at ≥0.75 µg/kg = 14.8% (8/54 patients)

- ORR in blast count ≤ 25% population = 25.9% (7/27 patients)

- Stable Disease in an additional 38 patients (70.4%)

- Reduction of marrow blasts in 52% of patients

Data as of 28 OCT 2020

Regarding PR response; Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%
Data as of 28 OCT 2020
AML Evaluable Population 8A-1D Cohort (N=54)

*Regarding the PR response; Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%
# XmAb14045/SQZ622 Data by Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>8A</th>
<th>9A</th>
<th>10A</th>
<th>1B</th>
<th>2B</th>
<th>3B</th>
<th>4B</th>
<th>9C</th>
<th>10C</th>
<th>1D</th>
<th>Proposed 1E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C1 (Wk 1)</strong> Cumulative Dose (µg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.48 (3.98)</td>
</tr>
<tr>
<td></td>
<td>3 (0.75)</td>
<td>5.2 (1.3)</td>
<td>9.2 (2.3)</td>
<td>8.2 (1.3)</td>
<td>11.6</td>
<td>14.6</td>
<td>24.3 (1.3)</td>
<td>5.2 (1.29)</td>
<td>9.2 (2.31)</td>
<td>15.6 (3.55)</td>
<td></td>
</tr>
<tr>
<td>Total Efficacy Evaluable</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>CR+CRi+MLFS+PR</td>
<td>1 (MLFS)</td>
<td>2 (CR, CRi)</td>
<td>1 (CR)</td>
<td>1 (CRi)</td>
<td>0</td>
<td>0</td>
<td>1 (MLFS)</td>
<td>0</td>
<td>1 (CRi)</td>
<td>0</td>
<td>2 (PR**, CR***)</td>
</tr>
<tr>
<td>Efficacy Evaluable (≤25% blast*)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Baseline % Blast for Responders</td>
<td>4%</td>
<td>7.5%, 10%</td>
<td>25%</td>
<td>16%</td>
<td>5%</td>
<td>8%</td>
<td>60%</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Baseline aspirate or core %blast ≤25%

**Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%**

***Patient in 1D achieved CR, however, missed 2 doses so was not efficacy evaluable***

Data as of 28 OCT 2020
Responders Associated with Low absolute Blast Counts

Baseline leukemic burden of bone marrow is most associated with nonresponse.

Blood

Bone Marrow

Blast Percent in Blood
p-value Wilcoxon: 0.007061, t-test: 4e-06

nonresponder
responder

Blast Percent in Bone Marrow
p-value Wilcoxon: 0.014353, t-test: 0.025337

nonresponder
responder
Responders Associated with Low PD-1 Expression on CD8 and CD4 T Cells
AML Blast Count % in Marrow vs % PD1+ of CD8+ Cells in Blood*

- Suggests:
  - low blast and PD-1 appear to be independent predictors of response
  - 2 preliminary cut offs for selecting patients who could benefit
  - needs further study

*Efficacy evaluable population
Conclusions

• XmAb14045 has clinical activity in relapsed AML
  - ORR AML with ≤ 25% blast count = 25.9%
• Activity in low blast AML suggests potential opportunity in MDS and MRD
  - 7/8 responders had blast count ≤ 25%
• CRS is the primary toxicity of XmAb14045
• CRS mitigation strategy is effective in limiting severity
  - Lowered priming dose, intermittent dosing QOD & no weekly step ups
  - Enables bolus dosing
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