Maturing Clinical Profile of IMGN779, a Next-Generation CD33-Targeting Antibody-Drug Conjugate, in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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CD33-Targeting ADCs in AML

- CD33 is a sialic acid binding receptor, expressed on the surface of the majority of AML blasts
- CD33 is an established ADC target in AML, as evidenced by the recent re-approval of gemtuzumab ozogamicin (Mylotarg®)
- Safety and efficacy limitations of existing CD33-targeting ADCs → opportunity for improvement
- Next generation CD33-directed ADCs with alternate MOAs and broader therapeutic windows may provide additional benefit for patients

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IMGN779
A Next-Generation CD33-Targeting ADC

- High-affinity, humanized anti-CD33 antibody
- Novel DNA-alkylating payload, DGN462, with potent preclinical anti-leukemia activity
- IGNs: novel cytotoxic payload class
  - single strand DNA breaks (vs. double strand breaks)
  - better therapeutic index relative to cross-linking payloads

1 Miller 2016 Mol Cancer Ther 15:1870-78; 2 Miller 2018 Mol Cancer Ther 17:650-660
IMGN779 Phase 1 Study

Study Objectives

Primary

• Establish the MTD and RP2D of IMGN779 administered as monotherapy using once every two weeks (Q2W) and once weekly (QW) dosing schedules

Secondary

• Evaluate safety and tolerability of IMGN779, including determination of dose-limiting toxicities (DLT)

• Characterize the preliminary antitumor activity, pharmacokinetic (PK), and pharmacodynamic (PD) profiles
IMGN779 Phase 1 Study
Study Design

• Adults (≥18 years) with relapsed or refractory CD33+ AML
• CD33+ defined as ≥20% of blasts expressing CD33 by local flow cytometry
• Dose escalation follows a 3+3 design
• Two schedules tested
  - Q2W: administered i.v. on Days 1 and 15 of a 28-day cycle
  - QW: administered i.v. on Days 1, 8, 15, and 22 of a 28-day cycle
**IMGN779 Phase 1 Study**  
**Dose Escalation and Patient Allocation**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0.02</th>
<th>0.04</th>
<th>0.08</th>
<th>0.16</th>
<th>0.26</th>
<th>0.39</th>
<th>0.54</th>
<th>0.7</th>
<th>0.91</th>
<th>1.2</th>
<th>1.5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2W schedule</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5*</td>
<td>3</td>
<td>3</td>
<td>4*</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>QW schedule</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7*</td>
<td>6*</td>
<td>5*</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>21</td>
</tr>
</tbody>
</table>

* Includes replaced and expansion patients

- Based on PK/PD and safety data through 0.54 mg/kg Q2W, opening of the QW schedule was initiated at the 0.39 mg/kg dose

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# IMGN779 Phase 1 Study

## Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median [range], or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68 [26-88]</td>
</tr>
<tr>
<td>Sex</td>
<td>31 (54)</td>
</tr>
<tr>
<td>Prior therapy*</td>
<td></td>
</tr>
<tr>
<td>Non-intensive only</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Intensive</td>
<td>40 (70)</td>
</tr>
<tr>
<td>Prior SCT</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>First relapse</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Relapsed refractory</td>
<td>28 (49)</td>
</tr>
</tbody>
</table>

* Non-intensive therapy includes HMA, IDH inhibitors; intensive therapy includes 7+3, HiDAC, Vyxeos, SCT

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Plasma IMGN779 concentrations indicate consistent and sustained exposure through 7 days at doses ≥0.39 mg/kg.

With QW dosing, trend for modestly higher end of infusion values with 0.39 mg/kg compared to Q2W schedule; similar for 0.54 and 0.7 mg/kg doses.
**IMGN779 Phase 1 Study**

**Pharmacodynamics: CD33 saturation**

**Schedule A - Q2W**

- Cohort A6 (0.39 mg/kg)
- Cohort A7 (0.54 mg/kg)
- Cohort A8 (0.70 mg/kg)
- Cohort A9 (0.91 mg/kg)
- Cohort A10 (1.2 mg/kg)
- Cohort A11 (1.5 mg/kg)

**Schedule B - QW**

- Cohort B1 (0.39 mg/kg)
- Cohort B2 (0.54 mg/kg)
- Cohort B3 (0.70 mg/kg)
- Cohort B4 (0.91 mg/kg)

- Q2W Schedule: Complete CD33 saturation is transient (<14 days)
- QW Schedule: More consistent saturation than Q2W schedule

**Preliminary analyses**

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Treatment-Emergent Adverse Events >15%

- Febrile neutropenia
- Epistaxis
- Nausea
- Diarrhea
- Fatigue
- Abdominal pain
- Constipation
- Hyperbilirubinemia
- Hypokalemia
- Hypotension
- Vomiting
- Bacteremia
- Alkaline phosphatase increased
- Pneumonia
- Rash

Related Grade 3+4
Related Grade 1+2
Grade 5
Grade 3+4
Grade 1+2
Related TEAE vs TEAE >=15% (N=57)
IMGN779 Phase 1 Study
Safety Summary

- Median number of doses administered: 4 (range, 1-40)
- Most frequent SAEs infection-related: febrile neutropenia (37%), bacteremia (14%), and pneumonia (14%)
  - Three SAEs considered related to IMGN779: Grade 3 infusion-related reaction (n=2), and febrile neutropenia (n=1)
- No pattern of dose-dependent hepatotoxicity
  - Hyperbilirubinemia (19%), ALT elevation (14%)
  - One DLT (1.2 mg/kg QW): VOD with acute kidney injury (fatal)
- 10 deaths within 30 days of last dose: pneumonia / respiratory (n=6), sepsis / multi-organ (n=2), VOD (n=1) and myocardial infarction (n=1)
IMGN779 Phase 1 Study
Best Decrease in Bone Marrow Blasts
(Q2W and QW dosing, ≥0.39 mg/kg)

Maximum decrease in BM blasts (%)

Dose (mg/kg)

QW dosing
Q2W dosing

* <8% residual blasts

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IMGN779 Phase 1 Study
Time on Study (Q2W and QW dosing, ≥0.39 mg/kg)

Schedule
- Q2W
- QW

Dosing
- CRi
- SD
- PD

Response
- CRi
- SD
- PD

Dose Level (mg/kg)
- 0.39
- 0.54
- 0.70
- 0.91
- 1.20
- 1.50

Time on Study (weeks)
- 0
- 4
- 8
- 12
- 16
- 20

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IMGN779 Phase 1 Study
Conclusions

• IMGN779 displays tolerability with repeat dosing across a wide range of doses in patients with relapsed AML
  - Limited cytopenias, one DLT reported
  - AEs consistent with underlying disease
  - No cumulative toxicity following multiple doses (up to 40 doses)

• IMGN779 demonstrates anti-leukemia activity in 41% (12 of 29) patients with evaluable bone marrows (≥0.39 mg/kg), although with limited CR/CRis at doses examined to date

• Enrollment continues to identify the RP2D and schedule, which may warrant further development as combination therapy in AML
Thank you to the patients and families