IMGN779, a Next-Generation CD33-Targeting Antibody-Drug Conjugate, Demonstrates Initial Antileukemia Activity in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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BACKGROUND
Acute myeloid leukemias (AML) account for the highest number of leukemia-related deaths. Despite standard chemotherapy options and newly approved agents, outcomes remain poor, particularly in patients unable to tolerate intense chemotherapy and stem cell transplantation.

Antibody-drug conjugates (ADCs) are engineered molecules consisting of a monoclonal antibody, directed towards tumor-associated antigens, to which cytotoxic agents are conjugated via pharmaceutically acceptable linkers. In this manner, ADCs deliver potent antileukemia activity that results in cell cycle arrest and apoptosis, with relative sparing of normal hematopoietic progenitors.

Novel IGN payload class
DGN462 is prototypical of a novel chemical class of cytotoxic agents, known as IGNs, that consist of a DNA-alkylating payload that, when released within AML cells exerts potent antileukemia activity that results in cell cycle arrest and apoptosis, with relative sparing of normal hematopoietic progenitors.

IMGN779 reflects the evolution of ADC design combining several key attributes:
1) a high-affinity, antibody-dependent cell mediated cytotoxicity (ADCC)-competent, humanized anti-CD33 antibody which is distinct from other CD33-targeting antibodies currently in clinical trials; and
2) a novel DNA-alkylating payload DGN621, which when released within AML cells elicits potent antileukemia activity that results in cell cycle arrest and apoptosis, with relative sparing of normal hematopoietic progenitors.

First-in-human trial
Here we report early-phase findings from the dose-escalation stage of the first-in-human Phase 1 study of IMGN779 administered as monotherapy to adult AML patients with CD33–positive (CD33+) disease.

Primary objectives:
To establish the MTD and define the recommended Phase 2 dose (RP2D) of IMGN779 when administered as monotherapy on both once every two weeks (Q2W) and once weekly (QW) schedules.

Secondary objectives:
To evaluate the safety and tolerability of IMGN779 and characterize its pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antileukemia activity.

Objectives, Patient Population, and Methods

Primary endpoints: To establish the MTD and define the recommended Phase 2 dose (RP2D) of IMGN779 when administered as monotherapy on both once every two weeks (Q2W) and once weekly (QW) schedules.

Secondary objectives: To evaluate the safety and tolerability of IMGN779 and characterize its pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antileukemia activity.

Trial Design:
• Adult patients (≥18 years) with relapsed or refractory AML; and
• CD33+ AML is defined as ≥35% of AML blasts expressing CD33 by flow cytometry.

Dose escalation follows a standard 3+3 design.

Cycle 1 Exposure

Cycle 2 Exposure

Cycle 3 Exposure

Cycle 4 Exposure

IMGN779 administered IV QW on Days 1, 8, 15, and 22 of a 28-day cycle

Dosing and Patient Allocation

Demographics

<table>
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<th>Age (years)</th>
<th>%</th>
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<tbody>
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<td>18-20</td>
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<td>21</td>
<td>(8)</td>
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</tbody>
</table>

Concomitant medications

Primary objectives: To establish the MTD and define the recommended Phase 2 dose (RP2D) of IMGN779 when administered as monotherapy on both once every two weeks (Q2W) and once weekly (QW) schedules.

Secondary objectives: To evaluate the safety and tolerability of IMGN779 and characterize its pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antileukemia activity.

Cycle 1 Exposure

Cycle 2 Exposure

Cycle 3 Exposure

Cycle 4 Exposure

IMGN779 administered IV QW on Days 1, 8, 15, and 22 of a 28-day cycle

Pharmacokinetics and Pharmacodynamics

• Continued increases in maximal concentrations and exposure through the highest dose level observed in the dose-escalation stages (0.39 mg/kg QW)

• Increased duration of CD33 saturation with increased dosing

Antileukemia Activity

• No increase in the nature, frequency, or severity of any treatment-emergent adverse events (TEAEs) observed with increasing dose

• No DLTs have been observed on either administration schedule at doses ≤0.39 mg/kg

• In addition, 1 patient treated at a lower dose (0.16 mg/kg Q2W) showed a 93% decrease in peripheral blasts within 10 days after first dose (median maximal decrease [16% to 100%])

CONCLUSIONS

These findings reflect the first-in-human clinical experience with a next-generation CD33-targeting ADC, IMGN779, in relapsed or refractory adult AML.

References:
1. Tindle et al. (2017)

59th ASH Annual Meeting, December 9-12, 2017
The authors would like to especially thank the patients who have consented to be included in this study, as well as their families.

Saturday Dec 9, 5:30-7:30pm, GWCC – Bldg A – Hall A2

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