Initial results from a first-in-human study of IMGN779, a CD33-targeting antibody-drug conjugate (ADC) with novel DNA alkylation activity, in patients with relapsed or refractory AML

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Abstract P562

BACKGROUND
Acute myeloid leukemia (AML) accounts for the highest number of leukemia-related deaths. Despite standard chemotherapy options, outcomes remain poor, particularly in patients unable to tolerate intense chemotherapy and stem cell transplantation. Thus, there is a need to improve outcomes in these patients with more targeted therapy that delivers potent anti-leukemia activity with a tolerable safety profile.

One clinically validated approach entails the use of antibody-drug conjugate (ADC) technology. ADCs are engineered molecules consisting of a monoclonal antibody, directed towards tumor-associated antigens, to which cytotoxic agents are conjugated via a cell-penetrable linkage. This review, ADCs couple the targeting and pharmacokinetic features of the antibody moiety with the intracellular anticancer impact of the cytotoxic payload.

The myeloid differentiation antigen CD33 is a validated AML target, with CD33 expression in greater than 90% of AML cases and clinical activity demonstrated with both CD33-targeting ADCs.

IMGN779: The Next Generation CD33-Targeting ADC

IMGN779 reflects the evolution of ADC design combining several key attributes:
- A high-affinity, humanized CD33 antibody.
- A stable, secondary aminooxy polyvalent payload which has demonstrated achievable pre-clinical maximum tolerable dose (MTD) and reductions in hepatotoxicity compared to non-cleavable linkers
- A novel DNA-alkylating payload DOGN32, which, when released within AML cells, results potent anti-leukemia activity that results in cell cycle arrest and apoptosis, with relative sparing of normal hematopoietic progenitors.

Novel IGN payload class
DOGN32 is prototypic of a novel chemical class of cytotoxic agents, known as IGNs, that consist of an indolino-benzodiazepine dimer containing a mono-imine moiety. IGNs are designed to exhibit unique DNA alkylating activity, in patients with relapsed or refractory AML.

Objectives, Patient Population, and Methods

Primary objectives: To establish the MTD and define the recommended phase 2 dose (RP2D) of IMGN779 when administered as monotherapy

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

Trial design:
- Only adult patients (≥ 18 years) with relapsed or refractory AML expressing CD33 (CD33+)

Following first-in-human Phase 1 study of IMGN779 administered as monotherapy to adult patients with relapsed or refractory AML expressing CD33 (CD33+). IMGN779 administered intravenously for <2 hours, once every two weeks on days 1 and 15 of a 28-day cycle. Escalation commenced with a starting dose of 0.02 mg/kg; low starting dose chosen based on first-in-human (FIH) phase 1 study of IMGN779.\(^2\)

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

No DLTs have been observed through Cohort 7 (0.54 mg/kg)
- Adverse events were consistent with the underlying disease
- No increase in the number, frequency, or severity of any treatment-emergent adverse event has been observed with increasing dose
- No evidence of cumulative toxicity with repeated dosing
- Favorable PK/PD reveal prolonged exposure and CD33 saturation in cohorts 6-7

Initial anti-leukemia activity was observed in cohorts 6+7 in three patients who achieved complete remission (CR) after second dose (day 15).

No deaths related to study drug. Four deaths occurred during the treatment period for reasons other than progressive disease; two respiratory failures, one sepsis, one renal failure.

Treatment-Emergent Adverse Events (TEAEs) >10%

- Cytopenias: neutropenia (39%), anemia (17%), thrombocytopenia (9%)
- Respiratory: pneumonia (22%), respiratory failure (17%)
- Hematologic: febrile neutropenia (39%), febrile neutropenic infection (17%)
- Gastrointestinal: constipation (22%), diarrhea (22%), abdominal pain (17%)
- Peripheral blood blasts progressed after the first 3-8 days of first dose.
- Five patients whose peripheral blood blasts disappeared after the first dose (day 3); all showed decreased blasts after second dose (day 15).

The authors would like to especially thank the patients who have consented to be included in this study, as well as their families.

References:

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Notes on page for all figures IPOD 2017, the expected to be the end of the year 2017″ / June 7, 2017.

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