Abstract 1312

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

Jorge E. Cortes[1], Elie Traer[2], Eunice S. Wang[3], Harry P. Erba[4], William Blum[5], Cecilia Arana-Yi[6], Callum M. Sloss[7], Kerry Culm-Merdek[7], Jeanette Towles[7], Patrick A. Zweidler-McKay[7], and Daniel J. DeAngelo[8]

[1]MD Anderson Cancer Center, Houston, TX; [2]Oregon Health and Science University, Portland, OR; [3]Roswell Park Cancer Institute, Buffalo, NY; [4]University of Alabama at Birmingham, Birmingham, AL; [5]The Ohio State University, Columbus, OH; [6]University of New Mexico Cancer Center, Albuquerque, NM; [7]ImmunoGen Inc., Waltham, MA; [8]Dana-Farber Cancer Institute, Boston, MA

BACKGROUND

Acute myeloid leukemia (AML) accounts 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 plasma-stable linkage. In this manner, ADCs couple the targeting and pharmacokinetic features of the antibody moiety with the additional cancer-killing impact of the cytotoxic payload.

The myeloid differentiation antigen CD33 is an established therapeutic target in AML, with CD33 expression seen in greater than 90% of AML cases and clinical validation provided by the recent re-approval of the CD33-targeting ADC gemtuzumab ozogamicin (Mylotarg®). Next generation CD33-directed ADCs with novel mechanisms and improved safety profiles may provide additional benefit.

IMGN779: The Next Generation CD33-Targeting ADC

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;

2) a cleavable s-SPDB linker which increases the preclinical maximum tolerated dose (MTD), facilitates bystander killing of nearby AML cells, and limits hepatotoxicity compared to noncleavable linkers; and

3) a novel DNA-alkylating payload DGN462, which when released within AML cells exerts 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 an indolino-benzodiazepine dimer containing a mono-imine moiety.[1] IGNs are purpose-designed to exhibit unique DNA-alkylating activity and a high therapeutic index when compared with DNA cross-linking versions.[2]

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 (NCT02674763).

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 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 antitumor activity

Trial Design:

- Adult patients (≥18 years) with relapsed or refractory CD33$^+$ AML are eligible to enroll
- CD33$^+$ AML is defined as ≥20% of AML blasts expressing CD33 by flow cytometry
- Dose escalation follows a standard 3+3 design
- Escalation commenced with a starting dose of 0.02 mg/kg

Treatment:

- IMGN779 administered intravenously (IV) Q2W on Days 1 and 15 of a 28-day cycle
- IMGN779 administered IV QW on Days 1, 8, 15, and 22 of a 28-day cycle

Note: Data cut for all figures 27 Oct 2017, with the exception of the bone marrow blast results (07 Nov 2017)

Dosing and Patient Allocation

Dose (mg/kg)	0.02	0.04	0.08	0.16	0.26	0.39	0.54	0.7	0.91	Total
Q2W schedule, *n*	3	3	3	3	5*	3	3	4*	3	30
QW schedule, *n*	-	-	-	-	-	6*				6

* patients replaced due to not completing the DLT period (not for DLT)

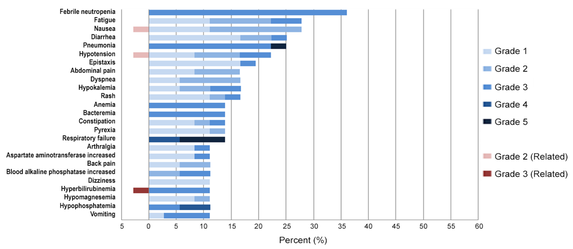
Based on PK/PD and safety data through 0.54 mg/kg Q2W, opening of the QW schedule was initiated at the 0.39 mg/kg dose. Enrollment on both schedules is continuing.

Demographics

Characteristic	Patients (n = 36)* No.	%
Age, years		
Median (range)	67 (34-81)	
Sex		
Female	20	56
Male	16	44
Race		
White	32	89
Black	2	6
Hawaiian/Pacific Islander	1	3
Other	1	3
Prior therapy		
Treatment naive	0	0
Non-intense therapy only (Aza, Dec, IDHi, *etc.*)	10	28
Intense (7+3, HiDAC, SCT, *etc.*)	26	72
Prior stem cell transplant	(6)	(17)
Disease status		
de novo	0	0
First relapse	9	25
Primary refractory	11	31
Relapsed refractory	16	44

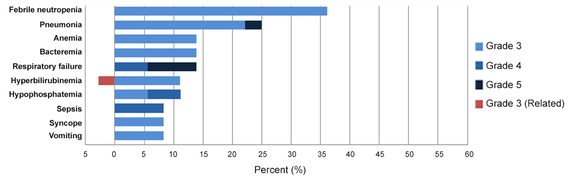
*Note: all patients (Q2W and QW) are combined for demographics

Treatment-Emergent Adverse Events (TEAEs) >10%



- Frequent TEAEs (N=36):
  - Cytopenias: febrile neutropenia (n=13), anemia (n=5)
  - Gastrointestinal: nausea (n=10), diarrhea (n=9), abdominal pain (n=6), constipation (n=5), vomiting (n=4)
  - Respiratory: pneumonia (n=9), dyspnea (n=6), respiratory failure (n=5)

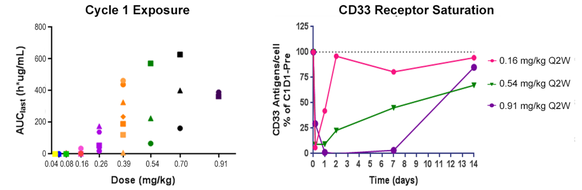
Grade 3$^+$ TEAEs (>2 patients)



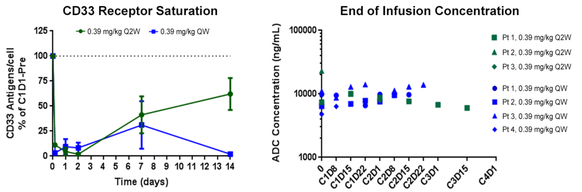
- **AEs of interest (N=36):**
  - Infusion reaction (n=1; related, Grade 3, no recurrence on rechallenge)
  - Isolated TBili elevation (n=4; 1 related, all Grade 3)
  - Isolated ALT elevation (n=1; Grade 3)
- **Frequent SAEs:**
  - Febrile neutropenia (n=13), pneumonia (n=8), respiratory failure (n=5), and bacteremia (n=4)
- **DLTs:** No DLTs have been observed at doses up to 0.91 mg/kg Q2W and 0.39 mg/kg QW
- **Deaths:** Five deaths occurred during the treatment period for reasons other than progressive disease; none was considered related to study drug

Pharmacokinetics and Pharmacodynamics

- Continued increases in maximal concentrations and exposure through the highest doses given to date (0.91 mg/kg Q2W)
- Increased duration of CD33 saturation with increased dosing

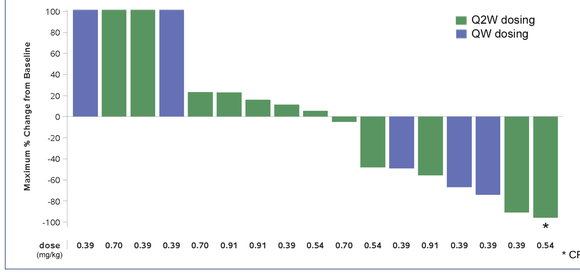


- Weekly dosing increases duration of saturation compared with Q2W dosing
- No substantial ADC accumulation with repeated weekly dose cohort (0.39 mg/kg QW) when compared with every other week (0.39 mg/kg Q2W)



Antileukemia Activity (≥0.39 mg/kg)

- **Circulating blasts**
  - Sixteen of 17 patients treated at 0.39 mg/kg or above showed a decrease in peripheral blasts within 10 days after first dose (median maximal decrease 71% [16% to 100%])
- **Bone marrow blasts**
  - Seven of 17 patients showed a 48%-96% reduction in bone marrow blasts. Of these 7, prior intense treatment (n=6), primary-refractory disease (n=3), mutations present: RAS (n=3), TP53 (n=2), IDH (n=2), FLT3 (n=2)
  - In addition, 1 patient treated at a lower dose (0.16 mg/kg Q2W) showed a 93% (48% to 3%) reduction in bone marrow blasts with extended treatment (Cycle 5) and continues on treatment through Cycle 14



CONCLUSIONS

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

- IMGN779 displays a tolerable safety profile
  - No DLTs have been observed on either administration schedule at doses examined to date
  - No increase in the nature, frequency, or severity of any treatment-emergent adverse event has been observed with increasing dose
- PK exposures and PD CD33 saturation continue to increase with dose and support further escalation and exploration of QW and Q2W schedules
- Antileukemia activity was seen at doses ≥0.39 mg/kg in both schedules in seven patients with poor prognostic features (e.g. prior intense therapy, primary refractory disease, RAS/TP53/FLT3/IDH mutations)

PK, PD, and antileukemia activity alignment, along with cumulative safety, support further escalation in both schedules which is ongoing.

Pre-clinical abstract 1357

IMGN779, A Next Generation CD33-Targeting ADC, Combines Effectively With Cytarabine in Acute Myeloid Leukemia (AML) Preclinical Models, Resulting in Increased DNA Damage Response, Cell Cycle Arrest and Apoptosis In Vitro, and Prolonged Survival In Vivo
Saturday Dec 9, 5:30-7:30pm, GWCC – Bldg A – Hall A2

References: 1. M Miller et al. (2016) *Mol Cancer Ther* 15:1870-78; 2. S Adams et al. (2017) *22nd EHA Annual Meeting* [abstract 526]

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.