Abstract 1334

A Phase I Study of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia, Blastic Plasmacytoid Dendritic Cell Neoplasm, and Other CD123-Positive Hematologic Malignancies

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BACKGROUND

CD123, the alpha-subunit of interleukin-3 receptor (IL3RA), is expressed in the majority of acute myeloid leukemia (AML) and B- and T-cell acute lymphoblastic leukemia (ALL) cases, and nearly all blastic plasmacytoid dendritic cell neoplasm (BPDCN) with the highest CD123 levels in the latter.[1,2]

IL3R/CD123 is a clinically validated target in BPDCN.

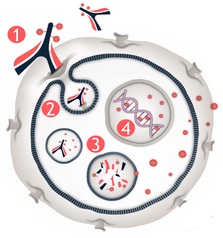
CD123 expression is elevated on AML blasts and leukemic stem cells compared with normal hematopoietic stem and progenitor cells. Recent studies indicate that CD123 may contribute to the proliferative advantage of leukemic cells. [3]

CD123 is rapidly internalized making it well suited for antibody-drug conjugate (ADC)-based therapeutic strategies. [4]

IMGN632 is a CD123-targeting ADC, comprising a high affinity anti-CD123 antibody coupled to a DNA alkylating payload of the novel IGN (indolinobenzodiazepine pseudodimer) class.[4]

Previously published data ASH 2018: (n=33) demonstrated clinical activity across multiple dose levels (0.015-0.45 mg/kg) with complete remission(CR)/complete remission without complete hematological recovery (CRi) in 26% of R/R AML and responses in 2 of 3 relapsed BPDCN patients. DLTs seen only at higher dose levels ≥ 0.18, 2 reversible veno-occlusive disease (VOD) and 1 prolonged neutropenia.

Expansion cohorts enrolling at 0.045 and 0.09 mg/kg.[5] Updates on Monday, December 9th at 3PM (Oral Abstract #734).



MECHANISM OF ACTION
1: ADC binds CD123
2: ADC internalized
3: Payload released
4: Payload alkylates DNA

Novel Anti-CD123 Antibody
- Higher affinity binding to CD123
- Unique epitope in extracellular domain

Novel IGN Payload (DGN549)
- DNA-alkylating activity, single strand DNA breaks (vs. double strand)
- Uniform drug-antibody ratio (DAR=2)

Novel Peptide Linker
- Confers stability in circulation and efficient intracellular payload release

Study Design

The IMGN632-0801 study is a multi-center, Phase 1 study to determine the Recommended Phase 2 Dose (RP2D) and assess the safety, tolerability, PK, immunogenicity, and preliminary anti-leukemia activity of IMGN632 when administered as monotherapy to patients with CD123+ hematologic malignancies.

The study is enrolling eligible adults with CD123-positive AML, BPDCN and ALL.
- CD123 criteria: any detectable level by flow or IHC by local assessment

IMGN632 administered as a <1 hour IV infusion on Day 1 of a 21-day cycle.

Trial Endpoints

Primary
- Maximum Tolerated Dose (MTD) and RP2D

Secondary
- Treatment emergent adverse events
- Objective Response Rate (ORR)
- Pharmacokinetic parameters
  - Maximum plasma concentration (Cmax) of IMGN632
  - Area under the time-concentration curve (AUC) of IMGN632
  - Terminal half-life ($t_{½}$) of IMGN632
- Immunogenicity
  - Presence of Antibody-Drug Antibody (ADA)

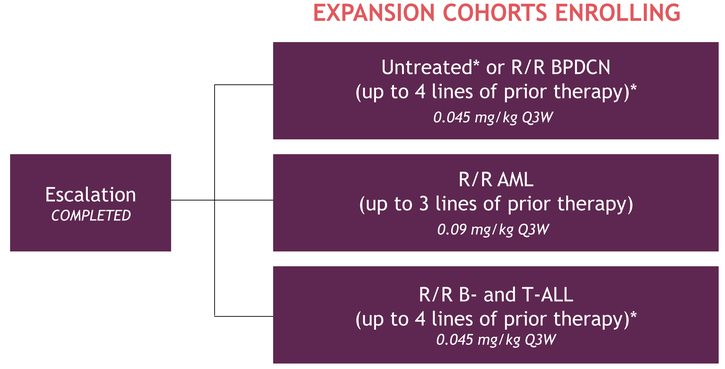
Eligibility

Key Inclusion
- CD123+ AML, ALL or BPDCN
- Relapsed/refractory (R/R) AML (up to 3 prior lines)
- R/R B- and T-ALL (up to 4 prior lines)*
- Selected untreated patients with BPDCN (i.e. those who are inappropriate for available therapies)* or R/R BPDCN (up to 4 prior lines)*
- Patients with prior bone marrow transplant are eligible (greater than 120 days)
- Washout period 14 days (except for checkpoint inhibitors 28 days)

Key Exclusion
- History of veno-occlusive disease, Grade 4 capillary leak syndrome, or non-cardiac grade 4 edema

*Amendment pending to include selected untreated BPDCN and to increase number of prior lines from 3 to 4

Schema



*Amendment pending to expand eligibility

IMGN632 Program Updates

- Clinical safety and efficacy updates to the Phase 1 trial will be presented on Monday, December 9th at 3PM (Oral Abstract #734)
- Preclinical data of IMGN632 in combination with azacitidine and venetoclax will be presented Saturday, December 7th from 6-8PM (Abstract #1375)
- A recently opened phase 1b/2 trial of IMGN632 in combination in AML will be presented Sunday, December 8th from 6-8PM (Abstract #2601)

Registration

This study is registered at clinicaltrials.gov: NCT03386513.

For additional information please contact medicalaffairs@immunogen.com.

REFERENCES
[1]Testa U, Pelosi E, and Frankel A. *Biomarker Research*; 2:4, 2014
[2]Angelova E, Audette C, Kovtun Y et al. *Haematologica*; 104:749-755, 2018
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[5]Daver NG et al. Blood. 2018;132: Abstract 27.