Abstract 2601

A Phase 1b/2 Study of IMGN632 as Monotherapy or Combination with Venetoclax and/or Azacitidine for Patients with CD123-Positive Acute Myeloid Leukemia

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BACKGROUND

CD123, the alpha-subunit of interleukin-3 receptor (IL3RA), expression is elevated on Acute Myeloid Leukemia (AML) blasts and leukemic stem cells compared with normal hematopoietic stem and progenitor cells.[1]

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

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.

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.[4] Updates on Monday, December 9th at 3PM (Oral Abstract #734).

Pre-clinical data indicate IMGN632 combinations with azacitidine (AZA), venetoclax (VEN), and AZA with VEN result in increased survival in mouse models of AML (Abstract #1375).[2]

IMGN632: A Novel CD123-Targeting ADC[3]

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

Novel Anti-CD123 Antibody
- High 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 IMGN632-0802 study is a multi-center Phase 1b/2 study to assess the safety and efficacy of IMGN632 when administered in monotherapy for patients in remission with minimal residual disease (MRD+) after induction or consolidation or in combination in adult patients with CD123-positive, relapsed/refractory (R/R) or treatment-naïve AML
- 3+3 escalation, with ability to expand multiple dose-levels
- IMGN632 administered in 4 distinct regimens:
  - IMGN632 + azacitidine
  - IMGN632 + venetoclax
  - IMGN632 + azacitdine + venetoclax (enrollment follows safety assessment of doublets)
  - Patients who benefitted from combination regimens may continue to receive IMGN632 monotherapy as maintenance
- IMGN632 monotherapy at 0.045 mg/kg for MRD+ patients in remission after induction/consolidation
- IMGN632 dosing levels for combinations: 0.015, 0.045 and 0.09 mg/kg/dose

Trial Endpoints

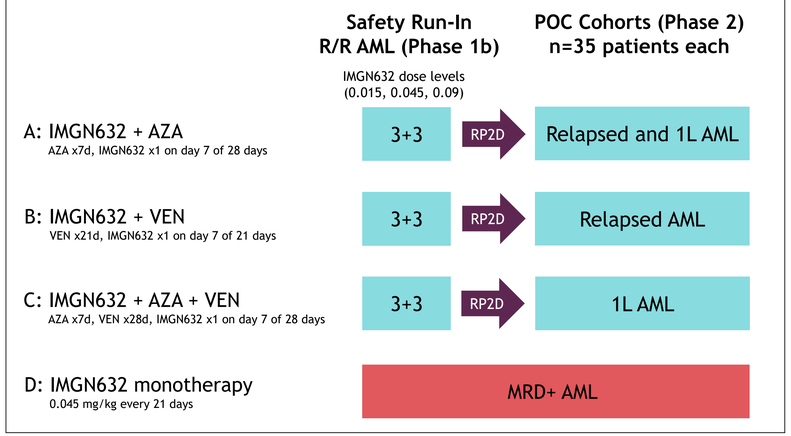
Primary
- Combination cohorts
  - Evaluate safety and tolerability and Recommended Phase 2 Dose (RP2D) when IMGN632 is administered with AZA, VEN, or with AZA and VEN in patients with R/R AML
  - Assess preliminary antileukemia activity when IMGN632 is administered in combination with AZA, VEN, or with AZA and VEN in patients with relapsed AML or untreated AML
- MRD+ cohort: IMGN632 monotherapy
  - Assess MRD conversion rate using central flow cytometry-based testing
  - Relapse-free survival (RFS)

Eligibility

Key Inclusion
- CD123+ AML
- Relapsed/refractory AML (up to 2 prior lines) or treatment-naïve
- Patients with prior bone marrow transplant are eligible (greater than 120 days)
- Washout period 14 days (except for checkpoint inhibitors 28 days)
- MRD+ AML confirmed by central lab

Key Exclusion
- Patients with history of veno-occlusive disease

Schema



Program Updates

- This trial is open and enrolling; ~35 centers in US and Europe plan to participate
- Continued phase I trial of IMGN632 as a single agent, currently enrolling three expansion cohorts: Untreated or R/R BPDCN, AML and B- or T-ALL, will be presented Sunday, December 8th from 6-8PM (Abstract #1334)
- Clinical safety and efficacy updates to the Phase 1 trial will be presented on Monday, December 9th at 3PM (Oral Abstract #734)

Registration

This study is registered at clinicaltrials.gov NCT04086264.

For more information please contact medicalaffairs@immunogen.com.

REFERENCES
[1]Ehninger A , Kramer M, Röllig C et al. *Blood Cancer J* 4:e218, 2014
[2]Kuruvilla VM, McCarthy R, Zhang Q et al. ASH 2019, Abstract #1375
[3]Kovtun Y, Jones G, Adams S et al. *Blood Adv* 2:848-858, 2018
[4]Daver NG et al. Blood. 2018;132: Abstract 27.