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

Authors: Naval Daver[1], Harry P. Erba[2], Nikolaos Papadantonakis[3], Daniel J. DeAngelo[4], Eunice S. Wang[5], Marina Konopleva[1], Callum M. Sloss[6], Jiuzhou Wang[6], Kara E. Malcolm[6], Patrick A. Zweidler-McKay[6], and Hagop Kantarjian[1]

[1]MD Anderson Cancer Center, Houston, TX; [2]Duke Cancer Center, Durham, NC; [3]University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [6]ImmunoGen, Inc., Waltham, MA

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]

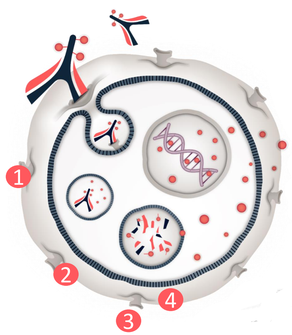
With broad expression in AML and rapid internalization, CD123 is well suited for antibody-drug conjugate (ADC)-based therapeutic strategies.

IMGN632 is a CD123-targeting antibody-drug conjugate (ADC) comprising a novel anti-CD123 antibody coupled, via a peptide linker, to a unique DNA-alkylating cytotoxic payload of the recently developed IGN (indolinobenzodiazepine pseudodimer) class.

Previously published data ASH 2019: Clinical activity across a wide range of dose levels (0.015-0.45 mg/kg) with CR/CRi rates of 26% and 40% of relapsed AML and R/R de novo AML respectively at the RP2D of 0.045 mg/kg Q3W. No DLTs seen at the dose levels being tested in the current study, 0.015-0.09 mg/kg.[3]

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

MECHANISM OF ACTION



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

Escalation and Expansion Cohorts are Enrolling in AML

	Escalation R/R AML (Ph 1b) IMGN632 dose levels (0.015, 0.045, 0.09 mg/kg)		Expansion Cohorts (Ph 2)
A: IMGN632 + AZA AZA x7d IMGN632 x1 on day 7 of 28 days	3+3	RP2D	Relapsed and 1L AML
B: IMGN632 + VEN VEN x21d IMGN632 x1 on day 7 of 21 days	3+3	RP2D	Relapsed AML
C: IMGN632 + AZA + VEN AZA x7d VEN x28d IMGN632 x1 on day 7 of 28 days	3+3	RP2D	1L AML
D: IMGN632 monotherapy 0.045 mg/kg every 21 days	MRD+ AML		

Key Inclusion
- CD123+ AML
- Relapsed and/or 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

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]Daver NG et al. Blood. 2018;132: Abstract 27.

STUDY DESIGN

The IMGN632-0802 study is a multi-center Phase 1b/2 study to assess the safety and efficacy of IMGN632 when administered as 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
- 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
- Maximum Tolerated Dose (MTD) and RP2D
- Assess anti-leukemia activity of IMGN632 when administered in combination with azacitidine and/or venetoclax in patients with relapsed or untreated AML
- Assess anti-leukemia activity of IMGN632 as monotherapy in MRD+ AML patients

Secondary
- Treatment emergent adverse events
- Objective Response Rate (ORR)
- Pharmacokinetic parameters (Cmax, AUC)
- Immunogenicity
  - Presence of Antibody-Drug Antibody (ADA)

FUTURE DIRECTIONS FOR RESEARCH

The trial is open and enrolling at 6 centers in the US and Europe;
26 additional centers in US and Europe are planning to participate. See clinicaltrials.gov: **NCT04086264**.
IMGN632 is also being tested in BPDCN and ALL patients. See **NCT03386513**

Please contact: medicalaffairs@immunogen.com