Abstract 1047

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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INTRODUCTION

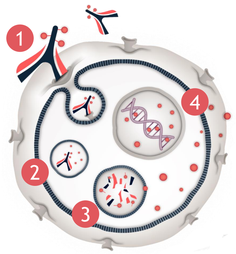
- CD123, the alpha-subunit of interleukin-3 receptor (IL3RA), expression is elevated on Acute Myeloid Leukemia (AML) blasts and leukemic stem cells (LSCs) compared with normal hematopoietic stem and progenitor cells[1]
- With broad expression in AML and rapid internalization, CD123 is well suited for antibody-drug conjugate (ADC)-based therapeutic strategies
- IMGN632 is a CD123-targeting ADC, comprising a high affinity anti-CD123 antibody coupled to a DNA alkylating payload of the novel IGN (indolinobenzodiazepine pseudodimer) class
- ASH 2019: Clinical activity was seen across a wide range of dose levels (0.015-0.45 mg/kg) with CR/CRi rates of 26-40% in subsets of relapsed AML at the RP2D of 0.045 mg/kg Q3W[3]
- Pre-clinical data support testing of IMGN632 combinations with azacitidine (AZA), venetoclax (VEN),[2] and AZA with VEN. **ASH Abstract #2886, Monday, December 7, 2020: 7:00 AM-3:30 PM, Poster Hall (Virtual Meeting)**

Mechanism of Action

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
- Efficient intracellular payload release



Mechanism of Action
1: ADC binds CD123
2: ADC internalized
3: Payload released
4: Payload alkylates DNA

Escalation and Expansion Cohorts are Enrolling in AML

	Escalation *Phase 1b* IMGN632 dose levels (0.015, 0.045, 0.09 mg/kg)		Expansion Cohorts *Phase 2*
IMGN632 + AZA AZA (75 mg/m2) x7d IMGN632 x1 on day 7 of 28 days	3+3	RP2D	Relapsed and 1L AML
IMGN632 + VEN VEN (400 mg) x21d IMGN632 x1 on day 7 of 21 days	3+3	RP2D	Relapsed AML
IMGN632 + AZA + VEN AZA (50-75 mg/m2) x7d VEN (400 mg) x8-28d IMGN632 x1 on day 7 of 28 days	3+3	RP2D	Relapsed and 1L AML
IMGN632 Monotherapy 0.045 mg/kg every 21 days			Unfit MRD+ AML Fit MRD+ AML

Key Inclusion
- Adults with CD123+ AML
- Treatment-naïve OR relapsed/refractory AML (up to 2 prior lines)
- MRD+ AML confirmed by central lab
- Patients with prior HSCT are eligible (>120 days)
- Washout period 14 days (except for checkpoint inhibitors 28 days)

Key Exclusion
- Patients with history of veno-occlusive disease

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 combination with azacytidine and/or venetoclax OR monotherapy for patients in remission with minimal residual disease (MRD+ Fit or Unfit) after induction and consolidation
- 3+3 escalation, with ability to expand multiple dose-levels
- IMGN632 administered in 3 combinations:
  - IMGN632 + azacitidine
  - IMGN632 + venetoclax
  - IMGN632 + azacitdine + venetoclax
- IMGN632 dosing levels for combinations: 0.015, 0.045 and 0.09 mg/kg
- IMGN632 administered as monotherapy at 0.045 mg/kg for MRD+ (Fit or Unfit) patients in remission after induction/consolidation.

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+ (Fit or Unfit) 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

This trial is enrolling at 14 centers in the US and Europe

- clinicaltrials.gov: NCT04086264
- Combining IMGN632, a Novel CD123-Targeting Antibody Drug Conjugate with Azacitidine and Venetoclax Facilitates Apoptosis in Vitro and Prolongs Survival In Vivo in AML Models. **ASH Abstract #2886, Monday, December 7, 2020: 7:00 AM-3:30 PM, Poster Hall (Virtual Meeting)**
- Clinical Profile of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Blastic Plasmacytoid Dendritic Cell Neoplasm. **ASH Abstract #167, Saturday, December 5, 2020: 12:00 PM-1:30 PM, Channel 12 (Virtual Meeting)**
- **IMGN632 trial for BPDCN patients. Clinicaltrials.gov NCT03386513**

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