A Phase 1/2 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

Overexpression of CD123 occurs in multiple hematological malignancies, including acute myeloid leukemia (AML), blastic plasmacytoid dendritic cell neoplasm (BPDCN), acute lymphoblastic leukemia (ALL) and others, thus making this antigen an attractive target for the development of new therapeutics.

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.

Preclinically, IMGN632 has demonstrated potent activity against AML, BPDCN and ALL models, with a wide therapeutic index in animal models, as well as a 150-fold differential cytotoxicity in AML patient samples compared to normal hematopoietic progenitors (PMIDs: 29661755, 30361418). Remarkable sensitivity of BPDCN patient derived xenografts to IMGN632 has been demonstrated (Blood 2018 132:3956).

MECHANISM OF ACTION

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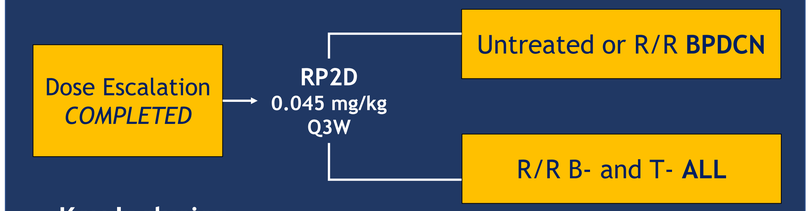
1: ADC binds CD123
2: ADC internalized
3: Payload released
4: Payload alkylates DNA

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

Expansion Cohorts are enrolling in BPDCN and ALL



Key Inclusion
- CD123 positive BPDCN or ALL
- Selected untreated patients with BPDCN (i.e. those who are inappropriate for available therapies)
- R/R BPDCN (up to 4 prior lines)
- R/R B- and T-ALL (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
- Active CNS disease
- History of veno-occlusive disease, Grade 4 capillary leak syndrome, or non-cardiac grade 4 edema

REFERENCES
[1]Testa U, Pelosi E, and Frankel A. *Biomarker Research*; 2:4, 2014
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[3]Su R and Chen M. *American Journal of Clinical Pathology*, 144:2, 2015
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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 BPDCN and ALL. 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)

FUTURE DIRECTIONS FOR RESEARCH

The trial is open and enrolling at 11 centers in the US and Europe; 2 additional centers in Europe are planning to participate. See clinicaltrials.gov: **NCT03386513**

IMGN632 is also being tested in AML patients as monotherapy and in combination with azacitidine and venetoclax.
See **NCT04086264**

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