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. 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 (indolino benzodiazepine pseudodimer) class. Previously published data ASH 2019: Clinical activity across a wide range of dose levels (0.15-0.45 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.

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 and efficient intracellular payload release

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

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-naive AML. 3-3 escalation, with ability to expand multiple dose-levels. IMGN632 administered in 4 distinct regimens: IMGN632 + azacitidine, IMGN632 + venetoclax, IMGN632 + azacitidine + 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. For more information please contact: medicalaffairs@immunogen.com

REFERENCES