**IMGN632: A NOVEL ANTIBODY-DRUG CONJUGATE (ADC) OF A CD123-TARGETING ANTIBODY WITH A POTENT DNA-ALKYLATOR IS HIGHLY ACTIVE IN PRECLINICAL MODELS OF AML WITH POOR PROGNOSIS**

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**BACKGROUND**

Targeted delivery of cytotoxic molecules by ADCs recognizing cancer-specific antigens is a promising therapeutic approach. CD123, the IL-3 receptor alpha-subunit, is an attractive cancer target implicated in AML cell survival and proliferation. CD123 is universally expressed on AML blasts, is differentially expressed on AML stem cells relative to normal hematopoietic cells, and is associated with aggressive disease. Here, we report the preclinical evaluation of IMGN632, a novel conjugate of a humanized anti-CD123 antibody with a payload that alkylates DNA.

**IMGN632 is a conjugate of a unique anti-CD123 antibody and a novel payload**

- **Antibody**
  - humanized IgG1
  - binds to hCD123 with a sub-nanomolar affinity
- **Payload**
  - alkylates DNA without cross-linking
  - highly potent in cell lines of hematopoietic malignancies, particularly leukemia
- **Linker**
  - peptide, stable in circulation, cleaved intracellularly
- **Conjugation**
  - site-specific, via engineered cysteines
  - 2 payload molecules are attached per antibody

**Mechanism of cell killing by an ADC with DNA alkylator**

- **ADC binds to the antigen triggering**
  - internalization of ADC
  - trafficking to lysosomes
  - catabolism of ADC
  - payload release
- **Payload induces**
  - DNA alklylation
  - cell cycle arrest in S-phase
  - apoptosis and cell death

**IMGN632 exhibits potent, CD123-specific cytotoxicity in AML cell lines, including those with poor prognostic factors**

- **IMGN632 induces DNA damage leading to cell cycle arrest in S-phase and apoptotic cell death of CD123-positive MV-111 cells**
- **Cytotoxicity was assessed with WST-8 reagent after continuous incubation with ADCs for up to 7 days**

**IMGN632 is highly active and CD123-specific against MV-11 (FLT-3/ITD) and Kasumi-3 (PS3 mutated and multidrug resistant) AML xenografts in mice**

- **MV-11 subcutaneous model**
  - SCID mice were injected subcutaneously with MV-11 cells. When tumor volume reached 100 mm³, mice were IP injected with 400 mg/kg of human IgG1 to block Fc receptors. The next day, mice were randomized and received a single IV injection of either vehicle, or an ADC.

**Single injection of IMGN632 resulted in durable complete responses**

- **Kasumi-3-Luciferase disseminated model**
  - NSG mice were injected intravenously with Kasumi-3-Luc cells. Six days later, mice were randomized based on tumor burden as quantified by imaging, and IP injected with 400 mg/kg of human IgG1 to block Fc receptors. On days 7 and 41, mice received single IV injections of either vehicle, or an ADC.

**Survival of progenitors after 1 day exposure to a compound as assessed by colony forming unit assays**

**CONCLUSIONS**

- **IMGN632 is more potent than gemtuzumab ozogamicin (GO) in AML patient samples in vitro**
  - Multidrug resistance (MDR) activity was assessed by flow-cytometry. AML blast cells, but not monocytes, demonstrate MDR activity.

**Summary of sample analysis from 15 AML patients**

- **Treatment Status**
  - **MDR status**
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment
    - Pre Treatment

**IMGN632 exhibits potent in vitro and in vivo activity against AML cell lines and patient samples, including those with poor prognostic markers.**

- These findings support advancing IMGN632 into clinical trials.

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