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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



Red: imine (site of DNA alkylation) Blue: amine (non-

covalently binds DNA) Purple: peptide linker

Dashed line: Site of catabolism

- Antibody
- humanized IgG1
- binds to huCD123 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 alkylation
- cell cycle arrest in S-phase
- apoptosis and cell death



IMGN632 is highly active and CD123-specific against MV4-11 (FLT-3/ITD) and Kasumi-3 (P53 mutated and multidrug resistant) AML xenografts in mice

MV4-11 subcutaneous model:

SCID mice were injected subcutaneously with MV4-11 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.

Mice tumor burden as quantified by bioluminescence imaging on day 26 IMGN632 3 µg/kg Vehicle

Survival of Kasumi-3-Luc bearing

IMGN632 reduced tumor burden and extended survival in 6/6 mice with P53 mutated and multidrug resistant AML

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CONCLUSIONS

- 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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