IMGN632: AN ANTIBODY-DRUG CONJUGATE (ADC) OF A CD123-TARGETING ANTIBODY WITH A NOVEL DNA-ALKYLATING PAYLOAD IS HIGHLY ACTIVE AND PROLONGS SURVIVAL IN AML XENOGRAFT MODELS

2832
Sharlene Adams1, Alan Wilhelm1, Lauren Harvey1, Chen Bai1, Nicholas C. Yoder1, Yelena Kovtun1, Thomas Chittenden1, Jan Pinkas1
1ImmuNoGen, Inc., Waltham, United States

BACKGROUND
Targeted delivery of cytotoxic molecules by ADCs that recognize cancer-specific antigens is a promising therapeutic approach. CD123, the alpha subunit of the IL3 receptor, 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, in AML xenograft models, of IMGN632, a novel conjugate of a humanized anti-CD123 antibody with a novel IGN mono-Imine payload that alkylates DNA without cross-linking. Monoclonal antibody was selected over di-imine due to superior selective toxicity against AML progenitors vs. normal progenitors, and superior tolerability in mice.

IMGN632 is an ADC combining an anti-CD123 antibody and a novel DGN949 IGN payload

Methods
Unique anti-CD123 antibodies were generated in mice through immunization with a human CD123-expressing cell line. Following antibody selection and humanization in the IgG1 format, IMGN632 was produced by conjugating a novel peptide-linked DNA alkylating, mono-imine payload to engineered cysteine residues, resulting in an ADC with a drug:antibody ratio of ~2. The in vitro cytotoxicity of IMGN632 or a non-targeted control ADC was evaluated on AML cell lines after continuous exposure for up to 7 days, and the IC50 was determined for each conjugate. Antibodies in vivo activity of IMGN632, or a non-targeted control ADC, was assessed in immunodeficient mice bearing disseminated or subcutaneous human AML xenografts. The maximum tolerated dose (MTD) of IMGN632 was determined by administering single IV injections of IMGN632 to C57 mice. ADC doses are expressed as mg/kg or µg/kg by antibody. Azacitidine and cytarabine are dosed at 75% of MTD in mice.

IMGN632 is highly active and CD123-specific in Molm-13 disseminated AML xenografts, resulting in a TI of ≥1000

Molm-13 disseminated xenograft (FLT3-ITD):
Nude mice injected IV with Molm-13 cells on Day 0 were randomized into study groups on Day 0 and were injected with 400 µg/kg of non-targeted human IgG1 antibody to block Fc receptors on the Molm-13 cells. On Day 7, the mice received a single IV injection of either vehicle or an ADC. On days 4 and 9 post-ADC dosing, the mice were injected with 100 mg/kg human IgG1 to maintain Fc receptor blockade on the Molm-13 cells.

M4V-11 disseminated xenograft (FLT3-ITD):
MV4-11 cells were pre-inoculated with 150 µg/kg cytarabine on days -3 and -2, followed by IV injection of MV4-11 cells on Day 0. On day 6 post-MV4-11 inoculation, mice were randomized into study groups and received an IV injection of 400 µg/kg of non-targeted human IgG1 antibody to block Fc receptors on the MV4-11 cells. On Day 7, the mice received a single IV injection of either vehicle or an ADC.

CONCLUSIONS
IMGN632 exhibits potent, CD123-specific in vitro activity against AML cell lines, including those with markers of poor prognosis. IMGN632 is well tolerated in mice at doses ≤5 mg/kg, and is highly active in vivo against Molm-13, Kasumi-3 and MV4-11 disseminated xenografts, resulting in prolonged survival and reduced tumor burden.

IMGN632 achieves a high TI in the AML xenograft models. IMGN632 is highly active against EOL-1 subcutaneous xenografts, resulting in tumor regression and prolonged tumor-free survival in this cytarabine- and azacitidine-resistant model. These findings support advancing IMGN632 into clinical trials.

Dr. Yelena Kovtun will be presenting additional IMGN632 preclinical data on Monday, Dec. 5, at 11:45 AM, at Oral Session # 616, Abstract # 768. Title: A CD123-Targeting Antibody Drug Conjugate (ADC), IMGN632, Designed to Eradicating Acute Myeloid Leukemia (AML) Cells While Sparlncering Bone Marrow Cells.

ASH, December 3-6, 2016, San Diego, CA ©2016 ImmuNoGen, Inc., Waltham, MA, USA