IMGN779, a CD33-Targeted Antibody-Drug Conjugate (ADC) with a Novel DNA-Alkylating Effector Molecule, Induces DNA Damage, Cell Cycle Arrest, and Apoptosis in AML Cells.

Krystal Watkins¹, Russell M. Walker¹, Nathan Fishkin², Charlene Audette³, Yelena Kovtun⁴, Angela Romanelli⁴
ImmuGen, Inc., Waltham, MA, USA; ¹Translational Medicine, ²Biochemistry, ³Cell Biology

INTRODUCTION
IMGN779 is a CD33-targeting ADC created for the treatment of acute myeloid leukemia (AML) and other CD33-positive malignancies.

CD33 is highly expressed on AML cell lines and primary patient samples in vitro and causes complete regression of tumors in AML xenograft models in vivo with a favorable therapeutic index.⁵

To investigate the mechanism of action of DGN462 and of IMGN779, we used AML cell lines and primary patient AML samples to evaluate:

- DNA binding
- DNA alkylation versus crosslinking
- Cell cycle effects
- DNA damage signaling, apoptosis, and cell death

**Structure of IMGN779**

![Structure of IMGN779](https://example.com/structure.png)

**IMGN779 profile**

IMGN779 is comprised of a humanized anti-CD33 antibody, Z4681A, to which approximately three DGN462 molecules per antibody are conjugated using a cleavable disulfide linker.

DGN462 is a member of the novel IGN class of DNA-acting cytotoxic agents and consists of an indolino-benzodiazepine dimer containing a mono-imine moiety.

**DGN462 and IMGN779 induce apoptosis and cell death**

- Exposure to DGN462 or IMGN779 causes apoptosis and cell death.

**DGN462 and IMGN779 induce DNA damage response and apoptosis signaling**

- (A) Phosphorylated H2AX and Cleaved Caspase3, markers of DNA damage and apoptosis, respectively, were induced in a time dependent manner following exposure to either DGN462 or IMGN779.

**DGN462 and IMGN779 induce cell cycle arrest**

- Exposure to DGN462 or IMGN779 causes cell cycle arrest in G2/M phase, S-phase accumulation, and appearance of a sub G0/G1 population.

**CONCLUSIONS**

IMGN779 is advanced to clinical testing for the treatment of relapsed/refractory CD33+ AML. Pharmacodynamic studies utilizing phosphorylated H2AX as a biomarker will be implemented to verify the mechanism of this novel alkylating ADC.

**References**


3. whiteman2014theaadc.png


5. Z4681A, to which approximately three DGN462 molecules per antibody are conjugated using a cleavable disulfide linker.