The Antibody-Drug Conjugate (ADC) IMGN779 Is Highly Active In Vitro and In Vivo Against Acute Myeloid Leukemia (AML) With FLT3-ITD Mutations

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INTRODUCTION

IMGN779 is a CD33-targeted ADC utilizing DGN462, a novel DNA-alkylating agent consisting of an indolino-benzodiazepine dimer containing a mono-imine moiety. AML with mutations in FMS-like tyrosine kinase 3 (FLT3) are associated with poor prognosis; the most common FLT3 mutation is the internal tandem duplication (FLT3-ITD). Patients with FLT3-ITD AML have a worse prognosis than those with wild-type (WT) FLT3, with an increased rate of relapse and a shorter duration of response to induction chemotherapy.

To investigate the activity of IMGN779 in FLT3-ITD AML, we evaluated the in vitro potency of IMGN779 against cell lines and primary patient AML cells with FLT3-ITD mutations, and the antitumor activity against both FLT3-ITD and FLT3 WT AML xenograft models.

IMGN779 Profile

IMGN779 consists of a humanized anti-huCD33 antibody with approximately three DGN462 molecules attached per antibody using a disulfide linker. Toxicology studies in mice demonstrated:

- IMGN779 does not cause delayed toxicity - the mono-imine DGN462 effector molecule alkylates DNA without DNA-crosslinking. Delayed toxicity has been observed with ADCs employing DNA-crosslinking effector molecules.
- The cleavable disulfide linker avoids liver toxicity, the DLT observed with non-cleavable linker formats.

IMGN779 Causess a Dose-Dependent Decrease of Leukemic Colony Formation and Increase in Normal HSC Colonies in Long-Term FLT3-ITD/NPM1+ LSC Cultures

Patient AML Cells Are Highly Sensitive to IMGN779 In Vitro: FLT3-ITD Cells Are More Sensitive, Have Higher CD33 Expression

AML Cell Lines Are Highly Sensitive to IMGN779 In Vitro: FLT3-ITD AML Lines Are Among the Most Sensitive

CONCLUSIONS

- IMGN779 is highly active in vitro against primary patient AML samples, with increased potency observed against cells with FLT3-ITD mutations.
- The differential expression of CD33 on LSC compared to HSCs makes CD33 an attractive target for treatment of AML, with the potential to eliminate LSCs and, thus, minimal residual disease in FLT3-ITD AML.
- The activity of IMGN779 against AML cell lines in vitro and in xenograft models in vivo demonstrates that IMGN779 is active independent of FLT3 mutational status, and has high potency compared to FLT3 inhibitors in the clinic.
- These results support the advancement of IMGN779 as a potential treatment for AML, including FLT3-ITD AML.