Plasma Pharmacokinetics and Tumor Accumulation in Mice of IMGN779, an Antibody-Drug Conjugate for Acute Myeloid Leukemia

Abstract

IMGN779 is a highly active antibody-drug conjugate (ADC) in pre-clinical development for the treatment of acute myeloid leukemia (AML). IMGN779 is highly active in vitro against AML cell lines and primary patient AML cells and causes complete regression of AML xenograft tumors at non-toxic doses in vivo. To understand the fate of IMGN779 upon dosing and cellular uptake, we performed:

 ► in vitro catabolism studies on cultures of ADC-treated AML cells
 ► in vivo distribution studies in mice, including:
   - Plasma clearance
   - AML xenograft tumor accumulation

IMGN779 Composition and Mechanism of Action

IMGN779 is efficiently catabolized, with protein-free catabolites exuded from the cell, in a time-dependent manner.

IMGN779 is Degraded Within Cells, With Catabolites Both Effluxed From Cells and Associated With DNA

Cells and cellular debris were harvested and washed, acetone-precipitated, and DNA-isolated. Cell pellets were dissolved in 100 µL of 0.1 N NaOH for 1 h at 37 °C, and DNA pellets were dissolved in 25 µL of water. DNA associated values.

LC/MS of Affinity-Captured IMGN779

The Mass-Distribution Profile of captured IMGN779 shows a decrease in higher-conjugated species over time.

IMGN779 Demonstrates CD33 Binding and Time-Dependent Catabolism in vitro

MOLM-13 and HL60/QC express ~20,000 CD33 receptors per cell. IMGN779 is efficiently catabolized, with protein-free catabolites effluxed from the cell, in a time-dependent manner.

IMGN779 Demonstrates Antibody-Driven Clearance and Release of DGN462 Over Time

Liquid Scintillation Counting (LSC) was used to determine the plasma concentration of samples at various time points after a single 5 mg/kg i.p. injection of radiolabeled reagent.

IMGN779 Demonstrates CD33-targeted Tumor Localization in HL60/QC Xenografts

Most killing HL60/QC tumors were killed with 5 mg/kg IMGN779 or control (HG462). Tumors were harvested at 24, 48, and 60 h, homogenized and counted by LSC either directly, after autoradiography, or by DNA extraction.

Similar %ID/g levels of targeting and non-targeting ADC are found in total tumor homogenate at all time points.

Catabolism is CD33-specific: higher levels of protein-free and DNA-adducted DGN462 species with IMGN779 vs. control ADC

CONCLUSIONS

⇒ Similar %ID/g levels of targeting and non-targeting ADC are found in total tumor homogenate at all time points.
⇒ Catabolism is CD33-specific: higher levels of protein-free and DNA-adducted DGN462 species with IMGN779 vs. control ADC.

References:

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