Pre-clinical activity of ADCT-601, a novel pyrrolobenzodiazepine (PBD) dimeric antibody-drug conjugate (ADC) targeting AXL-expressing tumors


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Introduction

• AXL, the member of the tyrosine kinase receptor family TIE2, is a transmembrane receptor containing an extracellular (ECD) domain comprising two Ig-like and two fibronectin type III motifs and an intracellular (ICD) domain comprising 3 tyrosine kinase domains. The ECD contains a phosphotyrosine-binding domain and the ICD contains a single, highly conserved, tyrosine kinase domain (TKD) encoded by the ALK gene.

• There is evidence that AXL is involved in cell proliferation, survival, migration, and invasion. AXL is expressed in 20-30% of human solid tumors and is associated with poor prognosis.

• Antisense knockdown of AXL expression in vitro results in cell cycle arrest and induction of apoptosis in several cancer cell lines.

• In vivo, AXL expression is found in a variety of tumors, including breast, lung, prostate, and colon cancer.

• There is ongoing development of mono- and dimeric ADCs targeting AXL.

Material & Methods

• in vitro

Aim of this study

• The purpose of this study was to characterize the in vitro and in vivo tumor activity of ADCT-601 in human solid cancer cell lines and xenograft models and to determine its safety and tolerability in the rat.

• ADCT-601 is an ADC composed of a humanized IgG antibody against human AXL, specifically conjugated using GlycoConnect™ technology (3), which contains a nontoxic murine scFv payload and a 4-amino-4-carboxybenzyl linker and the PBD dimeric cytotoxin. The drug to antibody ratio (DAR) is ~2 (Figure 2).

Results

Figure 3: In vitro cytotoxicity

Figure 4: In vivo anti-tumor activity in the MDA-MB-231 TNBC xenograft

Figure 5: In vivo anti-tumor activity in the SHC13 renal cancer xenograft

Figure 6: In vivo anti-tumor activity in the PKA5667 pancreatic cancer PDX

Figure 7: In vivo anti-tumor activity in the AXL-negative Karpas299 ALCL xenograft

Figure 8: PK analysis in rat

Conclusions

• ADCT-601 showed potent and highly targeted in vitro cytotoxicity in a panel of AXL-expressing solid cancer cell lines.

• A single low dose of ADCT-601 demonstrated potent and durable tumor efficacy in xenograft models.

• PK analysis of ADCT-601 in non-tumor bearing rats showed that ADCT-601 has excellent stability in vivo, with a half-life of about 3.2 days at 3 mg/kg and about 4.3 days at the maximum tolerated dose of 6 mg/kg.

• In vivo, ADCT-601 showed tumor-radiating activity and durable anti-tumor efficacy in breast and renal cancer xenograft models, while ADCT-601 did not have a significant anti-tumor activity in an AXL-negative xenograft model.

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References


