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

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Introduction

AXL, a member of the tyrosine kinase receptor family TK1, is a transmembrane receptor containing an extracellular (EF-hand) domain comprising two tryptophan (W) and two histidine (H) type 2 receptor motifs. As an integrin-like receptor, AXL is involved in growth, survival, invasion and angiogenesis. Axl-deficient mice are protected from a variety of cancer models, suggesting that overexpression of AXL is tumorigenic and plays a role in mediating resistance to conventional therapies. A novel AXL-targeting antibody-drug conjugate (ADCT) targeting AXL-expressing tumors ADCT-601, which combines a potent PBD singlet oxygen prodrug with a viable humanized anti-human AXL antibody, was designed to achieve targeted cytotoxic effects in AXL-expressing tumors.

Objectives

The purpose of this study was to characterize the human cancer cell lines and xenograft models to determine its safety and tolerability in the rat.

Material & Methods

Cell lines: Cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). IHC: Narinder Janghra (UCL, UK). Discovery Research Services (USA and Germany GmbH). IHC: Narinder Janghra (UCL, UK). Chemistry and manufacturing: Synaffix BV (The Netherlands) and ADC Biotechnology (UK).

Results

Figure 1: Axl structure

Figure 2: ADCT-601

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 SHU18 cancer xenograft

Figure 6: In vivo anti-tumor activity in PA061567 pancreatic cancer PDX

Figure 7: In vivo anti-tumor activity in the AXL-negative Karpos289 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. In vivo, single low dose of ADCT-601 demonstrated potent and durable tumor-inhibitory effects in breast and melanoma cancer xenografts, while ADCT-601 did not show a significant anti-tumor activity in an AXL-negative xenograft model.

A single, low dose of 0.3 mg/kg ADCT-601 provided 8 out of 8 TFS in an AXL-expressing pancreatic PDX

PK analysis of ADCT-601 in non-tumor bearing rats showed that ADCT-601 has excellent stability in vivo, with a half-life of almost 5 days in high end and of about 4 days in the low end tumour targeted dose of 0.3 mg/kg.

Together, these data demonstrate that ADCT-601 has a favorable therapeutic index and this warrants further development of ADCT-601 for the treatment of AXL-expressing tumors.

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References


