ADCT-701, a novel prolyllobenzodiazepine (PBD) dimer-based antibody-drug conjugate (ADC) targeting DLK1-expressing tumors

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Introduction

Delta-like 1 homolog protein (DLK-1) is an EGF-like membrane bound protein consisting of six tandem EGF-like repeats, a juxtamembrane region with a TACE (ADAM17)-mediated cleavage site, a transmembrane domain, and an intracellular domain.

- DLK1 is strongly expressed during fetal development, and its expression is highly restricted in adults. Conversely, DLK1 gets re-expressed in several tumors, such as neuroblastomas, hepatocellular carcinoma (HCC), medulloblastomas, small cell lung cancer, myeloproliferative and acute myeloid leukemias. Intercellularly, DLK1 has been shown to be a marker of cancer stem cells, a subpopulation of cells responsible for tumor initiation, growth, metastasis, and recurrence.

- Although DLK1 has been identified as an attractive target for antibody-drug conjugate (ADC) approaches based on its overexpression in various tumor cell lines, its expression in normal adults and its unique role in normal and tumor physiology has not yet been elucidated.

- ADCT-701 is an ADC composed of a humanized IgG1 antibody against human DLK1 (site-specifically conjugated using DisulfobacK® technology) with SG3199, a valine-alanine cleavable linker and the PBD dimer cytotoxin SG3199. The drug to antibody ratio (DAR) is 1.9 (Figure 2).

- A single low dose of ADCT-701 at 5 mg/kg was well tolerated in rats. PK analysis of ADCT-701 in non-tumor bearing rats showed that ADCT-701 has excellent stability, with half life of 11 days.

- Together, these data demonstrate that ADCT-701 has a favorable pharmacokinetic profile and this warrants further development of ADCT-701 for the treatment of DLK1-expressing tumors.

Aim of this study

The purpose of this study was to characterize the in vitro and in vivo anti-tumor activity of ADCT-701 in human cancer cell lines and patient-derived xenograft (PDX) models, and to determine its safety and tolerability in adult rats.

Material & Methods

- In vitro studies were performed in cell lines and xenografts using the CellTiterGlo® assays (Promega).
- In vivo experiments: BIOENSIS (USA).
- Analysis of DLK1-expression on FFPE tumor section from LI1097 PDX was performed by immunohistochemistry (IHC) using a monoclonal anti-human IgG-Fc antibody, a DLK1 antigen and a biotinylated anti-PBD antibody was used.
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- PK analysis of ADCT-701 was performed in female Wistar Han IGS: Crl: WI (Han) rats. Serum samples were collected for each time point after a single dose administration (5 mg/kg in rat).

Results

- Table with PK parameters according to a non-compartmental PK analysis (NCA).

Conclusions

- ADCT-701 showed potent and targeted in vitro cytotoxicity in a panel of solid cancer cell lines.
- A single low dose of ADCT-701 at 5 mg/kg was well tolerated in rats. PK analysis of ADCT-701 in non-tumor bearing rats showed that ADCT-701 has excellent stability, with half life of 11 days.
- Together, these data demonstrate that ADCT-701 has a favorable pharmacokinetic profile and this warrants further development of ADCT-701 for the treatment of DLK1-expressing tumors.

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References