ADCT-701, a novel pyrrolobenzodiazepine (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 modules, small cell lung cancer, myelodysplastic syndrome and acute myeloid leukemia. DLK-1 expression is highly restricted in healthy organs, as well as its expression in a wide range of malignancies.
- DLK-1 is strongly expressed during fetal development, while its expression is highly restricted in adult. DLK-1 gets expressed in several tumors, such as neuroendocrine, hepatocellular carcinomas (HCC), rhabdomyosarcoma, small cell lung cancer, melanomas, myeloid leukemia, and breast cancer.
- Allergan, Glaxo, and Dianova are developing target antibody-drug conjugates (ADC) based on its expression in a wide range of malignancies and restricted expression in healthy organs, as well as its discovery of a monoclonal antibody (mAb) against human DLK1 in an EGF-specifically conjugated using Diaptomus Technology with SG3199, which contains hydrazide linker and the PBD dimer cysteine to PL1601, which contains hydrazide linker and the PBD dimer cysteine to PL1601, which contains hydrazide linker and the PBD dimer cysteine to PL1601.

Aim of this study

The purpose of this study was to characterize the ADCT-701 and its in vitro cytotoxicity and anti-tumor activity in SK-N-R cells.

Material & Methods

- In vitro cytotoxicity and anti-tumor activity in SK-N-R neuroblastoma xenografts were assessed in vitro and in vivo. The study was performed using immunocompromised mice xenografted with SK-N-R cells. The study was approved by the Institutional Animal Care and Use Committee (IACUC).
- In vivo studies in mice were carried out using the non-compartmental PK analysis (NCA) for the whole duration of the study (504 hours).

Results

- In vitro cytotoxicity in SK-N-R cells demonstrated a selective expression of DLK1 in SK-N-R cells.
- In vivo anti-tumor activity in SK-N-R neuroblastoma xenografts was assessed using the non-compartmental PK analysis (NCA) for the whole duration of the study (504 hours).

Conclusions

- ADCT-701 shows potent and targeted in vitro cytotoxicity and in vivo anti-tumor activity in SK-N-R cells.
- The in vivo study demonstrated that ADCT-701 has excellent stability, with a half-life of 11 days.
- Together, these data demonstrate that ADCT-701 has a favorable therapeutic index and this warrants further development of ADCT-701 for the treatment of SK-N-R expressing tumors.

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