Pre-clinical Development of ADCT-402, a Novel Pyrrolobenzodiazepine (PBD)-Based Antibody Drug Conjugate (ADC) Targeting CD19-Expressing B-cell Malignancies

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Introduction

- Human CD19 antigen is a 95 kDa transmembrane protein that bears glycopro fotes belonging to the immunoglobulin superfamily. (Figure 1A). In normal human tissue, expression of CD19 is limited to the various stages of B-cell development and differentiation in lymphoid organs and its expression is maintained on the majority of B-cell malignancies, including B-cell leukaemia and non-Hodgkin lymphomas of B-cell origin.

Figure 1- CD19

Results

- ADCT-402 has a DAR of 2.3. ADCT-402 site-selective chromatography (SSC), reversed phase (RP), and C18 hydrophilic interaction chromatography (HIC) analysis. B. Summary table of manufactured ADCT-402 analysis.

Figure 2- Scale-up production of ADCT-402 is a straightforward and high yielding process

Figure 3- Correlation between in vitro cytotoxicity and cell surface CD19 density

- PK analysis of ADCT-402 in non-tumor bearing rats showed a favorable efficacy of ADCT-402 was markedly superior to RB4v1.2-DM4 and to hBU12-mc-MMAF in the Ramos xenograft.

Figure 4- In vivo antitumor efficacy in subcutaneously (s.c.) implanted Ramos xenograft

Figure 5- In vivo antitumor efficacy in benchmarking study in s.c. implanted Ramos xenograft

Figure 6- In vivo antitumor efficacy in s.c. implanted Daudi xenograft

Figure 7- In vivo antitumor efficacy in disseminated Ramos and NALM-6 xenografts

Figure 8- PK analysis

Conclusions

- Generation of ADCT-402 with DAR 2.3 was achieved using a simple, robust and high yielding conjugation process.
- ADCT-402 showed potent and highly targeted in vivo cytotoxicity in CD19-expressing cell lines.

Materials & Methods

- In vitro cytotoxicity and cell surface CD19 density were determined by the CellTiter 96® AQueous One Solution Cell Proliferation Assay (MTS assay) (Promega) and Bangs Laboratories’ Quantum Simply Cellular Anti-Human IgG beads, respectively.
- In vivo ADCT-402 was administered intravenously (i.v.) to CB-17 SCID mice containing Ramos or NALM-6 xenografts and to NOD/scid mice containing GRANTA-519 xenografts. Each group had 10 mice.
- PK analysis of ADCT-402 administered once, at 1.5 mg/kg was performed in Sprague-Dawley Crl:CD(SD) rats. Each group had 10 mice.
- In vivo ADCT-402 was administered intravenously (i.v.) to CB-17 SCID mice containing Ramos or NALM-6 xenografts and to NOD/scid mice containing GRANTA-519 xenografts. Each group had 10 mice.

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References