Pre-Clinical Activity of ADCT-301, a Novel Pyrrolobenzodiazepine (PBD) Dimer-Containing Antibody Drug Conjugate (ADC) Targeting CD25-Expressing Hematological Malignancies

Michael J Flynn 1,2, Patrick van Berkel 3, Francesca Zammarchi 3, Jean-Noel Levy 2, Arnaud Tiberghien 3, Luke A Masterson 3, François D’Hooge 2, Peter C Tyser 4, Lauren Adams 3, David G Williams 2, Philip W Howard 2, 5 and John A Hartley 1,2, 5

1 University College London, London, United Kingdom; 2 Medimmune, Cambridge, United Kingdom; 3 ADC Therapeutics Sarl, Epalinges, Switzerland

Clinical proof of concept for treatment of CD25-positive malignancies in non-tumor bearing SCID mice.

The relationship between increased CD25 expression and poor patient outcome has been well established in solid tumors, hematological malignancies and autoimmunity.

The Interleukin-2 receptor (IL-2R) is one of a heterotrimeric cell surface receptor complex that includes the IL-2Rα (CD25) and IL-2Rβ (CD122) subunits.

Characterization of the in vitro mechanism of action and in vivo efficacy and tolerability of ADCT-301.

Materials & Methods

Flow cytometry and Surface Fluorescence Resonance (SFR) assays were used to measure binding affinity and binding avidity of ADCT-301.

The mean CD25 and CD122 molecules expressed per cell (Pearson’s correlation coefficient r = -0.37).

In vivo antitumor efficacy in subcutaneously implanted model

ADCT-301 and free warhead. The mean reduction in the product of the tail length and the fraction of total DNA in the tail i.e. the Olive Tail Moment (OTM) was measured.

The single cell gel electrophoresis (Comet) assay was carried out on cells treated with ADCT-301 and free warhead, or with an equimolar concentration of HuMax-TAC.

Results

The Interleukin-2 receptor (IL-2R) is one of a heterotrimeric cell surface receptor complex that includes the IL-2Rα (CD25) and IL-2Rβ (CD122) subunits.

Clinical proof of concept for treatment of CD25-positive malignancies has been previously established using radio-immunoconjugates and immunotoxins utilizing antibodies bispecific and diphtheria.

CD25 expression in human myeloma lines correlated with the GI50 values (Pearson's correlation coefficient r = 0.7).

ACKNOWLEDGMENTS

ADCT-301 was administered i.v. as a single dose to non-tumor bearing CB.17 SCID mice. The lower dose level indicates 33% of body weight dose. The MTD of ADCT-301 in non-tumor bearing SCID mice was 10 mg/kg.

Conclusions

ADCT-301 showed potent and highly targeted cytotoxicity in CD25-expressing cell lines.

Bystander killing can be demonstrated on CD25-negative cells.

DNA cross-linking is the likely mode of cytostatic action of ADCT-301. These cross-links persist for at least 36 hours in vitro.

In vivo, single-dose ADCT-301 administration shows excellent efficacy, superior to a single dose of Adcetris in Kappa 299 xenografts.

Together, these data clearly demonstrate the potent anti-tumor activity of ADCT-301 against CD25-expressing hematological tumors and warrants the rapid development of this agent into the clinic.

In vivo experiments: Charles River Discovery Research Services.

In vitro experimental setup: flow cytometric assay: Maria Verheul-Gormus (Medimmune) and Karin Harneit (ADC Therapeutics), cytometry assays: Sander Hermsen and Victoria Spano-Visscher (UCL).

References


