Conjugate in Models of Non-Hodgkin Lymphoma

Pre-clinical Activity of hLL2-PBD, a Novel Anti-CD22 Antibody-Pyrrolobenzodiazepine (PBD) Conjugate in Models of Non-Hodgkin Lymphoma

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Introduction

- CD22 is a type I transmembrane sialoglycoprotein, whose expression is restricted to the B- and T-cell lineages (1). CD22 is also found highly expressed on most malignant mature B cells, including follicular lymphoma (FL) marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL) (2, 3). Moreover, CD22 is expressed in ~90% of cases of B-precursor acute lymphoblastic leukemia (ALL) (4).
- The differential and favourable expression profile of CD22 in tumour versus normal tissue, together with its rapid internalization upon binding ligand or antibody (5), make CD22 an attractive target for antibody drug conjugate (ADC)-mediated treatment of B-cell malignancies.

- NLL2-PBD is an ADC composed of the humanized anti-human CD22 monoclonal antibody epratuzumab (hLL2), stochastically conjugated via a cathepsin-cleavable va-cleaved dipeptide linker (PBD). hLL2-PBD is an ADC composed of the humanized anti-human CD22 monoclonal antibody epratuzumab (hLL2), stochastically conjugated via a cathepsin-cleavable va-cleaved dipeptide linker (PBD).

- Overall, these data demonstrate the potent anti-tumour activity of hLL2-PBD against CD22-positive hematological tumours and warrant further development of this ADC into the clinic.

Materials & Methods

Characterization of the in vitro cytotoxicity, in vivo efficacy and pharmacokinetics (PK) of hLL2-PBD.

Results

Aim of this study

- Cytotoxicity of NLL2-PBD, Hu10F4-vcMMAE and non-binding ADC on human Ramos, Daudi and WSU-DLCL2 cells was determined by the CellTiter96® AQueous One Solution Cell Proliferation Assay (MTS assay). In vitro, in NLL2-PBD was administered as a single-dose to CB.17 Scid/beige C57BL/6J (Ramos cells) sera. Serum samples were collected from three mice per group for each time point after a single dose administration (1 mg/kg).

- Quantification of unconjugated and PBD-conjugated mAb hLL2 in mouse serum, obtained via an affinity chromatography (HIC) analysis. A. Eight-week-old SCID mice were s.c. implanted with 1 x 10^7 Daudi cells. When tumors reached mean volumes of 100 mm^3, mice were sorted into groups of 10 mice each and doses were administered. NLL2-PBD, administered i.v. as a single dose, at either 0.1 mg/kg or 0.3 mg/kg, induced a dose-dependent antitumor response. At the highest dose tested (0.3 mg/kg) all the animals were classified as tumor survivors at the end of the study (Fig. 6 A).

- Kaplan-Meier survival curves showing the dose-dependent extension of survival (log-rank test, p < 0.05 for each comparison). NLL2-PBD with a DAR of 2.5 was produced at the 100 mg scale with high yield (97%) without using an enzymatic process.

- Figure 3- Scale-up production of hLL2-PBD is a straightforward and high yielding process.

- Table with summary table of manufactured hLL2-PBD (mg/mL) concentration, DAR 2 or 1.97, DAR by SEC 2.0, DAR by IC 2.5, DAR by HIC 43.7, 2.5 by SEC 20.1, 2.5 by IC 43.7, 2.5 by HIC 24.4.

- Figure 5- In vivo antitumor efficacy in sc. implanted Ramos model.

- Summary table of manufactured hLL2-PBD (mg/mL) concentration, DAR 2 or 1.97, DAR by HIC 43.7, 2.5 by SEC 20.1, 2.5 by IC 43.7, 2.5 by HIC 24.4.

- Figure 7- PK analysis

Conclusions

- Generation of NLL2-PBD with DAR 2.5 was achieved using a simple, robust and high yielding process.

- NLL2-PBD and Hu10F4-vcMMAE showed comparable, potent and specific in vitro cytotoxicity in CD22-expressing human Burkitt’s lymphoma-derived cell lines Ramos and Daudi and in human diffuse large B-cell lymphoma-derived cell line WSU-DLCL2. An isotype control ADC showed a strongly reduced in vitro activity against the three cell lines.

- In vivo, single-dose NLL2-PBD administration demonstrated remarkable anti-tumour efficacy in Ramos and Daudi s.c. xenografts. At equivalent doses NLL2-PBD was markedly superior to Hu10F4-vcMMAE (an anti-CD22 ADC developed by Genentech) in the Ramos model.

- Analysis of NLL2-PBD in non-tumour bearing mice showed a favourable PK profile, with a blood half-life of approximately 9 days.

- Overall, these data demonstrate the potential in vitro and in vivo antitumor activity of NLL2-PBD against CD22-positive hematological tumours and warrant further development of this ADC into the clinic.

Acknowledgments


References