Preclinical characterization of a next-generation CD19/CD3-bispecific T cell engaging antibody construct CLN-978 with long serum half-life and superior potency against target cells expressing very low levels of CD19

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Structure of CLN-978

CLN-978 is a novel TCE designed with features to improve upon several shortcomings of approved therapies to provide a therapeutic option for refractory or relapsing NHL or ALL patients with cancer cells expressing very low levels of CD19.

CLN-978 is currently in IND-enabling studies

Features of CLN-978

- A very high-affinity human CD19-binding scfV to recognize and kill NHL and ALL cells with very low levels of CD19 target expression (blue)
- A humanized serum albumin-binding single-domain antibody (VHH) for half-life extension (brown)
- A medium-affinity human scfV to bind to the invariant CD3 ε episial chain of the T cell receptor (TCR) (green)
- CLN-978 is fully cross-reactive with non-human primate orthologs
- CLN-978 is produced at high titers in CHO cells, omits a His tag, and is purified via standard protein A binding methods

Background

- CD19 is a clinically and commercially validated target for the treatment of various B cell malignancies via T cell engaging antibodies (TCE), CAR-T cells, and monoclonal antibodies
- Blinatumomab (Blincyto®) is a CD19/CD3-bispecific TCE approved for the therapy of relapsed/refractory (r/r) minimal residual ALL expressing CD19
- Often low expression levels of CD19 or apparent loss of CD19 from malignant cells under therapy severely limit the therapeutic benefit of TCE and CAR-T cell therapies
- CLN-978 is a novel TCE designed with features to improve upon several shortcomings of approved therapies to provide a therapeutic option for refractory or relapsing NHL or ALL patients with cancer cells expressing very low levels of CD19

Results

Figure 1: Binding affinities of CLN-978

- CD19 Affinity (KD): 0.23 nM
- CD3 affinity (KD): 7.9 nM
- HSA Affinity (KD): 0.60 nM

Figure 2: Activation of T cells by CLN-978 co-cultured with Ramos B lymphoma cells

- Unstimulated PBMC were co-cultured with Ramos cells at an E:T ratio of 10:1 for 48 hours.
- Surface expression of CD69 and CD25 was determined by FACS, and cytokine levels by Luminex.

Figure 3: Redirected lysis by CLN-978 of Ramos and Raji B lymphoma cells with T cells in vitro

- Unstimulated PBMC were cocultured with Ramos or Raji cells at E:T ratios of 3:1 for 48 hours. Cytotoxicity was determined by flow cytometry.

Figure 4: Comparison of CLN-978 with blinatumomab for their potency of redirected lysis in vitro

- CLN-978 potently triggers redirected lysis of CD19-expressing target cells by cytotoxic T cells in cell coculture

Figure 5: In vivo efficacy of IV- and SC-administered CLN-978 in a Raji-Luciferase NCG mouse model

- Controls
- No Treatment
- PBMC B Cell Depletion
- PBMC + CLN-978 (IV) 3 mg/kg
- PBMC + CLN-978 (SC)

Figure 6: Comparison of CLN-978 with blinatumomab for in vivo efficacy in two mouse models

- A) hCD3
- B) Raji-Luciferase disseminated model in NCG mice

Figure 7: Pharmacokinetics, B cell depletion, T cell redistribution and cytokine release in Cynomolgus monkeys in response to a single IV- or SC-administered CLN-978 dose

- Pharmacokinetics
- B Cell Depletion
- T Cell Redistribution
- Cytokine Release

Conclusions

- CLN-978 is designed to be an off-the-shelf CD19-targeted therapy with improved properties relative to existing therapies
- CLN-978 is differentiated from blinatumomab (BLINCYTO®)
  - Higher affinity to CD19 enables redirected lysis of low CD19 expressing target cells
  - Extended serum half-life of CLN-978 enables a convenient dosing regimen
- CLN-978 affinities to CD19 and CD3 were optimized to maximize therapeutic index
- CLN-978 potently triggers redirected lysis of CD19 expressing target cells by cytotoxic T cells in cell coculture assays, mouse models and non-human primates
- Subcutaneous delivery of CLN-978 promises a wider therapeutic window than IV delivery
- CLN-978 has the potential to treat patients having relapsed from therapies with BLINCYTO® and CD19 CAR-T cells due to reduced CD19 target expression
- CLN-978 is currently in IND-enabling studies

Key Points

- CLN-978 is a novel TCE with high affinity to CD19 and CD3
- CLN-978 shows long serum half-life and superior potency against target cells expressing very low levels of CD19
- CLN-978 is currently in IND-enabling studies

Supporting Information

- Abstract Supporting Information