CLN-617 is an intratumorally injected and locally retained fusion of IL-2 and IL-12 that drives systemic anti-tumor activity

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Background IL-2 and IL-12 synergistically trigger the stimulation and proliferation of T and NK cells to mediate anti-tumor immunity. Although aldesleukin (recombinant IL-2 for high-dose infusion) has been approved for the treatment of melanoma and renal cell carcinoma, adoption has been hindered by frequent grade 3 and 4 severe adverse events. No IL-12 therapy has been approved yet due to dose-limiting toxicities. CLN-617 is comprised of IL-2, leukocyte-associated immunoglobulin-like receptor 2 (LAIR2), human serum albumin (HSA), and IL-12, and is designed for intra-tumoral (IT) administration. Upon injection, tumor retention is enabled by LAIR2, which binds to collagen, and by HSA, which increases the molecular weight, to reduce toxicity and enhance efficacy.

Methods Proteins were expressed in HEK293 or CHO cells. Collagen binding was measured by ELISA. Cytokine bioactivity was evaluated by treating PBMCs with CLN-617 followed by flow cytometry and protein microarray analysis. In vivo studies were conducted in B16F10 and MC38 murine syngeneic tumor models. Cytokine concentrations were determined by Mesoscale Discovery, and immunophenotyping was performed in blood and digested tissue samples.

Results CLN-617 triggered signal transducer and activator of transcription 4 and 5 (STAT4 and STAT5) signaling pathways in T cells and NK cells in vitro comparable to recombinant IL-2 and IL-12. When a murine surrogate of CLN-617 (mCLN-617) was injected IT in MC38 tumors, IT concentrations of mCLN-617 were >20x serum concentrations. In the checkpoint-refractory B16F10 and MC38 tumor models, mCLN-617 demonstrated 95% tumor growth inhibition and 100% CRs, respectively. All mice cured of their primary MC38 tumors were either protected from re-challenge or showed delayed tumor growth kinetics (figure 1A). In mice bearing two MC38 tumors, only one of which was treated IT, the number of CD8+ T cell infiltrates more than doubled (figure 1B) and the CD8+ to T regulatory cell ratio increased to >10 (figure 1C) in both treated and distal untreated tumors. The frequency of tumor-specific T cells in the periphery increased >7-fold (figure 1D). 100% of treated tumors and 90% of untreated tumors were eliminated when mCLN-617 was combined with an anti-PD1 antibody (figure 1E), demonstrating a robust abscopal response.

Conclusions Fusion to LAIR2 and HSA enables well-tolerated and effective IT delivery of IL-2 and IL-12 in a single multi-functional molecule. Despite local administration and retention, CLN-617 mobilizes systemic immunity to drive abscopal responses. CLN-617 is currently in IND-enabling studies.

Abstract 1061 Figure 1 CLN-617 drives memory responses and systemic immunity. A) MC38 tumors were treated IT with mCLN-617. Surviving mice were re-challenged with MC38 tumors after two months. B-D) Mice were implanted with two MC38 tumors, and one was treated IT. Treated and untreated tumors (B, C) as well as peripheral blood (D) were evaluated by flow cytometry. E) In a dual flank MC38 tumor model, one tumor was treated with mCLN-617 IT with or without systemic anti-PD1 administered intraperitoneally. For B-D, statistics were analyzed by t-test, *p<0.05 ****p<0.0001