CLN-617 is a first-in-class fusion protein that retains IL-2 and IL-12 in the injected tumor and potentially triggers systemic anti-tumor immunity

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Background

- IL-2 and IL-12 synergistically trigger the stimulation and proliferation of T cells and NK cells to mediate anti-tumor immunity, but have been hindered in the clinic due to significant toxicity1,2
- Although aldesleukin, a high-dose IL-2 intravenous (IV) infusion regimen, has been approved for the treatment of melanoma and renal cell carcinoma, adoption in clinical practice has been limited by frequent grade 3 and 4 adverse events
- No IL-2 therapy has been approved yet due to toxicity

CLN-617 Rationale

- CLN-617 is designed for intratumoral delivery of both IL-2 and IL-12 and retention in the tumor microenvironment via a LAIR2 collagen-binding domain
- CLN-617 was designed by integrating three primary principles:
  1. Cytokines are autocrine/paracrine in nature, not endocrine
  2. A protein injected locally will not stay local without retention
  3. Natural immune responses trigger a cytokine milieu, and do not rely on an individual cytokine
- CLN-617 combines IL-2 and IL-12 in a single polypeptide

Results

- IL-2 and IL-12 act synergistically in promoting T\textsubscript{H}1 anti-tumor immunity

Conclusions

- CLN-617 combines IL-2 and IL-12 in a single molecule in a safe and effective manner via retention domains
- CLN-617 activates T cells in a manner indistinguishable from recombinant IL-2 and IL-12
- CLN-617 can eradicate large, established primary and distal checkpoint-resistant tumors
- CLN-617 demonstrates single agent activity and synergizes with anti-PD1 therapy
- CLN-617 drives robust, functional, and systemically mobilized tumor-specific cellular immunity
- Preclinical data suggests that CLN-617 may be effective for the treatment of solid tumors with minimal toxicities in the clinic
- IND filing has cleared, and clinical trial initiation is expected in 2023

Figure 1: Schematic of CLN-617 design
IL-2 and IL-12 act synergistically in promoting T\textsubscript{H}1 anti-tumor immunity

Figure 2: CLN-617 binds to collagen and exhibits full bioactivity of IL-2 and IL-12 in vitro

Figure 3: IT administration reduces systemic exposure of mCLN-617

Figure 4: mCLN-617 is effective in checkpoint refractory syngeneic models

Figure 5: Local administration triggers systemic immunity and shows synergy in combination with anti-PD1 therapy

Figure 6: mCLN-617 mediates local release of interferon-gamma

Figure 7: Local administration mobilizes a systemic, tumor-specific cellular immune response, remodeling both the injected and un.injected tumors

References

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